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(73) Jogosult(ak):

**GlaxoSmithKline Biologicals SA, 1330
Rixensart (BE)**

(72) Feltaláló(k):

Comanducci, Maurizio, 53100 Siena (IT)**Pizza, Mariagrazia, 53100 Siena (IT)**

(74) Képviselő:

**Danubia Szabadalmi és Jogi Iroda Kft.,
Budapest**

(54)

NMB1870 menningococcus-fehérje többszörös változatai

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Mehrfache meningokokkale Protein NMB 1870 Varianten

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(73) Proprietor: **GlaxoSmithKline Biologicals SA**
1330 Rixensart (BE)

(72) Inventors:
• **Comanducci, Maurizio**
53100 Siena (IT)
• **Pizza, Mariagrazia**
53100 Siena (IT)

(74) Representative: **Courgeon, Antoine**
GlaxoSmithKline
Global Patents CN925.1
980 Great West Road
Brentford, Middlesex TW8 9GS (GB)

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Description**TECHNICAL FIELD**

5 **[0001]** This invention is in the field of vaccination and, in particular, vaccination against disease caused by pathogenic bacteria in the genus *Neisseria*, such as *N.meningitidis* (meningococcus).

BACKGROUND ART

10 **[0002]** *Neisseria meningitidis* is a Gram-negative encapsulated bacterium which colonises the upper respiratory tract of approximately 10% of human population. Approximately once in every 10,000 colonised people (or once in 100,000 population) the bacterium enters the blood stream where it multiplies and causes sepsis. From the blood stream the bacterium can cross the blood-brain barrier and cause meningitis. Both diseases are devastating and can kill 5-15% of affected children and young adults within hours, despite the availability of effective antibiotics. Up to 25% of those who survive are left with permanent sequelae.

15 **[0003]** Prevention of disease has been partially accomplished by vaccination. Immunisation was made possible in 1969 when it was discovered that protection from disease correlates with the presence of serum antibodies able to induce complement-mediated killing of bacteria, and that purified capsular polysaccharide was able to induce these antibodies. Although polysaccharide and conjugate vaccines are available against serogroups A, C, W135 and Y, this approach cannot be applied to serogroup B because the capsular polysaccharide is a polymer of polysialic acid, which is a self antigen in humans. To develop a vaccine against serogroup B, surface-exposed proteins contained in outer membrane vesicles (OMVs) have been used. These vaccines elicit serum bactericidal antibody responses and protect against disease, but they fail to induce cross-strain protection [1].

20 **[0004]** The complete genome sequence of serogroup B *N.meningitidis* has been published [2] and has been subjected to analysis in order to identify vaccine antigens [3]. The complete genome sequence of serogroup A *N.meningitidis* is also known [4], and the complete genome sequence of *Neisseria gonorrhoeae* strain FA1090 is available [5]. References 6 to 9 disclose proteins from *Neisseria meningitidis* and *Neisseria gonorrhoeae*, and approaches to expression of these proteins are disclosed in references 10 to 12.

25 **[0005]** It is an object of the invention to provide further and improved compositions for providing immunity against meningococcal disease and/or infection, particularly for serogroup B.

DISCLOSURE OF THE INVENTION

30 **[0006]** One of the ~2200 proteins disclosed in reference 2 is 'NMB1870'. The protein was originally disclosed as protein '741' from strain MC58 [SEQ IDs 2535 & 2536 in ref. 8; SEQ ID 1 herein], and has also been referred to as 'GNA1870' [following ref. 3] or as 'ORF2086' [13].

35 **[0007]** It has now been found that NMB1870 is an extremely effective antigen for eliciting anti-meningococcal antibody responses, and that it is expressed across all meningococcal serogroups. NMB 1870 has been found in all meningococcal strains tested to date. Forty-two different meningococcal NMB1870 sequences have been identified, and it has been found that these sequences group into three variants. Furthermore, it has been found that serum raised against a given variant is bactericidal within the same variant group, but is not active against strains which express one of the other two variants *i. e.* there is intra-variant cross-protection, but not inter-variant cross-protection. For maximum cross-strain efficacy, therefore, more than one variant should be used for immunising a patient.

40 **[0008]** The invention therefore provides a composition comprising (a) a first protein which is able to induce bactericidal antibodies, comprising an amino acid sequence having at least *a*% sequence identity to SEQ ID NO: 24, and (b) a second protein which is able to induce bactericidal antibodies, comprising an amino acid sequence having at least *b*% sequence identity to SEQ ID NO: 41; wherein the first and second proteins have less than *i*% sequence identity to each other. The composition can also include (c) a third protein which is able to induce bactericidal antibodies, comprising an amino acid sequence having at least *c*% sequence identity to SEQ ID NO: 33; wherein the first, second and third proteins all have less than *i*% sequence identity to each other. The values of *a*, *b*, *c* and *i* are discussed below.

Variability in and between (a), (b) and (c)

45 **[0009]** The value of *a* is at least 85 *e.g.* 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5, or more. The value of *b* is at least 85 *e.g.* 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5, or more. The value of *c* is at least 85 *e.g.* 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5, or more. The values of *a*, *b* and *c* are not intrinsically related to each other.

50 **[0010]** Protein (a) has less than *i*% sequence identity to protein (b). The value of *i* is 75

[0011] In a two-protein embodiment of the invention, therefore, protein (a) has >85% sequence identity to SEQ ID 24, protein (b) has >85% sequence identity to SEQ ID 41, but protein (a) and (b) have less than 75% sequence identity to each other. Proteins (a) and (b) are therefore each closely related to their 'prototype' sequences, but they are not so closely related to each other.

[0012] In an example three-protein embodiment of the invention, therefore, protein (a) might have >85% sequence identity to SEQ ID 24, protein (b) might have >85% sequence identity to SEQ ID 33, protein (c) might have >85% sequence identity to SEQ ID 41, but protein (a) and (b) have less than 75% sequence identity to each other, protein (a) and (c) have less than 75% sequence identity to each other, and protein (b) and (c) have less than 75% sequence identity to each other.

[0013] The mixture of two or more of (a), (b) and (c) can preferably elicit an antibody response which is bactericidal against at least one *N.meningitidis* strain from each of at least two of the following three groups of strains:

(a) MC58, gb185 (=M01-240185), m4030, m2197, m2937, iss1001, NZ394/98, 67/00, 93/114, bz198, m1390, nge28, 1np17592, 00-241341, f6124, 205900, m198/172, bz133, gb149 (=M01-240149), nm008, nm092, 30/00, 39/99, 72/00, 95330, bz169, bz83, cu385, h44/76, m1590, m2934, m2969, m3370, m4215, m4318, n44/89, 14847.

(b) 961-5945, 2996, 96217, 312294, 11327, a22, gb013 (=M01-240013), e32, m1090, m4287, 860800, 599, 95N477, 90-18311, c11, m986, m2671, 1000, m1096, m3279, bz232, dk353, m3697, ngh38, L93/4286.

(c) M1239, 16889, gb355 (=M01-240355), m3369, m3813, ngp165.

[0014] For example, the mixture can elicit a bactericidal response effective against each of serogroup B *N.meningitidis* strains MC58, 961-5945 and M1239.

[0015] The mixture of two or more of (a), (b) and (c) can preferably elicit an antibody response which is bactericidal against at least 50% of clinically-relevant meningococcal serogroup B strains (e.g. at least 60%, 70%, 80%, 90%, 95% or more).

[0016] The mixture of two or more of (a), (b) and (c) can preferably elicit an antibody response which is bactericidal against strains of serogroup B *N.meningitidis* and strains of at least one (e.g. 1, 2, 3, 4) of serogroups A, C, W135 and Y.

[0017] The mixture of two or more of (a), (b) and (c) can preferably elicit an antibody response which is bactericidal against strains of *N.gonococcus* and/or *N.cinerea*.

[0018] The mixture of two or more of (a), (b) and (c) can preferably elicit an antibody response which is bactericidal against strains from at least two of the three main branches of the dendrogram shown in Figure 9 (i.e. the dendrogram obtained by analysing SEQ IDs 1 to 23 by the Kimura & Jukes-Cantor algorithm).

[0019] The mixture of two or more of (a), (b) and (c) can preferably elicit an antibody response which is bactericidal against *N.meningitidis* strains in at least 2 (e.g. 2, 3, 4, 5, 6, 7) of hypervirulent lineages ET-37, ET-5, cluster A4, lineage 3, subgroup I, subgroup III, and subgroup IV-1 [14, 15].

[0020] Compositions of the invention may additionally induce bactericidal antibody responses against one or more hyperinvasive lineages.

[0021] The mixture of two or more of (a), (b) and (c) can preferably elicit an antibody response which is bactericidal against *N.meningitidis* strains in at least at least 2 (e.g. 2, 3, 4, 5, 6, 7) of the following multilocus sequence types: ST1, ST4, ST5, ST8, ST11, ST32 and ST41 [16]. The mixture may also elicit an antibody response which is bactericidal against ST44 strains.

[0022] Bactericidal antibody responses are conveniently measured in mice and are a standard indicator of vaccine efficacy [e.g. see end-note 14 of reference 3]. The composition need not induce bactericidal antibodies against each and every MenB strain within the specified lineages or MLST; rather, for any given group of four or more strains of serogroup B meningococcus within a particular hypervirulent lineage or MLST, the antibodies induced by the composition are bactericidal against at least 50% (e.g. 60%, 70%, 80%, 90% or more) of the group. Preferred groups of strains will include strains isolated in at least four of the following countries: GB, AU, CA, NO, IT, US, NZ, NL, BR, and CU. The serum preferably has a bactericidal titre of at least 1024 (e.g. 2^{10} , 2^{11} , 2^{12} , 2^{13} , 2^{14} , 2^{15} , 2^{16} , 2^{17} , 2^{18} or higher, preferably at least 2^{14}) i.e. the serum is able to kill at least 50% of test bacteria of a particular strain when diluted 1/1024 e.g. as described in end-note 14 of reference 3.

Lipoproteins

[0023] NMB1870 is naturally a lipoprotein in *N.meningitidis*. It has also been found to be lipidated when expressed in *E.coli*.

[0024] It is preferred that one or more (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10) NMB1870 proteins included in compositions of the invention is a lipoprotein.

[0025] Preferably, the lipoprotein has a N-terminal cysteine residue, to which the lipid is covalently attached. To prepare the lipoprotein via bacterial expression generally requires a suitable N-terminal signal peptide to direct lipidation by

diacylglycerol transferase, followed by cleavage by lipoprotein-specific (type II) SPase. While the lipoprotein of the invention may have a N-terminal cysteine (e.g. SEQ IDs 24 to 45), therefore, it will be a product of post-translational modification of a nascent protein which has the usual N-terminal methionine (e.g. SEQ IDs 1 to 22).

[0026] The lipoprotein may be associated with a lipid bilayer and may be solubilised with detergent.

Sequences

[0027] A preferred subset of proteins useful with the invention does not include the amino acid sequence TRSKP (SEQ ID NO: 70) or TRSKPV (SEQ ID NO: 71) within 10 amino acids of the protein's N-terminus. Another preferred subset of proteins does not include the amino acid sequence PSEPPFG (SEQ ID NO: 72) within 10 amino acids of the protein's N-terminus.

[0028] Another preferred subset of proteins for use with the invention includes the amino acid sequence (Gly)_n, where n is 1, 2, 3, 4 or more e.g. SEQ ID NO: 73.

[0029] A characteristic of proteins used with the invention is the ability to induce bactericidal anti-meningococcal antibodies after administration to a host animal.

[0030] Proteins can be prepared by various means e.g. by chemical synthesis (at least in part), by digesting longer polypeptides using proteases, by translation from RNA, by purification from cell culture (e.g. from recombinant expression or from *N.meningitidis* culture). etc. Heterologous expression in an *E. coli* host is a preferred expression route (e.g. strains DH5α, BL21(DE₃), BLR, etc.).

[0031] Proteins of the invention may be attached or immobilised to a solid support.

[0032] Proteins of the invention may comprise a detectable label e.g. a radioactive label, a fluorescent label, or a biotin label. This is particularly useful in immunoassay techniques.

[0033] Proteins can take various forms (e.g. native, fusions, glycosylated, non-glycosylated, lipidated, disulfide bridges, etc.). Proteins are preferably meningococcal proteins.

[0034] Proteins are preferably prepared in substantially pure or substantially isolated form (i.e. substantially free from other Neisserial or host cell proteins) or substantially isolated form. In general, the proteins are provided in a non-naturally occurring environment e.g. they are separated from their naturally-occurring environment. In certain embodiments, the subject protein is present in a composition that is enriched for the protein as compared to a control. As such, purified protein is provided, whereby purified is meant that the protein is present in a composition that is substantially free of other expressed proteins, where by substantially free is meant that less than 90%, usually less than 60% and more usually less than 50% of the composition is made up of other expressed proteins.

[0035] The term "protein" refers to amino acid polymers of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, proteins containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), as well as other modifications known in the art. Proteins can occur as single chains or associated chains.

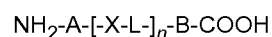
Hybrid and tandem proteins

[0036] As mentioned above, NMB1870 may be used in the form of a fusion protein, although the proteins may also be expressed other than as a fusion protein (e.g. without GST, MBP, his-tag or similar).

[0037] Fusion proteins can have a C-terminus and/or N-terminus fusion partner. Where a N-terminus fusion partner is used with SEQ IDs 1 to 23, the skilled person will realise that the start codon will (if included) be expressed as a valine, because GTG is translated as valine except when it is used as a start codon, in which case it is translated as N-formyl-methionine.

[0038] Suitable N-terminus fusion partners include leader peptides from other proteins (particularly other lipoproteins), which may be substituted for the natural NMB1870 leader peptides (i.e. the sequence prior to the N-terminus cysteine may be replaced with another leader peptide of interest). Examples are sequences comprising SEQ ID 46, and the *H.influenzae* P4 lipoprotein leader sequence [e.g. 17].

[0039] A preferred type of fusion protein is disclosed in references 10, 11 & 12 in which two or more (e.g. 3, 4, 5, 6 or more) Neisserial proteins are joined such that they are translated as a single polypeptide chain. In general, such hybrid proteins can be represented by the formula:



wherein X is an amino acid sequence comprising a Neisserial sequence, L is an optional linker amino acid sequence,

A is an optional N-terminal amino acid sequence, B is an optional C-terminal amino acid sequence, and n is an integer greater than 1. The value of n is between 2 and x , and the value of x is typically 3, 4, 5, 6, 7, 8, 9 or 10. Preferably n is 2, 3 or 4; it is more preferably 2 or 3; most preferably, $n = 2$.

[0040] According to the present invention, at least one of the -X- moieties is a NMB1870 sequence as defined above. In some hybrid proteins, referred to as 'tandem' proteins, at least one of the -X- moieties has sequence identity to at least one of the other X moieties e.g. X_1 is SEQ ID NO: 24 and X_2 is a SEQ ID NO: 25. Proteins in which two or three of the three NMB1870 variants are joined as a tandem protein are preferred.

[0041] For X moieties other than X_1 , it is preferred that the native leader peptide should be omitted, particularly where X_1 is not a NMB1870 sequence. In one embodiment, the leader peptides will be deleted except for that of the -X- moiety located at the N-terminus of the hybrid protein i.e. the leader peptide of X_1 will be retained, but the leader peptides of $X_2 \dots X_n$ will be omitted. This is equivalent to deleting all leader peptides and using the leader peptide of X_1 as moiety -A-.

[0042] Preferred NMB1870 sequences for use as -X- moieties are truncated up to and including the poly-glycine sequence found near the mature N-terminus e.g. the NMB1870 sequence will begin VAA... (or IAA... for strain m3813). Such NMB1870 sequences include SEQ ID NOs: 80, 81 & 84.

[0043] For each n instances of [-X-L-], linker amino acid sequence -L- may be present or absent. For instance, when $n=2$ the hybrid may be $\text{NH}_2\text{-X}_1\text{-L}_1\text{-X}_2\text{-L}_2\text{-COOH}$, $\text{NH}_2\text{-X}_1\text{-X}_2\text{-COOH}$, $\text{NH}_2\text{-X}_1\text{-L}_1\text{-X}_2\text{-COOH}$, $\text{NH}_2\text{-X}_1\text{-X}_2\text{-L}_2\text{-COOH}$, etc. Linker amino acid sequence(s) -L- will typically be short (e.g. 20 or fewer amino acids i.e. 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include short peptide sequences which facilitate cloning, poly-glycine linkers (i.e. Gly_n where $n = 2, 3, 4, 5, 6, 7, 8, 9, 10$ or more), and histidine tags (i.e. His_n where $n = 3, 4, 5, 6, 7, 8, 9, 10$ or more). Other suitable linker amino acid sequences will be apparent to those skilled in the art. A useful linker is GSGGGG (SEQ ID NO: 144), with the Gly-Ser dipeptide being formed from a *Bam*HI restriction site, thus aiding cloning and manipulation, and the Gly_4 tetrapeptide (SEQ ID NO: 73) is another typical poly-glycine linker. Another useful linker is SEQ ID NO: 78.

[0044] -A- is an optional N-terminal amino acid sequence. This will typically be short (e.g. 40 or fewer amino acids i.e. 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include leader sequences to direct protein trafficking, or short peptide sequences which facilitate cloning or purification (e.g. histidine tags i.e. His_n where $n = 3, 4, 5, 6, 7, 8, 9, 10$ or more). Other suitable N-terminal amino acid sequences will be apparent to those skilled in the art. If X_1 lacks its own N-terminus methionine, -A- may provide such a methionine residue in the translated protein (e.g. -A- is a single Met residue). A useful -A- moiety for expressing NMB1870 is SEQ ID NO: 86. In mature lipoproteins, -A- preferably provides a N-terminus cysteine (e.g. -A- is a single Cys residue).

[0045] -B- is an optional C-terminal amino acid sequence. This will typically be short (e.g. 40 or fewer amino acids i.e. 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include sequences to direct protein trafficking, short peptide sequences which facilitate cloning or purification (e.g. comprising histidine tags i.e. His_n where $n = 3, 4, 5, 6, 7, 8, 9, 10$ or more), or sequences which enhance protein stability. Other suitable C-terminal amino acid sequences will be apparent to those skilled in the art.

[0046] In preferred hybrid proteins of the invention, one of the X moieties is a 'protein 936' sequence. For example, where $n = 2$, A = Met, X_1 is a 936 sequence (e.g. SEQ ID NO: 76, which is the processed MC58 protein), L_1 = apoly-glycine linker (e.g. SEQ ID NO: 144), X_2 = aNMB1870 sequence in which the N-terminus has been deleted up to and including its own poly-glycine sequence, and L_2 and B may be omitted. An example of such a hybrid protein is SEQ ID NO: 77, in which truncated NMB1870 from strain m1239 is downstream of the processed 936 from strain MC58. Further examples of hybrid proteins of 936 (2996 strain) and truncated NMB1870 (strain 2996 or M1239) are SEQ ID NOs: 91, 92, 93 & 94.

[0047] Preferred tandem proteins where $n=3$ may have all three NMB1870 variants in any order:

X_1	1	1	2	2	3	3
X_2	2	3	1	3	1	2
X_3	3	2	3	1	2	1

[0048] Preferred tandem proteins where $n=2$ may have two different NMB1870 variants:

X_1	1	1	2	2	3	3
X_2	2	3	1	3	1	2

[0049] Examples of tandem proteins where $n=2$ (two different NMB1870 variants) are SEQ ID NOs: 79, 82, 83, 85, 87, 88, 89 & 90, which use strains MC58 (variant 1), 2996 (variant 2) and M1239 (variant 3).

[0050] An example of a tandem protein where $n=3$ is given as SEQ ID NO: 142.

Nucleic acids

[0051] The invention provides nucleic acid encoding a protein of the invention as defined above.

[0052] Nucleic acids of the invention can be prepared in many ways *e.g.* by chemical synthesis in whole or part, by digesting longer polynucleotides using nucleases (*e.g.* restriction enzymes), from genomic or cDNA libraries, from the bacterium itself, *etc.*

[0053] Nucleic acids of the invention can take various forms *e.g.* single-stranded, double-stranded, vectors, primers, probes, labelled, unlabelled, *etc.*

[0054] Nucleic acids of the invention are preferably in isolated or substantially isolated form.

[0055] The invention includes nucleic acid comprising sequences complementary to those described above *e.g.* for antisense or probing, or for use as primers.

[0056] The term "nucleic acid" includes DNA and RNA, and also their analogues, such as those containing modified backbones, and also peptide nucleic acids (PNA) *etc.*

[0057] Nucleic acid according to the invention may be labelled *e.g.* with a radioactive or fluorescent label. This is particularly useful where the nucleic acid is to be used in nucleic acid detection techniques *e.g.* where the nucleic acid is a primer or as a probe for use in techniques such as PCR, LCR, TMA, NASBA, *etc.*

[0058] The invention also provides vectors comprising nucleotide sequences of the invention (*e.g.* cloning or expression vectors, such as those suitable for nucleic acid immunisation) and host cells transformed with such vectors.

Further antigenic components

[0059] Compositions of the invention include a small number (*e.g.* fewer than t antigens, where t is 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4 or 3) of purified serogroup B antigens. It is particularly preferred that the composition should not include complex or undefined mixtures of antigens *e.g.* it is preferred not to include outer membrane vesicles in the composition. The antigens are preferably expressed recombinantly in a heterologous host and then purified.

[0060] The composition of the invention includes at least two different NMB1870 proteins. It may also include another neisserial antigen, as a vaccine which targets more than one antigen per bacterium decreases the possibility of selecting escape mutants. Neisserial antigens for inclusion in the compositions include proteins comprising:

- (a) the 446 even SEQ IDs (*i. e.* 2, 4, 6, ... , 890, 892) disclosed in reference 6.
- (b) the 45 even SEQ IDs (*i.e.* 2, 4, 6, ... , 88, 90) disclosed in reference 7;
- (c) the 1674 even SEQ IDs 2-3020, even SEQ IDs 3040-3114, and all SEQ IDs 3115-3241, disclosed in reference 8;
- (d) the 2160 amino acid sequences NMB0001 to NMB2160 from reference 2;
- (e) an amino acid sequence disclosed in reference 10, 11 or 12;
- (f) a variant, homolog, ortholog, paralog, mutant *etc.* of (a) to (e); or
- (g) an outer membrane vesicle prepared from *N.meningitidis* [*e.g.* see ref. 139].

[0061] In addition to Neisserial antigens, the composition may include antigens for immunising against other diseases or infections. For example, the composition may include one or more of the following further antigens:

- antigens from *Helicobacter pylori* such as CagA [18 to 21], VacA [22, 23], NAP [24, 25, 26], HopX [*e.g.* 27], HopY [*e.g.* 27] and/or urease.
- a saccharide antigen from *N.meningitidis* serogroup A, C, W135 and/or Y, such as the oligosaccharide disclosed in ref. 28 from serogroup C [see also ref. 29] or the oligosaccharides of ref. 30.
- a saccharide antigen from *Streptococcus pneumoniae* [*e.g.* 31, 32, 33].
- an antigen from hepatitis A virus, such as inactivated virus [*e.g.* 34, 35].
- an antigen from hepatitis B virus, such as the surface and/or core antigens [*e.g.* 35, 36].
- a diphtheria antigen, such as a diphtheria toxoid [*e.g.* chapter 3 of ref. 37] *e.g.* the CRM₁₉₇ mutant [*e.g.* 38].
- a tetanus antigen, such as a tetanus toxoid [*e.g.* chapter 4 of ref. 37].
- an antigen from *Bordetella pertussis*, such as pertussis holotoxin (PT) and filamentous haemagglutinin (FHA) from *B.pertussis*, optionally also in combination with pertactin and/or agglutinogens 2 and 3 [*e.g.* refs. 39 & 40].
- a saccharide antigen from *Haemophilus influenzae* B [*e.g.* 29].
- an antigen from hepatitis C virus [*e.g.* 41].
- an antigen from *N.gonorrhoeae* [*e.g.* 6, 7, 8, 42].
- an antigen from *Chlamydia pneumoniae* [*e.g.* refs. 43 to 49].
- an antigen from *Chlamydia trachomatis* [*e.g.* 50].

- an antigen from *Porphyromonas gingivalis* [e.g. 51].
- polio antigen(s) [e.g. 52, 53] such as IPV.
- rabies antigen(s) [e.g. 54] such as lyophilised inactivated virus [e.g. 55, RabAvert™].
- measles, mumps and/or rubella antigens [e.g. chapters 9, 10 & 11 of ref. 37].
- 5 - influenza antigen(s) [e.g. chapter 19 of ref. 37], such as the haemagglutinin and/or neuraminidase surface proteins.
- an antigen from *Moraxella catarrhalis* [e.g. 56].
- an protein antigen from *Streptococcus agalactiae* (group B streptococcus) [e.g. 57, 58].
- a saccharide antigen from *Streptococcus agalactiae* (group B streptococcus).
- an antigen from *Streptococcus pyogenes* (group A streptococcus) [e.g. 58, 59, 60].
- 10 - an antigen from *Staphylococcus aureus* [e.g. 61].
- an antigen from *Bacillus anthracis* [e.g. 62, 63, 64].
- an antigen from a virus in the flaviviridae family (genus flavivirus), such as from yellow fever virus, Japanese encephalitis virus, four serotypes of Dengue viruses, tick-borne encephalitis virus, West Nile virus.
- a pestivirus antigen, such as from classical porcine fever virus, bovine viral diarrhoea virus, and/or border disease virus.
- 15 - a parvovirus antigen e.g. from parvovirus B 19.
- a prion protein (e.g. the CJD prion protein)
- an amyloid protein, such as a beta peptide [65]
- a cancer antigen, such as those listed in Table 1 of ref. 66 or in tables 3 & 4 of ref. 67.

20 **[0062]** The composition may comprise one or more of these further antigens.

[0063] Toxic protein antigens may be detoxified where necessary (e.g. detoxification of pertussis toxin by chemical and/or genetic means [40]).

25 **[0064]** Where a diphtheria antigen is included in the composition it is preferred also to include tetanus antigen and pertussis antigens. Similarly, where a tetanus antigen is included it is preferred also to include diphtheria and pertussis antigens. Similarly, where a pertussis antigen is included it is preferred also to include diphtheria and tetanus antigens. DTP combinations are thus preferred.

30 **[0065]** Saccharide antigens are preferably in the form of conjugates. Carrier proteins for the conjugates include the *N.meningitidis* outer membrane protein [68], synthetic peptides [69,70], heat shock proteins [71,72], pertussis proteins [73,74], protein D from *H.influenzae* [75], cytokines [76], lymphokines [76], streptococcal proteins, hormones [76], growth factors [76], toxin A or B from *C.difficile* [77], iron-uptake proteins [78], etc. A preferred carrier protein is the CRM197 diphtheria toxoid [79].

[0066] Antigens in the composition will typically be present at a concentration of at least 1µg/ml each. In general, the concentration of any given antigen will be sufficient to elicit an immune response against that antigen.

35 **[0067]** Immunogenic compositions of the invention may be used therapeutically (i.e. to treat an existing infection) or prophylactically (i.e. to prevent future infection).

[0068] As an alternative to using proteins antigens in the immunogenic compositions of the invention, nucleic acid (preferably DNA e.g. in the form of a plasmid) encoding the antigen may be used.

40 **[0069]** Particularly preferred compositions of the invention include one, two or three of: (a) saccharide antigens from meningococcus serogroups Y, W135, C and (optionally) A; (b) a saccharide antigen from *Haemophilus influenzae* type B; and/or (c) an antigen from *Streptococcus pneumoniae*.

Meningococcus serogroups Y, W135, C and (optionally) A

45 **[0070]** Polysaccharide vaccines against serogroups A, C, W135 & Y have been known for many years. These vaccines (MENGEVAX ACWY™ and MENOMUNE™) are based on the organisms' capsular polysaccharides and, although they are effective in adolescents and adults, they give a poor immune response and short duration of protection, and they cannot be used in infants.

50 **[0071]** In contrast to the unconjugated polysaccharide antigens in these vaccines, the recently-approved serogroup C vaccines (Menjugate™ [80,28], Meningitec™ and NeisVac-C™) include conjugated saccharides. Menjugate™ and Meningitec™ have oligosaccharide antigens conjugated to a CRM₁₉₇ carrier, whereas NeisVac-C™ uses the complete polysaccharide (de-O-acetylated) conjugated to a tetanus toxoid carrier. The proposed MenActra™ vaccine contains conjugated capsular saccharide antigens from each of serogroups Y, W135, C and A.

55 **[0072]** Compositions of the present invention preferably include capsular saccharide antigens from one or more of meningococcus serogroups Y, W135, C and (optionally) A, wherein the antigens are conjugated to carrier protein(s) and/or are oligosaccharides. For example, the composition may include a capsular saccharide antigen from: serogroup C; serogroups A and C; serogroups A, C and W135; serogroups A, C and Y; serogroups C, W135 and Y; or from all four of serogroups A, C, W135 and Y.

[0073] A typical quantity of each meningococcal saccharide antigen per dose is between 1 µg and 20 µg e.g. about 1 µg, about 2.5 µg, about 4 µg, about 5 µg, or about 10 µg (expressed as saccharide).

[0074] Where a mixture comprises capsular saccharides from both serogroups A and C, the ratio (w/w) of MenA saccharide:MenC saccharide may be greater than 1 (e.g. 2:1, 3:1, 4:1, 5:1, 10:1 or higher). Where a mixture comprises capsular saccharides from serogroup Y and one or both of serogroups C and W135, the ratio (w/w) of MenY saccharide:MenW135 saccharide may be greater than 1 (e.g. 2:1, 3:1, 4:1, 5:1, 10:1 or higher) and/or that the ratio (w/w) of MenY saccharide:MenC saccharide may be less than 1 (e.g. 1:2, 1:3, 1:4, 1:5, or lower). Preferred ratios (w/w) for saccharides from serogroups A:C:W135:Y are: 1:1:1:1; 1:1:1:2; 2:1:1:1; 4:2:1:1; 8:4:2:1; 4:2:1:2; 8:4:1:2; 4:2:2:1; 2:2:1:1; 4:4:2:1; 2:2:1:2; 4:4:1:2; and 2:2:2:1. Preferred ratios (w/w) for saccharides from serogroups C:W135:Y are: 1:1:1; 1:1:2; 1:1:1; 2:1:1; 4:2:1; 2:1:2; 4:1:2; 2:2:1; and 2:1:1. Using a substantially equal mass of each saccharide is preferred.

[0075] Capsular saccharides will generally be used in the form of oligosaccharides. These are conveniently formed by fragmentation of purified capsular polysaccharide (e.g. by hydrolysis), which will usually be followed by purification of the fragments of the desired size.

[0076] Fragmentation of polysaccharides is preferably performed to give a final average degree of polymerisation (DP) in the oligosaccharide of less than 30 (e.g. between 10 and 20, preferably around 10 for serogroup A; between 15 and 25 for serogroups W135 and Y, preferably around 15-20; between 12 and 22 for serogroup C; etc.). DP can conveniently be measured by ion exchange chromatography or by colorimetric assays [81].

[0077] If hydrolysis is performed, the hydrolysate will generally be sized in order to remove short-length oligosaccharides [29]. This can be achieved in various ways, such as ultrafiltration followed by ion-exchange chromatography. Oligosaccharides with a degree of polymerisation of less than or equal to about 6 are preferably removed for serogroup A, and those less than around 4 are preferably removed for serogroups W135 and Y.

[0078] Preferred MenC saccharide antigens are disclosed in reference 80, as used in Menjugate™.

[0079] The saccharide antigen may be chemically modified. This is particularly useful for reducing hydrolysis for serogroup A [82; see below]. De-O-acetylation of meningococcal saccharides can be performed. For oligosaccharides, modification may take place before or after depolymerisation.

[0080] Where a composition of the invention includes a MenA saccharide antigen, the antigen is preferably a modified saccharide in which one or more of the hydroxyl groups on the native saccharide has/have been replaced by a blocking group [82]. This modification improves resistance to hydrolysis.

[0081] The number of monosaccharide units having blocking groups can vary. For example, all or substantially all the monosaccharide units may have blocking groups. Alternatively, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% of the monosaccharide units may have blocking groups. At least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 monosaccharide units may have blocking groups.

[0082] Likewise, the number of blocking groups on a monosaccharide unit may vary. For example, the number of blocking groups on a monosaccharide unit may be 1 or 2. The blocking group will generally be at the 4 position and/or 3-position of the monosaccharide units.

[0083] The terminal monosaccharide unit may or may not have a blocking group instead of its native hydroxyl. It is preferred to retain a free anomeric hydroxyl group on a terminal monosaccharide unit in order to provide a handle for further reactions (e.g. conjugation). Anomeric hydroxyl groups can be converted to amino groups (-NH₂ or -NH-E, where E is a nitrogen protecting group) by reductive amination (using, for example, NaBH₃CN/NH₄Cl), and can then be regenerated after other hydroxyl groups have been converted to blocking groups.

[0084] Blocking groups to replace hydroxyl groups may be directly accessible via a derivatizing reaction of the hydroxyl group *i. e.* by replacing the hydrogen atom of the hydroxyl group with another group. Suitable derivatives of hydroxyl groups which act as blocking groups are, for example, carbamates, sulfonates, carbonates, esters, ethers (e.g. silyl ethers or alkyl ethers) and acetals. Some specific examples of such blocking groups are allyl, Alloc, benzyl, BOM, t-butyl, trityl, TBS, TBDPS, TES, TMS, TIPS, PMB, MEM, MOM, MTM, THP, etc. Other blocking groups that are not directly accessible and which completely replace the hydroxyl group include C₁₋₁₂ alkyl, C₃₋₁₂ alkyl, C₅₋₁₂ aryl, C₅₋₁₂ aryl-C₁₋₆ alkyl, NR¹R² (R¹ and R² are defined in the following paragraph), H, F, Cl, Br, CO₂H, CO₂(C₁₋₆ alkyl), CN, CF₃, CCl₃, etc. Preferred blocking groups are electron-withdrawing groups.

[0085] Preferred blocking groups are of the formula: -O-X-Y or -OR³ wherein: X is C(O), S(O) or SO₂; Y is C₁₋₁₂ alkyl, C₁₋₁₂ alkoxy, C₃₋₁₂ cycloalkyl, C₅₋₁₂ aryl or C₅₋₁₂ aryl-C₁₋₆ alkyl, each of which may optionally be substituted with 1, 2 or 3 groups independently selected from F, Cl, Br, CO₂H, CO₂(C₁₋₆ alkyl), CN, CF₃ or CCl₃; or Y is NR¹R²; R¹ and R² are independently selected from H, C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₅₋₁₂ aryl, C₅₋₁₂ aryl-C₁₋₆ alkyl; or R¹ and R² may be joined to form a C₃₋₁₂ saturated heterocyclic group; R³ is C₁₋₁₂ alkyl or C₃₋₁₂ cycloalkyl, each of which may optionally be substituted with 1, 2 or 3 groups independently selected from F, Cl, Br, CO₂(C₁₋₆ alkyl), CN, CF₃ or CCl₃; or R³ is C₅₋₁₂ aryl or C₅₋₁₂ aryl-C₁₋₆ alkyl, each of which may optionally be substituted with 1, 2, 3, 4 or 5 groups selected from F, Cl, Br, CO₂H, CO₂(C₁₋₆ alkyl), CN, CF₃ or CCl₃. When R³ is C₁₋₁₂ alkyl or C₃₋₁₂ cycloalkyl, it is typically substituted with 1, 2 or 3 groups as defined above. When R¹ and R² are joined to form a C₃₋₁₂ saturated heterocyclic group, it is meant that R¹ and R² together with the nitrogen atom form a saturated heterocyclic group containing any number of carbon

atoms between 3 and 12 (e.g. C₃, C₄, C₅, C₆, C₇, C₈, C₉, C₁₀, C₁₁, C₁₂). The heterocyclic group may contain 1 or 2 heteroatoms (such as N, O or S) other than the nitrogen atom. Examples of C₃₋₁₂ saturated heterocyclic groups are pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, imidazolidinyl, azetidiny and aziridinyl.

[0086] Blocking groups -O-X-Y and -OR³ can be prepared from -OH groups by standard derivatizing procedures, such as reaction of the hydroxyl group with an acyl halide, alkyl halide, sulfonyl halide, etc. Hence, the oxygen atom in -O-X-Y is preferably the oxygen atom of the hydroxyl group, while the -X-Y group in -O-X-Y preferably replaces the hydrogen atom of the hydroxyl group.

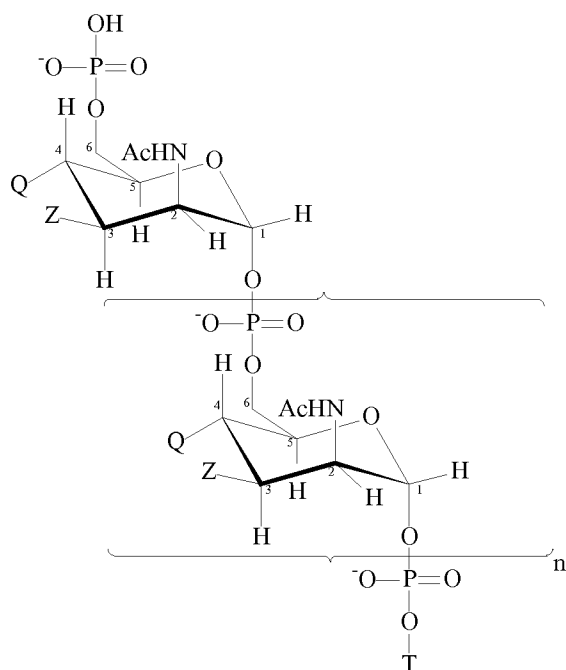
[0087] Alternatively, the blocking groups may be accessible via a substitution reaction, such as a Mitsunobu-type substitution. These and other methods of preparing blocking groups from hydroxyl groups are well known.

[0088] More preferably, the blocking group is -OC(O)CF₃ [83], or a carbamate group -OC(O)NR¹R², where R¹ and R² are independently selected from C₁₋₆ alkyl. More preferably, R¹ and R² are both methyl i.e. the blocking group is -OC(O)NMe₂. Carbamate blocking groups have a stabilizing effect on the glycosidic bond and may be prepared under mild conditions.

[0089] Preferred modified MenA saccharides contain *n* monosaccharide units, where at least *h*% of the monosaccharide units do not have -OH groups at both of positions 3 and 4. The value of *h* is 24 or more (e.g. 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 98, 99 or 100) and is preferably 50 or more. The absent -OH groups are preferably blocking groups as defined above.

[0090] Other preferred modified MenA saccharides comprise monosaccharide units, wherein at least *s* of the monosaccharide units do not have -OH at the 3 position and do not have -OH at the 4 position. The value of *s* is at least 1 (e.g. 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 60, 70, 80, 90). The absent -OH groups are preferably blocking groups as defined above.

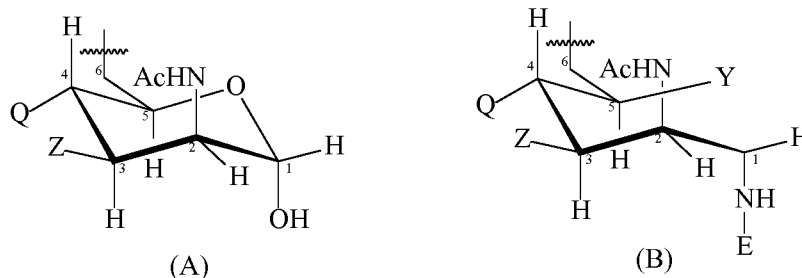
[0091] Suitable modified MenA saccharides for use with the invention have the formula:



wherein

n is an integer from 1 to 100 (preferably an integer from 15 to 25);

T is of the formula (A) or (B):



each Z group is independently selected from OH or a blocking group as defined above; and

each Q group is independently selected from OH or a blocking group as defined above;

Y is selected from OH or a blocking group as defined above;

E is H or a nitrogen protecting group;

and wherein more than about 7% (e.g. 8%, 9%, 10% or more) of the Q groups are blocking groups.

[0092] Each of the $n+2$ Z groups may be the same or different from each other. Likewise, each of the $n+2$ Q groups may be the same or different from each other. All the Z groups may be OH. Alternatively, at least 10%, 20, 30%, 40%, 50% or 60% of the Z groups may be OAc. Preferably, about 70% of the Z groups are OAc, with the remainder of the Z groups being OH or blocking groups as defined above. At least about 7% of Q groups are blocking groups. Preferably, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or even 100% of the Q groups are blocking groups.

[0093] Meningococcal capsular polysaccharides are typically prepared by a process comprising the steps of polysaccharide precipitation (e.g. using a cationic detergent), ethanol fractionation, cold phenol extraction (to remove protein) and ultracentrifugation (to remove LPS) [e.g. ref. 84]. A more preferred process [30], however, involves polysaccharide precipitation followed by solubilisation of the precipitated polysaccharide using a lower alcohol. Precipitation can be achieved using a cationic detergent such as tetrabutylammonium and cetyltrimethylammonium salts (e.g. the bromide salts), or hexadimethrine bromide and myristyltrimethylammonium salts. Cetyltrimethylammonium bromide ('CTAB') is particularly preferred [85]. Solubilisation of the precipitated material can be achieved using a lower alcohol such as methanol, propan-1-ol, propan-2-ol, butan-1-ol, butan-2-ol, 2-methyl-propan-1-ol, 2-methyl-propan-2-ol, diols, etc., but ethanol is particularly suitable for solubilising CTAB-polysaccharide complexes. Ethanol is preferably added to the precipitated polysaccharide to give a final concentration (based on total content of ethanol and water) of between 50% and 95%.

[0094] After re-solubilisation, the polysaccharide may be further treated to remove contaminants. This is particularly important in situations where even minor contamination is not acceptable (e.g. for human vaccine production). This will typically involve one or more steps of filtration e.g. depth filtration, filtration through activated carbon may be used, size filtration and/or ultrafiltration. Once filtered to remove contaminants, the polysaccharide may be precipitated for further treatment and/or processing. This can be conveniently achieved by exchanging cations (e.g. by the addition of calcium or sodium salts).

[0095] As an alternative to purification, capsular saccharides of the present invention may be obtained by total or partial synthesis e.g. Hib synthesis is disclosed in ref. 86, and MenA synthesis in ref. 87.

[0096] Compositions of the invention comprise capsular saccharides from at least two serogroups of *N.meningitidis*. The saccharides are preferably prepared separately (including any fragmentation, conjugation, modification, etc.) and then admixed to give a composition of the invention.

[0097] Where the composition comprises capsular saccharide from serogroup A, however, it is preferred that the serogroup A saccharide is not combined with the other saccharide(s) until shortly before use, in order to minimise the potential for hydrolysis. This can conveniently be achieved by having the serogroup A component (typically together with appropriate excipients) in lyophilised form and the other serogroup component(s) in liquid form (also with appropriate excipients), with the liquid components being used to reconstitute the lyophilised MenA component when ready for use. Where an aluminium salt adjuvant is used, it is preferred to include the adjuvant in the vial containing the with the liquid vaccine, and to lyophilise the MenA component without adjuvant.

[0098] A composition of the invention may thus be prepared from a kit comprising: (a) capsular saccharide from *N.meningitidis* serogroup A, in lyophilised form; and (b) the further antigens from the composition, in liquid form. The invention also provides a method for preparing a composition of the invention, comprising mixing a lyophilised capsular saccharide from *N.meningitidis* serogroup A with the further antigens, wherein said further antigens are in liquid form.

[0099] The invention also provides a kit comprising: (a) a first container containing capsular saccharides from two or more of *N.meningitidis* serogroups C, W135 and Y, all in lyophilised form; and (b) a second container containing in liquid form (i) a composition which, after administration to a subject, is able to induce an antibody response in that subject,

wherein the antibody response is bactericidal against two or more (e.g. 2 or 3) of hypervirulent lineages A4, ET-5 and lineage 3 of *N.meningitidis* serogroup B, (ii) capsular saccharides from none or one of *N.meningitidis* serogroups C, W135 and Y, and optionally (iii) further antigens (see below) that do not include meningococcal capsular saccharides, wherein, reconstitution of the contents of container (a) by the contents of container (b) provides a composition of the invention.

[0100] Within each dose, the amount of an individual saccharide antigen will generally be between 1-50 µg (measured as mass of saccharide), with about 2.5µg, 5µg or 10 µg of each being preferred. With A:C:W135:Y weight ratios of 1:1:1:1; 1:1:1:2; 2:1:1:1; 4:2:1:1; 8:4:2:1; 4:2:1:2; 8:4:1:2; 4:2:2:1; 2:2:1:1; 4:4:2:1; 2:2:1:2; 4:4:1:2; and 2:2:2:1, therefore, the amount represented by the number 1 is preferably about 2.5µg, 5µg or 10 µg. For a 1:1:1:1 ratio A:C:W:Y composition and a 10µg per saccharide, therefore, 40 µg saccharide is administered per dose. Preferred compositions have about the following µg saccharide per dose:

A	10	0	0	0	10	5	2.5
C	10	10	5	2.5	5	5	2.5
W135	10	10	5	2.5	5	5	2.5
Y	10	10	5	2.5	5	5	2.5

[0101] Preferred compositions of the invention comprise less than 50 µg meningococcal saccharide per dose. Other preferred compositions comprise ≤40 µg meningococcal saccharide per dose. Other preferred compositions comprise ≤30 µg meningococcal saccharide per dose. Other preferred compositions comprise ≤25 µg meningococcal saccharide per dose. Other preferred compositions comprise <20 µg meningococcal saccharide per dose. Other preferred compositions comprise ≤10 µg meningococcal saccharide per dose but, ideally, compositions of the invention comprise at least 10 µg meningococcal saccharide per dose.

[0102] The Menjugate™ and NeisVac™ MenC conjugates use a hydroxide adjuvant, whereas Meningitec™ uses a phosphate. It is possible in compositions of the invention to adsorb some antigens to an aluminium hydroxide but to have other antigens in association with an aluminium phosphate. For tetravalent serogroup combinations, for example, the following permutations are available:

Serogroup	Aluminium salt (H = a hydroxide; P = a phosphate)														
A	P	H	P	H	H	H	P	P	P	H	H	H	P	P	H
C	P	H	H	P	H	H	P	H	H	P	P	H	P	H	P
W135	P	H	H	H	P	H	H	P	H	H	P	P	P	H	P
Y	P	H	H	H	H	P	H	H	P	P	H	P	H	P	P

[0103] For trivalent *N.meningitidis* serogroup combinations, the following permutations are available:

Serogroup	Aluminium salt (H = a hydroxide; P = a phosphate)							
C	P	H	H	H	P	P	P	H
W135	P	H	H	P	H	P	H	P
Y	P	H	P	H	H	H	P	P

Haemophilus influenzae type B

[0104] Where the composition includes a *H.influenzae* type B antigen, it will typically be a Hib capsular saccharide antigen. Saccharide antigens from *H.influenzae* b are well known.

[0105] Advantageously, the Hib saccharide is covalently conjugated to a carrier protein, in order to enhance its immunogenicity, especially in children. The preparation of polysaccharide conjugates in general, and of the Hib capsular polysaccharide in particular, is well documented [e.g. references 88 to 96 etc.]. The invention may use any suitable Hib conjugate. Suitable carrier proteins are described below, and preferred carriers for Hib saccharides are CRM₁₉₇ ('HbOC'), tetanus toxoid ('PRP-T') and the outer membrane complex of *N.meningitidis* ('PRP-OMP').

[0106] The saccharide moiety of the conjugate may be a polysaccharide (e.g. full-length polyribosylribitol phosphate

(PRP)), but it is preferred to hydrolyse polysaccharides to form oligosaccharides (e.g. MW from ~1 to ~5 kDa).

[0107] A preferred conjugate comprises a Hib oligosaccharide covalently linked to CRM₁₉₇ via an adipic acid linker [97, 98]. Tetanus toxoid is also a preferred carrier.

[0108] Compositions of the invention may comprise more than one Hib antigen.

[0109] Where a composition includes a Hib saccharide antigen, it is preferred that it does not also include an aluminium hydroxide adjuvant. If the composition includes an aluminium phosphate adjuvant then the Hib antigen may be adsorbed to the adjuvant [99] or it may be non-adsorbed [100].

[0110] Hib antigens may be lyophilised e.g. together with meningococcal antigens.

Streptococcus pneumoniae

[0111] Where the composition includes a *S.pneumoniae* antigen, it will typically be a capsular saccharide antigen which is preferably conjugated to a carrier protein [e.g. refs. 31-33]. It is preferred to include saccharides from more than one serotype of *S.pneumoniae*. For example, mixtures of polysaccharides from 23 different serotype are widely used, as are conjugate vaccines with polysaccharides from between 5 and 11 different serotypes [101]. For example, PreVNar™ [102] contains antigens from seven serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) with each saccharide individually conjugated to CRM₁₉₇ by reductive amination, with 2µg of each saccharide per 0.5ml dose (4µg of serotype 6B), and with conjugates adsorbed on an aluminium phosphate adjuvant. Compositions of the invention preferably include at least serotypes 6B, 14, 19F and 23F. Conjugates may be adsorbed onto an aluminium phosphate.

[0112] As an alternative to using saccharide antigens from pneumococcus, the composition may include one or more polypeptide antigens. Genome sequences for several strains of pneumococcus are available [103,104] and can be subjected to reverse vaccinology [105-108] to identify suitable polypeptide antigens [109,110]. For example, the composition may include one or more of the following antigens: PhtA, PhtD, PhtB, PhtE, SpsA, LytB, LytC, LytA, Sp125, Sp101, Sp128 and Sp130, as defined in reference 111.

[0113] In some embodiments, the composition may include both saccharide and polypeptide antigens from pneumococcus. These may be used in simple admixture, or the pneumococcal saccharide antigen may be conjugated to a pneumococcal protein. Suitable carrier proteins for such embodiments include the antigens listed in the previous paragraph [111].

[0114] Pneumococcal antigens may be lyophilised e.g. together with meningococcal and/or Hib antigens.

Covalent conjugation

[0115] Capsular saccharides in compositions of the invention will usually be conjugated to carrier protein(s). In general, conjugation enhances the immunogenicity of saccharides as it converts them from T-independent antigens to T-dependent antigens, thus allowing priming for immunological memory. Conjugation is particularly useful for paediatric vaccines and is a well known technique [e.g. reviewed in refs. 112 and 88-96].

[0116] Preferred carrier proteins are bacterial toxins or toxoids, such as diphtheria toxoid or tetanus toxoid. The CRM₁₉₇ mutant diphtheria toxin [79,113,114] is particularly preferred. Other suitable carrier proteins include the *N.meningitidis* outer membrane protein [68], synthetic peptides [69,70], heat shock proteins [71,72], pertussis proteins [73,74], cytokines [76], lymphokines [76], hormones [76], growth factors [76], artificial proteins comprising multiple human CD4⁺ T cell epitopes from various pathogen-derived antigens [115], protein D from *H.influenzae* [75,116], pneumococcal surface protein PspA [117], iron-uptake proteins [78], toxin A or B from *C.difficile* [77], etc. Preferred carriers are diphtheria toxoid, tetanus toxoid, *H.influenzae* protein D, and CRM₁₉₇.

[0117] Within a composition of the invention, it is possible to use more than one carrier protein e.g. to reduce the risk of carrier suppression. Thus different carrier proteins can be used for different serogroups e.g. serogroup A saccharides might be conjugated to CRM₁₉₇ while serogroup C saccharides might be conjugated to tetanus toxoid. It is also possible to use more than one carrier protein for a particular saccharide antigen e.g. serogroup A saccharides might be in two groups, with some conjugated to CRM₁₉₇ and others conjugated to tetanus toxoid. In general, however, it is preferred to use the same carrier protein for all saccharides.

[0118] A single carrier protein might carry more than one saccharide antigen [118]. For example, a single carrier protein might have conjugated to it saccharides from serogroups A and C. To achieve this goal, saccharides can be mixed prior to the conjugation reaction. In general, however, it is preferred to have separate conjugates for each serogroup.

[0119] Conjugates with a saccharide:protein ratio (w/w) of between 1:5 (i.e. excess protein) and 5:1 (i.e. excess saccharide) are preferred. Ratios between 1:2 and 5:1 are preferred, as are ratios between 1:1.25 and 1:2.5 are more preferred. Excess carrier protein is preferred for MenA and MenC.

[0120] Conjugates may be used in conjunction with free carrier protein [119]. When a given carrier protein is present in both free and conjugated form in a composition of the invention, the unconjugated form is preferably no more than 5% of the total amount of the carrier protein in the composition as a whole, and more preferably present at less than 2%

by weight.

[0121] Any suitable conjugation reaction can be used, with any suitable linker where necessary.

[0122] The saccharide will typically be activated or functionalised prior to conjugation. Activation may involve, for example, cyanylating reagents such as CDAP (e.g. 1-cyano-4-dimethylamino pyridinium tetrafluoroborate [120,121,etc.]). Other suitable techniques use carbodiimides, hydrazides, active esters, norborane, p-nitrobenzoic acid, N-hydroxysuccinimide, S-NHS, EDC, TSTU; see also the introduction to reference 94).

[0123] Linkages via a linker group may be made using any known procedure, for example, the procedures described in references 122 and 123. One type of linkage involves reductive amination of the polysaccharide, coupling the resulting amino group with one end of an adipic acid linker group, and then coupling a protein to the other end of the adipic acid linker group [92,124,125]. Other linkers include B-propionamido [126], nitrophenyl-ethylamine [127], haloacyl halides [128], glycosidic linkages [129], 6-aminocaproic acid [130], ADH [131], C₄ to C₁₂ moieties [132] etc. As an alternative to using a linker, direct linkage can be used. Direct linkages to the protein may comprise oxidation of the polysaccharide followed by reductive amination with the protein, as described in, for example, references 133 and 134.

[0124] A process involving the introduction of amino groups into the saccharide (e.g. by replacing terminal =O groups with -NH₂) followed by derivatisation with an adipic diester (e.g. adipic acid N-hydroxysuccinimido diester) and reaction with carrier protein is preferred. Another preferred reaction uses CDAP activation with a protein D carrier e.g. for MenA or MenC.

[0125] After conjugation, free and conjugated saccharides can be separated. There are many suitable methods, including hydrophobic chromatography, tangential ultrafiltration, diafiltration etc. [see also refs. 135 & 136, etc.].

[0126] Where the composition of the invention includes a conjugated oligosaccharide, it is preferred that oligosaccharide preparation precedes conjugation.

Outer membrane vesicles

[0127] It is preferred that compositions of the invention should not include complex or undefined mixtures of antigens, which are typical characteristics of OMVs. However, one way in which the invention can be applied to OMVs is where OMVs are to be administered in a multiple dose schedule.

[0128] Where more than one OMV dose is to be administered, each dose may be supplemented (either by adding the purified protein or by expression of the protein within the bacteria from which the OMVs are derived) by one of the first protein, second protein or third protein as defined above. Preferably different doses are supplemented with different NMB1870 variants. In a three dose OMV schedule, for example, each dose could contain a different one of the first protein, second protein and third protein such that, after receiving three doses of OMVs, all three variants have been received. In a two dose OMV schedule, one variant could be used per OMV dose (thus omitting one variant), or one or both OMV doses could be supplemented with more than one variant in order to give coverage with all three variants. In preferred embodiments, there are three OMV doses, and each of the three OMV doses contains three different genetically-engineered vesicle populations each displaying three subtypes, thereby giving nine different subtypes in all.

[0129] This approach may be used in general to improve preparations of *N.meningitidis* serogroup B microvesicles [137], 'native OMVs' [138], blebs or outer membrane vesicles [e.g. refs. 139 to 144, etc.]. These may be prepared from bacteria which have been genetically manipulated [145-148] e.g. to increase immunogenicity (e.g. hyper-express immunogens), to reduce toxicity, to inhibit capsular polysaccharide synthesis, to down-regulate PorA expression, etc. They may be prepared from hyperblebbing strains [149-152]. Vesicles from a non-pathogenic *Neisseria* may be included [153]. OMVs may be prepared without the use of detergents [154,155]. They may express non-Neisserial proteins on their surface [156]. They may be LPS-depleted. They may be mixed with recombinant antigens [139,157]. Vesicles from bacteria with different class I outer membrane protein subtypes may be used e.g. six different subtypes [158,159] using two different genetically-engineered vesicle populations each displaying three subtypes, or nine different subtypes using three different genetically-engineered vesicle populations each displaying three subtypes, etc. Useful subtypes include: P1.7,16; P1.5-1,2-2; P1.19,15-1; P1.5-2,10; P1.12-1,13; P1.7-2,4; P1.22,14; P1.7-1,1; P1.18-1,3,6.

[0130] It is also possible, of course, to supplement vesicle preparations with two or three different variants.

Immunisation

[0131] The composition of the invention is preferably an immunogenic composition, and the invention provides an immunogenic composition of the invention for use as a medicament. For instance, the composition can be used in a method for raising an antibody response in a mammal, comprising administering an immunogenic composition of the invention to the mammal. The antibody response is preferably a protective and/or bactericidal antibody response.

[0132] The composition can be used for protecting a mammal against a Neisserial (e.g. meningococcal) infection by administering it to the mammal.

[0133] The mammal is preferably a human. The human may be an adult or, preferably, a child.

[0134] Immunogenic compositions of the invention may be used therapeutically (*i.e.* to treat an existing infection) or prophylactically (*i.e.* to prevent future infection).

[0135] The compositions are particularly useful for preventing/treating diseases including, but not limited to, meningitis (particularly bacterial meningitis) and bacteremia.

[0136] Efficacy of therapeutic treatment can be tested by monitoring Neisserial infection after administration of the composition of the invention. Efficacy of prophylactic treatment can be tested by monitoring immune responses against NMB1870 after administration of the composition. Immunogenicity of compositions of the invention can be determined by administering them to test subjects (*e.g.* children 12-16 months age, or animal models [160]) and then determining standard parameters including serum bactericidal antibodies (SBA) and ELISA titres (GMT) of total and high-avidity anti-capsule IgG. These immune responses will generally be determined around 4 weeks after administration of the composition, and compared to values determined before administration of the composition. A SBA increase of at least 4-fold or 8-fold is preferred. Where more than one dose of the composition is administered, more than one post-administration determination may be made.

[0137] Preferred compositions of the invention can confer an antibody titre in a patient that is superior to the criterion for seroprotection for each antigenic component for an acceptable percentage of human subjects. Antigens with an associated antibody titre above which a host is considered to be seroconverted against the antigen are well known, and such titres are published by organisations such as WHO. Preferably more than 80% of a statistically significant sample of subjects is seroconverted, more preferably more than 90%, still more preferably more than 93% and most preferably 96-100%.

[0138] Compositions of the invention will generally be administered directly to a patient. Direct delivery may be accomplished by parenteral injection (*e.g.* subcutaneously, intraperitoneally, intravenously, intramuscularly, or to the interstitial space of a tissue), or by rectal, oral, vaginal, topical, transdermal, intranasal, ocular, aural, pulmonary or other mucosal administration. Intramuscular administration to the thigh or the upper arm is preferred. Injection may be via a needle (*e.g.* a hypodermic needle), but needle-free injection may alternatively be used. A typical intramuscular dose is 0.5 ml.

[0139] The compositions may be used to elicit systemic and/or mucosal immunity.

[0140] Dosage treatment can be a single dose schedule or a multiple dose schedule. Multiple doses may be used in a primary immunisation schedule and/or in a booster immunisation schedule. A primary dose schedule may be followed by a booster dose schedule. Suitable timing between priming doses (*e.g.* between 4-16 weeks), and between priming and boosting, can be routinely determined.

[0141] The immunogenic composition of the invention will generally include a pharmaceutically acceptable carrier, which can be any substance that does not itself induce the production of antibodies harmful to the patient receiving the composition, and which can be administered without undue toxicity. Suitable carriers can be large, slowly-metabolised macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, and inactive virus particles. Such carriers are well known to those of ordinary skill in the art. Pharmaceutically acceptable carriers can include liquids such as water, saline, glycerol and ethanol. Auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, can also be present in such vehicles. Liposomes are suitable carriers. A thorough discussion of pharmaceutical carriers is available in *ref.* 161.

[0142] Neisserial infections affect various areas of the body and so the compositions of the invention may be prepared in various forms. For example, the compositions may be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be prepared. The composition may be prepared for topical administration *e.g.* as an ointment, cream or powder. The composition may be prepared for oral administration *e.g.* as a tablet or capsule, or as a syrup (optionally flavoured). The composition may be prepared for pulmonary administration *e.g.* as an inhaler, using a fine powder or a spray. The composition may be prepared as a suppository or pessary. The composition may be prepared for nasal, aural or ocular administration *e.g.* as drops.

[0143] The composition is preferably sterile. It is preferably pyrogen-free. It is preferably buffered *e.g.* at between pH 6 and pH 8, generally around pH 7. Where a composition comprises an aluminium hydroxide salt, it is preferred to use a histidine buffer [162]. Compositions of the invention may be isotonic with respect to humans.

[0144] Immunogenic compositions comprise an immunologically effective amount of immunogen, as well as any other of other specified components, as needed. By 'immunologically effective amount', it is meant that the administration of that amount to an individual, either in a single dose or as part of a series, is effective for treatment or prevention. This amount varies depending upon the health and physical condition of the individual to be treated, age, the taxonomic group of individual to be treated (*e.g.* non-human primate, primate, *etc.*), the capacity of the individual's immune system to synthesise antibodies, the degree of protection desired, the formulation of the vaccine, the treating doctor's assessment of the medical situation, and other relevant factors. It is expected that the amount will fall in a relatively broad range that can be determined through routine trials. Dosage treatment may be a single dose schedule or a multiple dose schedule (*e.g.* including booster doses). The composition may be administered in conjunction with other immunoregulatory agents.

[0145] An immunogenic composition will generally include an adjuvant. Preferred adjuvants to enhance effectiveness

of the composition include, but are not limited to: (A) MF59 (5% Squalene, 0.5% Tween 80, and 0.5% Span 85, formulated into submicron particles using a microfluidizer) [see Chapter 10 of ref. 163; see also ref. 164]; (B) microparticles (*i.e.* a particle of ~100nm to ~150µm in diameter, more preferably ~200nm to ~30µm in diameter, and most preferably ~500nm to ~10µm in diameter) formed from materials that are biodegradable and non-toxic (*e.g.* a poly(α -hydroxy acid), a polyhydroxybutyric acid, a polyorthoester, a polyanhydride, a polycaprolactone *etc.*), with poly(lactide-co-glycolide) being preferred ('PLG'), optionally having a charged surface (*e.g.* by adding a cationic, anionic, or nonionic detergent such as SDS (negative) or CTAB (positive) [*e.g.* refs. 165 & 166]); (C) liposomes [see Chapters 13 and 14 of ref. 163]; (D) ISCOMs [see Chapter 23 of ref. 163], which may be devoid of additional detergent [167]; (E) SAF, containing 10% Squalene, 0.4% Tween 80, 5% pluronic-block polymer L 121, and thr-MDP, either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion [see Chapter 12 of ref. 163]; (F) Ribi™ adjuvant system (RAS), (Ribi Immunochem) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphoryl lipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (Detox™); (G) saponin adjuvants, such as QuilA or QS21 [see Chapter 22 of ref. 163], also known as Stimulon™; (H) chitosan [*e.g.* 168]; (I) complete Freund's adjuvant (CFA) and incomplete Freund's adjuvant (IFA); (J) cytokines, such as interleukins (*e.g.* IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, *etc.*), interferons (*e.g.* interferon- γ), macrophage colony stimulating factor, tumor necrosis factor, *etc.* [see Chapters 27 & 28 of ref. 163], RC529; (K) a saponin (*e.g.* QS21) + 3dMPL + IL-12 (optionally + a sterol) [169]; (L) monophosphoryl lipid A (MPL) or 3-O-deacylated MPL (3dMPL) [*e.g.* chapter 21 of ref. 163]; (M) combinations of 3dMPL with, for example, QS21 and/or oil-in-water emulsions [170]; (N) oligonucleotides comprising CpG motifs [171] *i.e.* containing at least one CG dinucleotide, with 5-methylcytosine optionally being used in place of cytosine; (O) a polyoxyethylene ether or a polyoxyethylene ester [172]; (P) a polyoxyethylene sorbitan ester surfactant in combination with an octoxynol [173] or a polyoxyethylene alkyl ether or ester surfactant in combination with at least one additional non-ionic surfactant such as an octoxynol [174]; (Q) an immunostimulatory oligonucleotide (*e.g.* a CpG oligonucleotide) and a saponin [175]; (R) an immunostimulant and a particle of metal salt [176]; (S) a saponin and an oil-in-water emulsion [177]; (T) *E. coli* heat-labile enterotoxin ("LT"), or detoxified mutants thereof, such as the K63 or R72 mutants [*e.g.* Chapter 5 of ref. 38]; (U) cholera toxin ("CT"), or detoxified mutants thereof [*e.g.* Chapter 5 of ref. 38]; (V) double-stranded RNA; (W) aluminium salts, such as aluminium hydroxides (including oxyhydroxides), aluminium phosphates (including hydroxyphosphates), aluminium sulfate, *etc.* [Chapters 8 & 9 in ref. 163] or calcium salts, such as calcium phosphate; and (X) other substances that act as immunostimulating agents to enhance the effectiveness of the composition [*e.g.* see Chapter 7 of ref. 163]. Aluminium salts (aluminium phosphates and particularly hydroxyphosphates, and/or hydroxides and particularly oxyhydroxide) and MF59 are preferred adjuvants for parenteral immunisation. Toxin mutants are preferred mucosal adjuvants. QS21 is another useful adjuvant for NMB1870, which may be used alone or in combination with any of (A) to (X) *e.g.* with an aluminium salt.

[0146] Muramyl peptides include N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-normuramyl-L-alanyl-D-isoglutamine (nor-MDP), N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-*sn*-glycero-3-hydroxyphosphoryloxy)-ethylamine MTP-PE), *etc.*

Protein expression

[0147] Bacterial expression techniques are known in the art. A bacterial promoter is any DNA sequence capable of binding bacterial RNA polymerase and initiating the downstream (3') transcription of a coding sequence (*e.g.* structural gene) into mRNA. A promoter will have a transcription initiation region which is usually placed proximal to the 5' end of the coding sequence. This transcription initiation region usually includes an RNA polymerase binding site and a transcription initiation site. A bacterial promoter may also have a second domain called an operator, that may overlap an adjacent RNA polymerase binding site at which RNA synthesis begins. The operator permits negative regulated (inducible) transcription, as a gene repressor protein may bind the operator and thereby inhibit transcription of a specific gene. Constitutive expression may occur in the absence of negative regulatory elements, such as the operator. In addition, positive regulation may be achieved by a gene activator protein binding sequence, which, if present is usually proximal (5') to the RNA polymerase binding sequence. An example of a gene activator protein is the catabolite activator protein (CAP), which helps initiate transcription of the lac operon in *Escherichia coli* (*E. coli*) [Raibaud et al. (1984) *Annu. Rev. Genet.* 18:173]. Regulated expression may therefore be either positive or negative, thereby either enhancing or reducing transcription.

[0148] Sequences encoding metabolic pathway enzymes provide particularly useful promoter sequences. Examples include promoter sequences derived from sugar metabolizing enzymes, such as galactose, lactose (*lac*) [Chang et al. (1977) *Nature* 198:1056], and maltose. Additional examples include promoter sequences derived from biosynthetic enzymes such as tryptophan (*trp*) [Goeddel et al. (1980) *Nuc. Acids Res.* 8:4057; Yelverton et al. (1981) *Nucl. Acids Res.* 9:731; US patent 4,738,921; EP-A-0036776 and EP-A-0121775]. The β -lactamase (*bla*) promoter system [Weissmann (1981) "The cloning of interferon and other mistakes." In *Interferon 3* (ed. I. Gresser)], bacteriophage lambda PL [Shimatake et al. (1981) *Nature* 292:128] and T5 [US patent 4,689,406] promoter systems also provide useful promoter

sequences. Another promoter of interest is an inducible arabinose promoter (pBAD).

[0149] In addition, synthetic promoters which do not occur in nature also function as bacterial promoters. For example, transcription activation sequences of one bacterial or bacteriophage promoter may be joined with the operon sequences of another bacterial or bacteriophage promoter, creating a synthetic hybrid promoter [US patent 4,551,433]. For example, the *tac* promoter is a hybrid *trp-lac* promoter comprised of both *trp* promoter and *lac* operon sequences that is regulated by the *lac* repressor [Amann et al. (1983) Gene 25:167; de Boer et al. (1983) Proc. Natl. Acad. Sci. 80:21]. Furthermore, a bacterial promoter can include naturally occurring promoters of non-bacterial origin that have the ability to bind bacterial RNA polymerase and initiate transcription. A naturally occurring promoter of non-bacterial origin can also be coupled with a compatible RNA polymerase to produce high levels of expression of some genes in prokaryotes. The bacteriophage T7 RNA polymerase/promoter system is an example of a coupled promoter system [Studier et al. (1986) J. Mol. Biol. 189:113; Tabor et al. (1985) Proc Natl. Acad. Sci. 82:1074]. In addition, a hybrid promoter can also be comprised of a bacteriophage promoter and an *E. coli* operator region (EPO-A-0 267 851).

[0150] In addition to a functioning promoter sequence, an efficient ribosome binding site is also useful for the expression of foreign genes in prokaryotes. In *E. coli*, the ribosome binding site is called the Shine-Dalgarno (SD) sequence and includes an initiation codon (ATG) and a sequence 3-9 nucleotides in length located 3-11 nucleotides upstream of the initiation codon [Shine et al. (1975) Nature 254:34]. The SD sequence is thought to promote binding of mRNA to the ribosome by the pairing of bases between the SD sequence and the 3' end of *E. coli* 16S rRNA [Steitz et al. (1979) "Genetic signals and nucleotide sequences in messenger RNA." In Biological Regulation and Development: Gene Expression (ed. R.F. Goldberg)]. To express eukaryotic genes and prokaryotic genes with weak ribosome-binding site [Sambrook et al. (1989) "Expression of cloned genes in Escherichia coli." In Molecular Cloning: A Laboratory Manual].

[0151] A promoter sequence may be directly linked with the DNA molecule, in which case the first amino acid at the N-terminus will always be a methionine, which is encoded by the ATG start codon. If desired, methionine at the N-terminus may be cleaved from the protein by *in vitro* incubation with cyanogen bromide or by either *in vivo* or *in vitro* incubation with a bacterial methionine N-terminal peptidase (EP-A-0219237).

[0152] Usually, transcription termination sequences recognized by bacteria are regulatory regions located 3' to the translation stop codon, and thus together with the promoter flank the coding sequence. These sequences direct the transcription of an mRNA which can be translated into the polypeptide encoded by the DNA. Transcription termination sequences frequently include DNA sequences of about 50 nucleotides capable of forming stem loop structures that aid in terminating transcription. Examples include transcription termination sequences derived from genes with strong promoters, such as the *trp* gene in *E. coli* as well as other biosynthetic genes.

[0153] Usually, the above described components, comprising a promoter, signal sequence (if desired), coding sequence of interest, and transcription termination sequence, are put together into expression constructs. Expression constructs are often maintained in a replicon, such as an extrachromosomal element (e.g. plasmids) capable of stable maintenance in a host, such as bacteria. The replicon will have a replication system, thus allowing it to be maintained in a prokaryotic host either for expression or for cloning and amplification. In addition, a replicon may be either a high or low copy number plasmid. A high copy number plasmid will generally have a copy number ranging from about 5 to about 200, and usually about 10 to about 150. A host containing a high copy number plasmid will preferably contain at least about 10, and more preferably at least about 20 plasmids. Either a high or low copy number vector may be selected, depending upon the effect of the vector and the foreign protein on the host.

[0154] Alternatively, the expression constructs can be integrated into the bacterial genome with an integrating vector. Integrating vectors usually contain at least one sequence homologous to the bacterial chromosome that allows the vector to integrate. Integrations appear to result from recombinations between homologous DNA in the vector and the bacterial chromosome. For example, integrating vectors constructed with DNA from various *Bacillus* strains integrate into the *Bacillus* chromosome (EP-A-0127328). Integrating vectors may also be comprised of bacteriophage or transposon sequences.

[0155] Usually, extrachromosomal and integrating expression constructs may contain selectable markers to allow for the selection of bacterial strains that have been transformed. Selectable markers can be expressed in the bacterial host and may include genes which render bacteria resistant to drugs such as ampicillin, chloramphenicol, erythromycin, kanamycin (neomycin), and tetracycline [Davies et al. (1978) Annu. Rev. Microbiol. 32:469]. Selectable markers may also include biosynthetic genes, such as those in the histidine, tryptophan, and leucine biosynthetic pathways.

[0156] Alternatively, some of the above described components can be put together in transformation vectors. Transformation vectors are usually comprised of a selectable market that is either maintained in a replicon or developed into an integrating vector, as described above.

[0157] Expression and transformation vectors, either extra-chromosomal replicons or integrating vectors, have been developed for transformation into many bacteria. For example, expression vectors have been developed for, *inter alia*, the following bacteria: *Bacillus subtilis* [Palva et al. (1982) Proc. Natl. Acad. Sci. USA 79:5582; EP-A-0 036 259 and EP-A-0 063 953; WO 84/04541], *Escherichia coli* [Shimatake et al. (1981) Nature 292:128; Amann et al. (1985) Gene 40:183; Studier et al. (1986) J. Mol. Biol. 189:113; EP-A-0 036 776, EP-A-0 136 829 and EP-A-0 136 907], *Streptococcus cremoris*

[Powell et al. (1988) Appl. Environ. Microbiol. 54:655]; *Streptococcus lividans* [Powell et al. (1988) Appl. Environ. Microbiol. 54:655], *Streptomyces lividans* [US patent 4,745,056].

[0158] Methods of introducing exogenous DNA into bacterial hosts are well-known in the art, and usually include either the transformation of bacteria treated with CaCl_2 or other agents, such as divalent cations and DMSO. DNA can also be introduced into bacterial cells by electroporation. Transformation procedures usually vary with the bacterial species to be transformed. See e.g. [Masson et al. (1989) FEMS Microbiol. Lett. 60:273; Palva et al. (1982) Proc. Natl. Acad. Sci. USA 79:5582; EP-A-0 036 259 and EP-A-0 063 953; WO 84/04541, *Bacillus*], [Miller et al. (1988) Proc. Natl. Acad. Sci. 85:856; Wang et al. (1990) J. Bacteriol. 172:949, *Campylobacter*], [Cohen et al. (1973) Proc. Natl. Acad. Sci. 69:2110; Dower et al. (1988) Nucleic Acids Res. 16:6127; Kushner (1978) "An improved method for transformation of *Escherichia coli* with ColEI-derived plasmids. In Genetic Engineering: Proceedings of the International Symposium on Genetic Engineering (eds. H.W. Boyer and S. Nicosia); Mandel et al. (1970) J. Mol. Biol. 53:159; Taketo (1988) Biochim. Biophys. Acta 949:318; *Escherichia*], [Chassy et al. (1987) FEMS Microbiol. Lett. 44:173 *Lactobacillus*]; [Fiedler et al. (1988) Anal. Biochem 170:38, *Pseudomonas*]; [Augustin et al. (1990) FEMS Microbiol. Lett. 66:203, *Staphylococcus*], [Barany et al. (1980) J. Bacteriol. 144:698; Harlander (1987) "Transformation of *Streptococcus lactis* by electroporation, in: Streptococcal Genetics (ed. J. Ferretti and R. Curtiss III); Perry et al. (1981) Infect. Immun. 32:1295; Powell et al. (1988) Appl. Environ. Microbiol. 54:655; Somkuti et al. (1987) Proc. 4th Evr. Cong. Biotechnology 1:412, *Streptococcus*].

General

[0159] The term "comprising" means "including" as well as "consisting" e.g. a composition "comprising" X may consist exclusively of X or may include something additional e.g. X + Y.

[0160] The term "about" in relation to a numerical value x means, for example, $x \pm 10\%$.

[0161] The word "substantially" does not exclude "completely" e.g. a composition which is "substantially free" from Y may be completely free from Y. Where necessary, the word "substantially" may be omitted from the definition of the invention.

[0162] 'Sequence identity' is preferably determined by the Smith-Waterman homology search algorithm as implemented in the MPSRCH program (Oxford Molecular), using an affine gap search with parameters *gap open penalty*=12 and *gap extension penalty*=1.

[0163] After serogroup, meningococcal classification includes serotype, serosubtype and then immunotype, and the standard nomenclature lists serogroup, serotype, serosubtype, and immunotype, each separated by a colon e.g. B:4:P1.15:L3,7,9. Within serogroup B, some lineages cause disease often (hyperinvasive), some lineages cause more severe forms of disease than others (hypervirulent), and others rarely cause disease at all. Seven hypervirulent lineages are recognised, namely subgroups I, III and IV-1, ET-5 complex, ET-37 complex, A4 cluster and lineage 3. These have been defined by multilocus enzyme electrophoresis (MLEE), but multilocus sequence typing (MLST) has also been used to classify meningococci [ref. 16]. The four main hypervirulent clusters are ST32, ST44, ST8 and ST11 complexes.

[0164] The term "alkyl" refers to alkyl groups in both straight and branched forms. The alkyl group may be interrupted with 1, 2 or 3 heteroatoms selected from -O-, -NH- or -S-. The alkyl group may also be interrupted with 1, 2 or 3 double and/or triple bonds. However, the term "alkyl" usually refers to alkyl groups having no heteroatom interruptions or double or triple bond interruptions. Where reference is made to C_{1-12} alkyl, it is meant the alkyl group may contain any number of carbon atoms between 1 and 12 (e.g. C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12}). Similarly, where reference is made to C_{1-6} alkyl, it is meant the alkyl group may contain any number of carbon atoms between 1 and 6 (e.g. C_1 , C_2 , C_3 , C_4 , C_5 , C_6).

[0165] The term "cycloalkyl" includes cycloalkyl, polycycloalkyl, and cycloalkenyl groups, as well as combinations of these with alkyl groups, such as cycloalkylalkyl groups. The cycloalkyl group may be interrupted with 1, 2 or 3 heteroatoms selected from -O-, -NH- or -S-. However, the term "cycloalkyl" usually refers to cycloalkyl groups having no heteroatom interruptions. Examples of cycloalkyl groups include cyclopentyl, cyclohexyl, cyclohexenyl, cyclohexylmethyl and adamantyl groups. Where reference is made to C_{3-12} cycloalkyl, it is meant that the cycloalkyl group may contain any number of carbon atoms between 3 and 12 (e.g. C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12}).

[0166] The term "aryl" refers to an aromatic group, such as phenyl or naphthyl. Where reference is made to C_{5-12} aryl, it is meant that the aryl group may contain any number of carbon atoms between 5 and 12 (e.g. C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12}).

[0167] The term " C_{5-12} aryl- C_{1-6} alkyl" refers to groups such as benzyl, phenylethyl and naphthylmethyl.

[0168] Nitrogen protecting groups include silyl groups (such as TMS, TES, TBS, TIPS), acyl derivatives (such as phthalimides, trifluoroacetamides, methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl (Boc), benzyloxycarbonyl (Z or Cbz), 9-fluorenylmethoxycarbonyl (Fmoc), 2-(trimethylsilyl)ethoxy carbonyl, 2,2,2-trichloroethoxycarbonyl (Troc)), sulfonfyl derivatives (such as β -trimethylsilyl ethanesulfonyl (SES)), sulfenyl derivatives, C_{1-12} alkyl, benzyl, benzhydryl, trityl, 9-phenylfluorenyl etc. A preferred nitrogen protecting group is Fmoc.

BRIEF DESCRIPTION OF DRAWINGS

[0169]

Figure 1 shows the nucleotide sequence of the upstream region of NMB1870.

Figure 2 is a schematic representation of the structure of TbpB proteins and of antigens NMB2132 and NMB1870. The leader peptides and proximal glycine-rich regions are indicated. Five conserved boxes are indicated by different motifs and their positions are mapped on the protein sequence.

Figure 3 shows the increase in NMB1870 levels in *N.meningitidis* MC58 during the growth curve.

Figure 4 shows the increase in NMB1870 levels in the supernatant over the same period. PorA levels and NMB1380 levels do not increase. Numbers above lanes refer to OD_{620nm} of the culture. KO indicates a NMB1870 knockout mutant of MC58, and Wcl stands for the whole cell lysate control.

Figure 5 shows OMVs probed with anti-NMB1870.

Figure 6 shows FACS analysis of encapsulated MC58 or a non-encapsulated mutant MC58 using anti-NMB1870.

Figure 7 is a western blot of a gradient SDS-PAGE gel loaded with total cell lysates of high (lanes 1 & 2), intermediate (3 & 4) and low (5 & 6) NMB1870 expressers. Lane 7 contains a MC58 NMB1870 knockout. Lanes are: (1) MC58; (2) H44/76; (3) NZ394/98; (4) 961-5945; (5) 67/00; (6) M1239; (7) MC58 Δ nmb1870.

Figure 8 shows FACS and bactericidal titres for each of a high, intermediate and low expresser, and also for the NMB1870 knockout. The intermediate and low expresser have identical NMB1870 amino acid sequences, with a 91.6% match to MC58.

Figure 9 is a dendrogram showing the strain clustering according to NMB1870 protein distances. The labels '1', '2' and '3' indicate the three variants. Numbers in square brackets indicate the number of strains with identical sequence present in each branch of the dendrogram. Hypervirulent lineages are indicated, followed by the number of strains when this is different from the total number. Serogroups other than B are also shown. The three type strains (MC58, 961-5965 and M1239) and the other strains used in the serological analysis are within circles.

Figure 10 is a sequence alignment of variant 1 (MC58), variant 2 (961-5945), and variant 3 (M1239). Amino acid numbers initiate from the cysteine predicted to be the first amino acid of the mature protein. Grey and black backgrounds indicate conserved and identical residues, respectively.

Figure 11 shows FACS analysis of sera against variant 1 (first row), variant 2 (second row), and variant 3 (third row), using the type strain of variant 1 (MC58), variant 2 (961-5945) and variant 3 (M1239). Control sera against the capsular polysaccharide is shown in row 4 (monoclonal antibody Seam3). Control serum against a cytoplasmic protein is shown in row 5 (anti-NMB1380). Row 6 contains the knock out mutants (KO) of each type strain, probed with the homologous antiserum.

Figures 12 (variant 1), 13 (variant 2) and 14 (variant 3) show dendrograms for the three separate variants of NMB1870, classified by multilocus sequence types (ST).

MODES FOR CARRYING OUT THE INVENTION

NMB1870 in serogroup B strain MC58 - identification of the start codon

[0170] The NMB1870 gene was identified in the genome sequences of MenB and MenA published by The Institute for Genomic Research (TIGR) and Sanger Center, respectively [2,4; NMB1870 and NMA0586]. However, there is a discrepancy over the position of the ATG start codon as the MenB start codon is 120bp upstream of the MenA start codon. In contrast to both prior art annotations, the present invention places the start codon as a GTG codon which is downstream of the prior art start codons (18bp downstream for MenA, 138bp for MenB) and agrees with reference 8.

[0171] As shown in Figure 1, the GTG start (+1) is consistent with the presence of a correctly spaced ribosome-binding site and with the prediction of the lipoprotein signature. The prior art TIGR MenB start codon is shown in a box, and the

Sanger MenA start codon is in a circle. Inverted repeats are shown by horizontal arrows.

[0172] NMB1870 is a monocistronic gene located 157 bases downstream the stop codon of the fructose-bisphosphate aldolase gene nmb1869. In MenA Z2491 the overall organisation is similar, but 31 base pairs upstream from the GTG starting codon there is an insertion of 186 nucleotides which are homologous to an internal repeat region of IS 1106 and are flanked by two 16 base pairs inverted repeats. A putative ribosome binding site (shaded) is present 8 bp upstream from the GTG starting codon. A fur box (11/19 matches with the *E. coli* fur box consensus [178]; SEQ ID NOs: 74 & 75) is located 35bp upstream of the start codon, as predicted by GCG FindPatterns starting from SEQ ID NO: 75 and allowing a maximum of nine mismatches. Putative promoter sequences were also detected.

[0173] The GCG Wisconsin Package suite (version 10.0) was used for computer sequence analysis of gene and protein sequences. The PSORT program [179] was used for localisation prediction. NMB1870 has the typical signature of a surface-exposed lipoprotein, characterised by a signal peptide with a lipo-box motif of the type -Leu-X-X-Cys-, where the Cysteine was followed by a Serine, an amino acid generally associated with outer membrane localisation of lipoproteins [180]. The lipo-box is lost in gonococcus due to a frame-shifting single base (G) insertion after MC58 nucleotide 36, with the correct reading frame being re-established by a 8bp insertion after position 73.

[0174] The mature MC58 protein is predicted to be a lipoprotein with a molecular weight of 26,964 Da and a pI of 7.96, and is characterised by the presence of four glycines downstream of the lipo-box motif.

[0175] Secondary structure prediction analysis using the PredictProtein software [181] indicates that NMB1870 is a globular protein mostly composed of beta sheets.

Sequence analysis

[0176] The PSI-BLAST algorithm was used for homology searches [182] using the non-redundant protein database. No homologous proteins were found by searching existing non-redundant prokaryotic and eukaryotic protein databases maintained at the NCBI site, including the human genome, suggesting that NMB1870 is specific for *Neisseria*. However, a domain with some homology (28% identity over 146 amino acids) was found with the C-terminal portion of the transferrin-binding protein TfbA of *Actinobacillus pleuropneumoniae* [183] (Figure 2). A closer look at this domain revealed homologies also with the transferrin-binding proteins from *N. meningitidis* [184], *H. influenzae* [185], *Moraxella catarrhalis* [186] and with the *N. meningitidis* surface antigen NMB2132, previously annotated as TbpB homologue [3].

[0177] To see if this sequence homology reflects a functional homology, recombinant NMB1870 (see below), human transferrin hTF (Sigma T-4132) and the mix of the two (final concentration of 7 μ M) were dialysed O/N in PBS at 4°C. Following dialysis 20 μ l of each protein and the mixture of them were loaded on a HPLC Superdex 200 PC 3.2/30 gel filtration column (Amersham) using PBS as running buffer [187]. Blue Dextran 2000 and the molecular weight standards ribonuclease A, chymotrypsin A, ovalbumin A, bovine serum albumin (Amersham) were used to calibrate the column. Gel filtration was performed using a Smart system with a flow rate of 0.04 ml/min and the eluted material monitored at 214 nm and 280 nm. (The NMB1870 retention volume was 1.68 ml and 1.47 ml for htf.) Fractions of 40 μ l were collected and analysed by SDS-PAGE. The MC58 recombinant transferrin-binding protein 2 (Tbp2) was used as positive control.

[0178] The recombinant protein failed to bind human transferrin *in vitro*.

[0179] The Fur box in the promoter suggests that the expression of NMB1870 may be regulated by iron. However, expression of the protein does not seem to increase in low iron conditions.

[0180] An interesting feature of the protein is the presence of a stretch of four glycines downstream from the lipidated cysteine. Three or more consecutive glycines downstream from a lipidated cysteine are present also in other five lipoproteins in *N. meningitidis*, namely the transferrin-binding protein B (TbpB), the outer membrane component of an ABC transporter NMB0623, the hypothetical protein NMB1047, the TbpB homologue NMB2132, and the AspA lipoprotein [188]. In none of these proteins the poly-glycine stretch is encoded by a poly-G tract, suggesting that this feature is not used to generate antigenic modulation.

[0181] A search for lipoproteins with a glycine-rich region was carried out on 22 complete genomic sequences retrieved at the NCBI site [189] using FindPatterns. The search retrieved 29 lipoproteins in some but not all bacterial species. The organisms with this type of lipoproteins include both Gram-negative and Gram-positive bacteria, including *Haemophilus influenzae*, *Enterococcus faecalis*, *Mycobacterium tuberculosis*, *Lysteria monocytogenes* and *Staphylococcus aureus*, while others such as *E. coli*, *Bacillus subtilis*, *Helicobacter pylori*, *Streptococcus pneumoniae*, *S. pyogenes* and *Vibrio cholerae* have none. Most of the lipoproteins with this signature belong to ABC transporters, followed by proteins of unknown function. Although this common feature in the primary structure suggests a common role for the glycine repeats, so far, the function is unknown. However, it may serve to guide the lipoproteins to a specific pathway of secretion and surface localisation [190].

Sequencing for other strains

[0182] 70 strains representative of the genetic and geographic diversity of the *N. meningitidis* population were selected

for further investigation of NMB1870. Strains derive from 19 different countries, 73% belong to serogroup B, and 32 were isolated in the last five years. The strain panel mostly includes serogroup B strains, a few strains of serogroups A, C, Y, W-135 and Z, and one strain each of *N.gonorrhoeae* and *N.cinerea*. Strains are disclosed in more detail in references 191 & 192. Some strains are available from the ATCC (e.g. strain MC58 is available under reference BAA-335).

[0183] The NMB1870 gene was amplified using primers external to the coding sequence (A1, SEQ ID 55; and B2, SEQ ID 56). About 10 ng of chromosomal DNA was used as template for the amplification. PCR conditions were: 30 cycles, 94 °C for 40" 58 °C for 40" 68 °C for 40". PCR fragment were purified by the Qiagen QIAquick PCR Purification Kit, and submitted to sequence analysis, which was performed using an ABI 377 Automatic Sequencer. Sequencing was performed using primers A1, B2, 22 (SEQ ID 57) and 32 (SEQ ID 58).

[0184] The gene was detected by PCR in all 70 *Neisseria* strains. In *N.lactamica* a band could be detected by Western blotting, but the gene could not be amplified.

[0185] The nucleotide sequence of the gene was determined in all 70 strains. A total of 23 different protein sequences were encoded (SEQ ID NO^s 1 to 23). Computer analysis of these 23 sequences, using Kimura and Jukes-Cantor algorithm, divided them into three variants (Figure 9). The dendrogram was obtained starting from the multiple sequence alignment of NMB1870 protein sequences (PileUP) using the Protein Sequence Parsimony Method (ProtPars), a program available within the Phylogeny Inference Package (Phylip), and confirmed by the GCG program Distances, using the Kimura and Jukes-Cantor algorithms.

[0186] The NMB1870 sequences from 100 further strains were determined. Many of these were identical to one of SEQ ID NO^s 1 to 23, but 19 further unique sequences are given as SEQ ID NO^s 140 to 158.

[0187] Figures 12-14 show dendrograms of the various sequences, classified by ST multilocus sequence types. Within variant 1 (Figure 12) the reference strain is MC58, with the lowest sequence identity to the reference being 89.4% against an average of 93.7%. Within variant 2 (Figure 13) the reference strain is 2996 and sequences extend down to 93.4% identity (average 96.3%). Within variant 3 (Figure 14) the lowest identity to reference strain M1239 is 94.7% (average 95.8%). ST32cpx is the most homogeneous hypervirulent cluster, harbouring only one NMB1870 sequence from variant 1 (also also only one form of NMB 1343 and of NadA). Most ST44cpx strains harbour variant 1 (several different sequences) of NMB1870, with some having variant 3 (single sequence). These data suggest that ST32cpx is closer to ST44cpx, as compared to other clusters, which matches data based on porA genotype (class III). ST11 and ST8 complexes are mostly represented by different sequences within variant 2 of NMB1870, suggesting that these complexes are closer together, as compared to other clusters, and matching the porA genotype (class II). ST11cpx harbours all three variants, indicating that it is the most diverse hypervirulent cluster out of the four.

[0188] Strains MC58, 961-5945 and M1239 were arbitrarily selected as type strains for variants 1, 2 and 3, respectively. The sequence diversity between the three type strains is shown in Figure 10. Amino acid identity was 74.1 % between variant 1 and variant 2, 62.8% between variant 1 and variant 3, and 84.7% between variant 2 and variant 3. Sequences within each variant were well-conserved, the most distant showing 91.6%, 93.4% and 93.2% identity to their type strains, respectively. *N.cinerea* belongs to variant 1, and shares 96,7% homology with MC58. As shown in Figure 9, variant 1 harbours all strains from hypervirulent lineages ET-5, most lineage 3 strains, the serogroup A strains, two recent isolates of W-135 and one ET-37. Variant 2 harbours all strains from the hypervirulent complex A4, from serogroups Y and Z, one old W-135 isolate and five ET-37 strains. Variant 3 harbours four unique ST strains, one ET-37 strain, one lineage 3 strain and gonococcus.

[0189] The strains in each variant group, and their NMB1870 sequences, are as follows:

1	gb185 (sequence shared with ES14784, M.00.0243291) m4030 (sequence shared with M3812) m2197
	m2937 iss1001 (sequence shared with NZ394/98, 67/00, 93/114, bz198, m1390, nge28, 14996, 65/96, ISS1120, S59058, ISS1017, ISS1043, ISS1026, ISS1102, ISS1106, ISS656, ISS678, ISS740, ISS749, ISS995, ISS845, ISS1167, ISS1157, ISS1182, M4717, M6094, D8273) Inp17592 (sequence shared with 00-241341, 00-241357, 2ND80. 2ND221, ISS1142) f6124 (sequence shared with 205900) m198/172 (sequence shared with bz133, gb149, nm008, nm092, ES14963, FN131218, S5902, S90307, M4105, ISS1180, FN131345) mc58 (sequence shared with 30/00, 39/99, 72/00, 95330, bz169, bz83, cu385, h44/76, m1590, m2934, m2969, m3370, m4215, m4318, n44/89, 14847, ES14898, Inp15709, Inp17391, Inp17503, FN131654, M3985, S590104, S9029, S9097, D8346, FN131682, ISS832, ISS648, ISS1067,ISS1071,ISS1159) FN131217

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(continued)

5	ES14933 GB0993 M6190 F19324 ISS1113 gb0345 (sequence shared with M1820, ISS1082) M0445	
10		17 sequences, 98 strains
15	L93/4286 m2671 961-6945 (sequence shared with 2996, 96217, 312294, 11327, a22, ISS1141, ISS1173, ISS759, ISS743, ISS866, F17094, NMB, SWZ107) gb013 (sequence shared with e32, m1090, m4287, 66094, M3153, M4407, NGH36) 860800 (sequence shared with 599) 95N477 (sequence shared with 90-18311, c11, m986, F370/85, M.00.0243143, ISS838, ISS839, ISS1092, M1569)	
20	2 1000 (sequence shared with m1096, M2552, M4458, M5149, M6208) m3279 (sequence shared with bz232, dk353, m3697, ngh38, M5258, D8221) MK82 8047	
25	C4678 ISS1133 NG6/88 M0579 F16325	
30		15 sequences, 56 strains
35	3 16889 m3813 m1239 ngp165 gb355 (sequence shared with m3369, D8300, gb0364, M2441) gb988 [fa1090 gonococcus]	
40		7 sequences, 11 strains
NB: the abbreviation "gb" at the beginning of a strain name means "M.01.0240".		

[0190] SEQ ID NO^s 139 (strain 220173i), 140 (strains gb101 & ISS908) and 141 (strain nge31) are distant from these three variants (as is, to a lesser degree, strain m3813).

[0191] Within variant 1, the strain Inp17592 sequence (also seen in strains 00-241341, 00-241357, 2ND80. 2ND221 & ISS1142) is seen in the W-135 Haji serogroup. Within the Haji strains, the NadA sequence (SEQ ID NO: 143) is a recombination between alleles 2 and 3 [191,192].

Cloning, expression & purification in E.coli

[0192] NMB1870 genes were amplified by PCR from the genome of *N.meningitidis* MC58, 961-5945 and M1239 strains. Forward and reverse primers were designed in order to amplify the nmb1870 coding sequence devoid of the sequence coding for the putative leader peptide. M1239 and 961-5945 variants were found not to be expressible in *E.coli*. They were therefore expressed by adding to the N-terminal the sequence SEQ ID NO: 46 that is present in the gonococcus protein but absent in the meningococcus counterpart. Oligonucleotides used for the amplification were as follows:

Strain	Forward	Reverse
MC58	CGCGGATCCCATATGGTCGCCCGCCGACATCG ('For1'; SEQ ID 47)	CCCGCTCGAGTTGCTTGGCGGCAAGGC ('Rev1'; SEQ ID 48)
961/5945	CGCGGATCCCATATGGGCCCTGATTCTGACCGCCTGCAGCAGC GGAGGGTCGCCCGCACATCGG ('For2'; SEQ ID 49)	CCCGCTCGAGCTGTTTGGCCGGCGATGCC ('Rev2'; SEQ ID 50)
M1239	CGCGGATCCCATATGGGCCCTGATTCTTGACCGCC TGCAGCAGCGGAGGGGAGGGGGTGGTGTCCG ('For3'; SEQ ID 51)	GCCCAAGCTTCTGTTTGGCCGGCGATGCC ('Rev3'; SEQ ID 52)

[0193] Restriction sites, corresponding to *NdeI* for the forward primers and *XhoI* (*HindIII* for M1239) for the reverse primers, are underlined. For the 961-5945 and M1239 forward primers, the gonococcus sequence moiety is reported in italics, and the meningococcal NMB1870 matching sequences are reported in bold.

[0194] PCR conditions in the case of primer combination For1/Rev1 were: denaturation at 94°C for 30", annealing at 57°C for 30", elongation at 68°C for 1 min (5 cycles), denaturation at 94°C for 30", annealing at 68°C for 30", elongation at 68°C for 1 min (30 cycles). In the case of primer combinations: For2/Rev2 and For3/Rev2 and For3/Rev3: 94°C for 30", 56°C for 30", 68°C for 1 min (5 cycles), 94°C for 30", 71°C for 30", 68°C for 1 min (30 cycles).

[0195] Full-length *nmb1870* gene was amplified from the MC58 genome using the following primers: f-1For (CGCGGATCCCATATGAATCGAACTGCCTTCTGCTGCC; SEQ ID 53) and f-1Rev (CCCGCTCGAGTTATTGCTTGGCGGCAAGGC; SEQ ID 54) and the following conditions: 94°C for 30", 58°C for 30", 72°C for 1 min (30 cycles).

[0196] PCR were performed on approx. 10 ng of chromosomal DNA using High Fidelity Taq DNA Polymerase (Invitrogen). The PCR products were digested with *NdeI* and *XhoI* and cloned into the *NdeI/XhoI* sites of the pET-21b+ expression vector (Novagen).

[0197] Recombinant proteins were expressed as His-tag fusions in *E.coli* and purified by MCAC (Metal Chelating Affinity Chromatography), as previously described [3], and used to immunise mice to obtain antisera. *E.coli* DH5 α was used for cloning work, and BL21(DE₃) was used for expression.

***nmb1870* and *siaD* isogenic mutants**

[0198] Isogenic knockout mutants in which the *nmb1870* gene was truncated and replaced with an erythromycin antibiotic cassette, was prepared by transforming strains MC58, 961-5945 and M1239 with the plasmid *pBSΔnmb1870ERM*. This plasmid contains the erythromycin resistance gene within the *nmb1870* upstream and downstream flanking regions of 500bp. These regions were amplified from MC58 genome using the following oligonucleotides Ufor GCTCTAGACCAGCCAGGCGCATAC (SEQ ID 59, *XbaI* site underlined); URev TCCCCCGGGGACGGCATTGTTTACAGG (SEQ ID 60, *SmaI* underlined); DFor TCCCCCGGGCGCCAAGCAATAACCATTG (SEQ ID 61, *SmaI* underlined) and Drev CCCGCTCGAGCAGCGTATCGAACCATGC (SEQ ID 62, *XhoI* underlined). A capsule deficient mutant was generated using the same approach. The *siaD* gene was deleted and replaced with *ermC* using the plasmid *pBSΔCapERM*. The upstream and downstream flanking regions of 1000 bp and 1056 bp, respectively, were amplified from MC58 genome using the following primers: UCapFor GCTCTAGATTCTTTCCCAAGAACTCTC (SEQ ID 63, *XbaI* underlined); UcapRev TCCCCCGGGCCCGTATCATCCACCAC (SEQ ID 64, *SmaI* underlined); DCapFor TCCCCCGGGATCCACGCAAATACCCC (SEQ ID 65, *SmaI* underlined) and DCapRev CCCGCTCGAGATATAAGTGGGAAGACGGA (SEQ ID 66, *XhoI* underlined). Amplified fragments were cloned into pBluescript and transformed into naturally competent *N.meningitidis* strain MC58. The mixture was spotted onto a GC agar plate, incubated for 6 hrs at 37°C, 5% CO₂ then diluted in PBS and spread on GC agar plates containing 5 μg/ml erythromycin. The deletion of the *nmb1870* gene in the MC58Δ*nmb1870*, 961-5945Δ*nmb1870* and M1239Δ*nmb1870* strains was confirmed by PCR; lack of NMB1870 expression was confirmed by Western blot analysis. The deletion of the *siaD* gene and the lack of capsule expression in the MC58Δ*siaD* strain were confirmed by PCR and FACS, respectively.

Lipoproteins

[0199] To investigate lipidation of NMB1870, palmitate incorporation of recombinant *E.coli* BL21(DE₃) strain carrying the full-length *nmb1870* gene was tested as described in reference 193.

[0200] Meningococcal strains MC58 and MC58Δ*nmb1870* were grown in GC medium and labeled with [9,10-³H]-palmitic acid (Amersham). Cells from 5 ml culture were lysed by boiling for 10 min and centrifuged at 13,000 rpm. The supernatants were precipitated with TCA and washed twice with cold acetone. Proteins were suspended in 50 μl of 1.0% SDS and 15 μl analyzed by SDS-PAGE, stained with Coomassie brilliant blue, fixed and soaked for 15 min in Amplify solution (Amersham). Gels were exposed to Hyperfilm MP (Amersham) at -80°C for three days.

[0201] A radioactive band of the appropriate molecular weight was detected in MC58, but not in the Δ*nmb1870* knockout mutant.

[0202] Recombinant *E.coli* grown in the presence of [9,10-³H]-palmitic acid also produce a radioactive band at the expected molecular weight, confirming that *E.coli* recognises the lipoprotein motif and adds a lipid tail to the recombinant protein.

Protein detection

[0203] MC58 strain was grown at 37°C with 5% CO₂ in GC medium at stationary phase. Samples were collected during growth (OD_{620nm} 0.05-0.9). MC58Δ*nmb1870* was grown until OD_{620nm} 0.5. Bacterial cells were collected by centrifugation, washed once with PBS, resuspended in various volumes of PBS in order to standardise the OD values.

Culture supernatant was filtered using a 0.2 μ m filter and 1 ml precipitated by the addition of 250 μ l of 50% trichloroacetic acid (TCA). The sample was incubated on ice for 2 hr, centrifuged for 40 min at 4°C and the pellet washed with 70 % ice cold ethanol, and resuspended in PBS. 3 μ l of each sample (corresponding to an OD₆₂₀ 0.03) was then loaded on a 12% polyacrylamide gels and electrotransferred onto nitrocellulose membranes.

[0204] Western blot analysis were performed according to standard procedures, using polyclonal antibodies raised against protein expressed in *E.coli*, at a 1:1000 dilution, followed by a 1/2000 dilution of HRP-labeled anti-human IgG (Sigma). Scanning was performed using a LabScan (Pharmacia) and Imagemaster software (Pharmacia).

[0205] As shown in Figure 3, a protein of ~29.5 kDa was detected in the total cell extracts of *N.meningitidis*. The amount of the protein in the whole cell lysate approximately doubled during the growth curve, while the optical density of the culture increased from 0.05 to 0.9 OD_{620nm}. A band of the same size was also detected in the culture supernatant. The protein was not detected in the supernatant of the freshly inoculated culture (OD_{620nm} 0.05), and increased approximately four times during the growth from 0.1 to 0.9 OD_{620nm} (Figure 4, left-hand panel). The genuine nature of the expression in the supernatant was confirmed by testing the same samples for membrane blebs and cytoplasmic proteins. As shown in the middle panel of Figure 4, the absence of PorA in the supernatant preparations of PorA rules out a possible contamination with membrane blebs, while the absence in the supernatant of cytoplasmic protein NMB1380 confirmed that the supernatant samples do not result from cell lysis (right-hand panel).

[0206] The MC58 Δ nmb1870 knockout strain shows no protein in either whole cell lysate or culture supernatant (lanes 'KO' in Figures 3 & 4).

[0207] NMB1870 was detected by western blotting in outer membrane vesicles, confirming that the protein segregates with the membrane fractions of *N.meningitidis* (Figure 5). However, sera from mice immunised with the OMVs did not recognise recombinant NMB1870 in western blotting, suggesting that the protein is not immunogenic in OMV preparations.

[0208] FACS analysis using the anti-NMB1870 antibodies confirmed that the protein is surface-exposed and accessible to antibodies both in encapsulated and non-encapsulated *N.meningitidis* strains (Figure 6). FACS analysis used a FACS-Scan flow cytometer, with antibody binding detected using a secondary antibody anti-mouse (whole molecule) FITC-conjugated (Sigma). The positive FACS control used SEAM3, a mAb specific for the meningococcus B capsular polysaccharide [194]; the negative control consisted of a mouse polyclonal antiserum against the cytoplasmic protein NMB1380 [195].

[0209] Western blotting analysis of 43 strains showed that NMB1870 is expressed by all strains tested. As shown in Figure 7, however, the levels of expression varied considerably from strain to strain. The strains tested could be broadly classified as high, intermediate and low expressers:

Strains	High	Intermediate	Low
ET5	9/9	0/9	0/9
Lineage 3	7/9	1/9	1/9
ET37	2/3	1/3	0/3
A4	0/4	2/4	2/4
Other	6/15	7/15	2/15
<i>N. gonorrhoeae</i>	0/1	0/1	1/1
<i>N. cinerea</i>	0/1	0/1	1/1
<i>N. lactamica</i>	1/1	0/1	0/1
Total	25/43 (58%)	11/43 (25.5%)	7/43 (16.5%)

[0210] Most of the strains from hypervirulent lineages (ET-5, lineage 3, ET-37) expressed high levels of the protein, with the exception of A4 where two strains expressed intermediate levels and two expressed low levels. Interestingly, the protein was expressed at high level by strains that have been classically used as OMV vaccine strains. No obvious genetic patterns were found to predict the amount of protein expressed by each strain. Even the presence of the IS element in the promoter region, which was found in 8/70 strains (one from serogroup A, three from lineage 3, and four from those classified as others), did not show any correlation with the expression of the protein.

[0211] Scanning of the Western blots showed that the difference in expression between high and intermediate, intermediate and low or high and low could be two-, five- and nine-fold, respectively. There is no immediately-apparent reason for the different expression levels, and analysis of the DNA sequences upstream from the gene did not show any feature that correlates with expression.

Antibody responses

[0212] Sera from healthy and convalescent subjects were analysed for anti-NMB1870 antibodies by Western blot. Purified NMB1870 (1 µg/lane) was loaded onto 12.5% SDS-polyacrylamide gels and transferred to a nitrocellulose membrane. The bound protein was detected with 1/200 dilution of sera, followed by a 1/2000 dilution of HRP-labeled anti-human IgG (Sigma). While only 2/10 of sera from healthy people recognised NMB1870, 21/40 convalescent sera recognised the protein, leading to the conclusion that NMB 1870 is immunogenic *in vivo* during infection. Antisera from mice immunised with recombinant NMB 1870 were therefore investigated further.

[0213] To prepare antisera, 20 µg of variant 1, variant 2 and variant 3 NMB1870 recombinant proteins were used to immunise six-week-old CD1 female mice (Charles River). Four to six mice per group were used. The recombinant proteins were given i.p., together with complete Freund's adjuvant (CFA) for the first dose and incomplete Freund's adjuvant (IFA) for the second (day 21) and third (day 35) booster doses. The same immunization schedule were performed using aluminium hydroxide adjuvant (3 mg/ml) instead of Freund's adjuvant. Blood samples for analysis were taken on day 49.

[0214] The antisera were tested for their ability to induce complement-mediated killing of capsulated *N.meningitidis* strains, as previously described [3, 196] using pooled baby rabbit serum (CedarLane) used as complement source. Serum from a healthy human adult (with no intrinsic bactericidal activity when tested at a final concentration of 25 or 50%) was also used as complement source. Serum bactericidal titers were defined as the serum dilution resulting in 50% decrease in colony forming units (CFU) per ml after 60 mins. incubation of bacteria with reaction mixture, compared to control CFU per ml at time 0. Typically, bacteria incubated with the negative control antibody in the presence of complement showed a 150 to 200% increase in CFU/ml during the 60 min incubation.

[0215] Representative strains from the high, intermediate and low expressors were selected for the assay. The differential expression of the protein on the surface of the selected strains was confirmed by FACS analysis (Figure 8) - MC58, a representative of the high expresser strains was killed with high efficiency by the serum diluted up to 1/64,000; NZ394/98 (originally NZ98/254), a representative of the intermediate expressors was also killed with high efficiency, by the serum diluted up to 1/16,000 and even strain 67/00, a representative of the low expresser strains was killed by the antiserum diluted up to 1/2,048. Control strains, where the *nmb1870* gene had been knocked out, was not killed by the same antiserum.

[0216] To confirm whether the sera were also able to confer protection *in vivo*, they were tested for ability to induce passive protection in the infant rat model. Five-day-old infant rats were pre-treated i.p. with anti-NMB1870 antisera or with anti-PorA monoclonal antibody at time 0 and challenged two hours later i.p. with 5×10^3 CFU/rat of MenC 4243 (OAc-positive) or MenB NZ394/98. Quantitative blood cultures were obtained 24 hours later. Bacterial counts in the blood cultures (CFU/ml, geometric means) were obtained by plating blood on chocolate agar plates. Positive control serum was anti-PorA(P1.2) for MenC and SEAM3 for MenB. Results of the experiments were as follows:

Pre-treatment	Challenge Strain 4243		Challenge Strain NZ394/98	
	Positives	CFU/ml $\times 10^3$	Positives	CFU/ml $\times 10^3$
PBS	5/5	450	-	-
Negative control serum	5/5	500	9/14	1260
Positive control serum	1/5	0.003	0/7	<0.001
Anti-NMB1870	0/9	<0.001	0/14	<0.001

[0217] Therefore no bacterial colonies were recovered from the blood of the rats passively immunised with anti-NMB1870 serum, while most of the negative control animals were bacteremic.

Bactericidal activity is variant specific

[0218] Each type variant was expressed in *E. coli* as a His-tagged protein and used to immunise mice. The sera were used to test the immunological cross-reactivity between strains of the three variants by FACS and bactericidal assay. As shown in Figure 11, by FACS analysis, all strains were recognised by each serum, although the degree of recognition varied considerably, usually reflecting the amino acid homology between the proteins.

[0219] On closer analysis, the anti-variant-1 serum (Figure 11, first row) recognised MC58 strain very well (as expected), to a lower extent the 961-5945 strain (74.1% identity) and, to a lesser extent, the M1239 strain (62.8% identity). A similar trend was found for antisera against variants 2 and 3 (rows 2 and 3 of Figure 11), although with the anti-variant-2 serum the differences were not as striking.

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[0220] A monoclonal antibody against the capsule recognised all three strains equally well the (row 4), while a serum against the cytoplasmic protein NMB1380 used as negative control did not recognise any (row 5). Similarly, the nmb1870 knock-out mutants were not recognised by any sera (row 6).

[0221] The differences in immunorecognition between the variants were more evident by bactericidal assay:

Sera	MC58 (variant 1)	961/5945 (variant 2)	M1239 (variant 3)
Anti-variant 1	64000	256	<4
Anti-variant 2	<4	16000	128
Anti-variant 3	<4	2048	16000

[0222] The data show that the serum against each variant was able to induce an efficient complement-mediated killing of the homologous strain (titers ranging between 16,000 and 64,000), while the activity was low (128-2,048) or absent (<4) against strains of the other variants. As predicted from the close amino acid homology, the cross-bactericidal titers between variants 2 and 3 were higher than the others. When human complement was used, bactericidal titers of 4,096, 256 and 512 were obtained with variants 1, 2 and 3, respectively, using the homologous type strains. No titers were detected against the heterologous strains.

Hybrid and tandem proteins

[0223] Hybrid and tandem proteins can be represented by the formula: $\text{NH}_2\text{-A-}[-\text{X-L-}]_n\text{-B-COOH}$. Genes encoding various proteins of this type were constructed, where $n=2$, the N-termini of X_1 and X_2 are deleted up to the end of their poly-glycine regions, and $-\text{L}_2-$ and $-\text{B}-$ are absent (or else B is a poly-histidine tag used for purification). The following table shows the components of these proteins in their mature forms, and gives the SEQ ID NOs of the full polypeptide and the SEQ ID NOs and strains for the component sequences A, X_1 , L_1 and X_2 :

	SEQ ID	A	X_1	L_1	X_2	pI
(1)	79	-	MC58 (SEQ ID 80)	SEQ ID 78	2996 (SEQ ID 81)	6.74
(2)	82	-	MC58 (SEQ ID 80)	SEQ ID 144	2996 (SEQ ID 81)	6.63
(3)	83	-	MC58 (SEQ ID 80)	SEQ ID 78	M1239 (SEQ ID 84)	
(4)	85	-	MC58 (SEQ ID 80)	SEQ ID 144	M1239 (SEQ ID 84)	
(5)	87	SEQ ID 86	2996 (SEQ ID 81)	SEQ ID 78	M1239 (SEQ ID 84)	6.44
(6)	88	SEQ ID 86	2996 (SEQ ID 81)	SEQ ID 144	M1239 (SEQ ID 84)	6.35
(7)	89	SEQ ID 86	M1239 (SEQ ID 84)	SEQ ID 78	2996 (SEQ ID 81)	
(8)	90	SEQ ID 86	M1239 (SEQ ID 84)	SEQ ID 144	2996 (SEQ ID 81)	
(9)	91	Cys	'936' (SEQ ID 76)	SEQ ID 78	2996 (SEQ ID 81)	
(10)	92	Cys	'936' (SEQ ID 76)	SEQ ID 144	2996 (SEQ ID 81)	
(11)	93	Cys	'936' (SEQ ID 76)	SEQ ID 78	M1239 (SEQ ID 84)	
(12)	94	Cys	'936' (SEQ ID 76)	SEQ ID 144	M1239 (SEQ ID 84)	

[0224] Of these twelve proteins, therefore, eight are tandem NMB1870 proteins (MW ~ 55kDa) and four are hybrid proteins with '936₂₉₉₆' at the N-terminus (MW ~49kDa). Two linkers were used: (a) SEQ ID NO: 78, which is derived from the gonococcal NMB1870 homolog (SEQ ID NO: 46); and (b) a glycine-rich linker (SEQ ID NO: 144). SEQ ID NO: 78 was also used at the N-terminus of mature proteins, without its two N-terminus *Bam*HI residues (Gly-Ser) *i. e.* SEQ ID NO: 86.

[0225] All twelve proteins were soluble when expressed in *E. coli* and, after purification, were used to immunise mice. Serum bactericidal antibody (SBA) responses were assessed against up to four meningococcal strains, ensuring one from each of the three NMB1870 variants 1 to 3 (shown as superscripts). The adjuvant was either CFA (top) or an

aluminium hydroxide (bottom):

Protein	SBA			
	2996 ⁽²⁾	MC58 ⁽¹⁾	M1239 ⁽³⁾	961/5945 ⁽²⁾
(1)	4096 1024	262144 32768	2048 128	32768 2048
(2)	8192 1024	262144 16384	2048 512	32768 1024
(3)	- -	131072 32768	32768 4096	4096 1024
(4)	- -	262144 32768	32768 1024	8192 512
(5)	512 1024	<4 16	4096 4096	32768 8192
(6)	4096 2048	<4 16	32768 4096	32768 16384
(7)	- -	4 16	4096 4096	32768 8192
(8)	2048 1024	32 32	32768 8192	32768 16384
(9)	2048 4096	<4 <4	<4 512	32768 16384
(10)	4096 512	<4 <4	256 <4	131072 2048
(11)	256 4	<4 4	>32768 4096	2048 128
(12)	2048 16	<4 256	>32768 4096	4096 256

[0226] These results clearly show the variant-specific nature of the immune reactions. For example, proteins (1) and (2) include sequences from NMB1870 variants 1 and 2, and the best SBA results are seen against these two variants. Similarly, the best results are seen against variants 1 and 3 when using proteins (3) and (4). Good activity is seen using NMB1870 from variants 2 and 3, in either order from N-terminus to C-terminus, using proteins (5) to (8), with little activity against variant 1. The variant-specific nature of the NMB1870 response is also apparent when using the hybrid proteins, with some anti-2996 activity being provided by the '936' moiety.

[0227] The following oligonucleotide primers were used during the construction of the 12 proteins:

Protein	Primer SEQ ID NO ^s (Fwd & Rev)	Restriction sites
(1)	95 & 96	<i>Bam</i> HI & <i>Xho</i> I
(2)	97 & 98	<i>Bam</i> HI & <i>Xho</i> I
(3)	99 & 100	<i>Bam</i> HI & <i>Hind</i> III
(4)	101 & 102	<i>Bam</i> HI & <i>Hind</i> III
(5)	103 & 104	<i>Bam</i> HI & <i>Hind</i> III
(6)	105 & 106	<i>Bam</i> HI & <i>Hind</i> III
(7)	107 & 108	<i>Bam</i> HI & <i>Xho</i> I
(8)	109 & 110	<i>Bam</i> HI & <i>Xho</i> I

(continued)

Protein	Primer SEQ ID NO ^s (Fwd & Rev)	Restriction sites
(9)	111 & 112	<i>Bam</i> HI & <i>Xho</i> I
(10)	113 & 114	<i>Bam</i> HI & <i>Xho</i> I
(11)	115 & 116	<i>Bam</i> HI & <i>Hind</i> III
(12)	117 & 118	<i>Bam</i> HI & <i>Hind</i> III
NMB1870 _{M1239}	119 & 120	<i>Nde</i> I & <i>Bam</i> HI
NMB1870 ₂₉₉₆	121 & 122	<i>Nde</i> I & <i>Bam</i> HI

Triple tandem protein

[0228] A "triple tandem" protein, where $n=3$, was constructed based on strains (1) MC58, (2) 2996 and (3) m1239. The 757mer triple tandem protein NH₂-A-X₁-L₁-X₂-L₂-X₃-L₃-B-COOH has amino acid sequence SEQ ID NO: 142:

Moiety	A	X ₁	L ₁	X ₂	L ₂	X ₃	L ₃	B
Detail	-	NMB1870 _{MC58}	Gly-rich linker	NMB1870 ₂₉₉₆	Gly-rich linker	NMB1870 _{m1239}	-	-
SEQ ID	-	80	144	81	144	84	-	-
Variant	-	1	-	2	-	3	-	-

X₂ and X₃ both lack the N-terminus up to their poly-glycine regions (i. e. they are ΔG sequences).

Bactericidal SBA titres

[0229] Mice were immunised with nine different proteins and the bactericidal activity of the resulting sera were tested against different strains of meningococcus, including both strains which match those from which the immunising proteins were derived and strains which are different from the immunising proteins. The nine proteins were:

(A), (B) & (C) Hybrid proteins of 936 and NMB1870

(A) NMB1870_{MC58} = variant 1 [12]

(B) NMB1870₂₉₉₆ = variant 2 e.g. SEQ ID NO^s: 91 & 92

(C) NMB1870_{M1239} = variant 3 e.g. SEQ ID NO^s: 91 & 92

(D), (E) & (F) NMB 1870 from single strains

(D) NMB1870_{MC58} = variant 1 e.g. SEQ ID NO: 80

(E) NMB1870₂₉₉₆ = variant 2 e.g. SEQ ID NO: 81

(F) NMB1870_{M1239} = variant 3 e.g. SEQ ID NO: 84

(G), (H) & (I) NMB1870 tandem proteins

(G) NMB1870_{MC58}-NMB1870₂₉₉₆ = variants 1 & 2 e.g. SEQ ID NO^s: 79 & 82

(H) NMB1870₂₉₉₆-NMB1870_{M1239} = variants 2 & 3 e.g. SEQ ID NO^s: 87 & 88

(I) NMB1870_{MC58}-NMB1870_{M1239} = variants 1 & 3 e.g. SEQ ID NO^s: 83 & 85

[0230] Bactericidal responses were measured against up to 20 strains which possess variant 1 of NMB 1870, against up to 22 strains with variant 2 of NMB1870 and against up to 5 strains with variant 3.

[0231] The bactericidal efficacy of sera raised against proteins (A) to (C) matched the genotype of the test strains e.g. using CFA as adjuvant for the immunisations, the SBA titres against strain MC58 (variant 1) were: (A) 262144; (B) <4; (C) <4. Similarly, when sera were tested against strain 961-5945 (variant 2) the SBA were: (A) 256; (B) 32768; (C) 4096. Finally, against strain M1239 (variant 3) titres were: (A) <4; (B) 512; (C) 32768.

[0232] Using CFA or aluminium hydroxide as adjuvant, protein (A) gave SBA titres of ≥512 against the following strains:

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M01-240185, M2197, LPN17592, M6190 (all ET37); MC58, BZ83, CU385, N44/89, 44/76, M2934, M4215 (all ET5); BZ133; M1390, ISS1026, ISS1106, ISS1102 (lin. 3); F6124 (sIII); and M2937 (other). These strains cover serogroups A, B, C and W135; no serogroup Y strains were tested.

[0233] Using CFA or aluminium hydroxide as adjuvant, protein (B) gave SBA titres ≥ 512 against strains: 2996, 961-5945, 96217 (cluster A4); M01-240013, C11, NGH38, M3279, M4287, BZ232 (other). These strains cover serogroups B and C; no serogroup A, W135 or Y strains were tested.

[0234] Using CFA or aluminium hydroxide as adjuvant, protein (C) gave SBA titres ≥ 512 against strains: M01-0240364, NGP165 (ET37); M1239 (lin. 3); M01-240355, M3369 (other). These strains are in serogroup B, and no serogroup A, C, W135 or Y strains were tested.

[0235] The SBA patterns seen with proteins (A) to (C) were also seen with proteins (D) to (F). Against strain MC58, serum obtained using protein (D) and aluminium hydroxide adjuvant gave a SBA titre of 16384, whereas sera obtained using protein (E) or (F) and the same adjuvant gave SBA titres < 4 . Against strain 961-5945, protein (D) and (F) sera gave lower titres than those obtained using (E). Against, strain M1239, SBA titres were: (D) < 4 ; (E) 128; (F) 16384.

[0236] With tandem proteins, SBA efficacy was broadened. Sera obtained using protein (G) were bactericidal against strain MC58 and 961-5945, as well as other strains which possess variant 1 or variant 2 of NMB1870. Sera raised against protein (H) gave low titres against strains which possess variant 1 of NMB1870, but high titres against other strains e.g. 163 84 against strain 961-5945 (variant 2) and 32768 against strain M3369 (variant 3).

[0237] Sera obtained by immunisation with CFA-adjuvanted protein (H) gave SBA titres ≥ 512 against: LNP17094, 96217, 961-5945, 2996, 5/99 (cluster A4); C4678, MOI-0240364, NGP165 (ET37); M1239 (lin. 3); M2552, BZ232, M3279, M4287, 1000, NGH38, C11, M01-240013, M01-240355, M3369 (other). These strains cover serogroups B and C; activity against serogroups A, W135 or Y strains was not tested with protein (H).

[0238] Sera obtained by immunisation with CFA-adjuvanted protein (I) gave SBA titres ≥ 512 against: M01-0240364, 14784, M6190, MC58, LPN17592, M2197 (ET37); 44/76 (ET5); M1239, ISS1102, ISS1106, ISS1026, 394/98 (lin. 3); M2937 (other). These strains cover serogroups B, C and W135; activity against serogroups A or Y strains was not tested with protein (I).

[0239] After immunisation with proteins containing variant 1 of NMB 1870, sera tested against up to 20 strains which have a NMB 1870 in variant 1 gave SBA titres as follows:

Protein	(A)	(A)	(D)	(D)	(G)	(G)	(I)	(I)
Adjuvant	CFA	Alum	CFA	Alum	CFA	Alum	CFA	Alum
N° strains tested	18	20	20	20	13	13	11	11
SBA < 128	1	7	4	3	0	5	0	2
SBA 128-512	2	4	0	4	0	3	0	3
SBA > 512	15	9	16	13	13	5	11	6

[0240] After immunisation with proteins containing variant 2 of NMB1870, sera tested against up to 22 strains which have a NMB1870 in variant 2 gave SBA titres as follows:

Protein	(B)	(B)	(E)	(G)	(G)	(H)	(H)	(I)	(I)
Adjuvant	CFA	Alum	Alum	CFA	Alum	CFA	Alum	CFA	Alum
N° strains tested	16	19	22	16	15	22	22	7	6
SBA < 128	6	14	13	6	10	7	8	3	5
SBA 128-512	0	2	7	3	3	1	6	0	1
SBA > 512	10	3	2	7	2	14	8	4	0

[0241] After immunisation with proteins containing variant 3 of NMB1870, sera tested against up to 5 strains which have a NMB1870 in variant 3 gave SBA titres as follows:

Protein	(C)	(C)	(F)	(G)	(G)	(H)	(H)	(I)	(I)
Adjuvant	CFA	Alum	Alum	CFA	Alum	CFA	Alum	CFA	Alum

(continued)

Protein	(C)	(C)	(F)	(G)	(G)	(H)	(H)	(I)	(I)
N° strains tested	5	5	5	5	5	5	5	3	3
SBA <128	0	1	1	1	1	0	0	1	1
SBA 128-512	0	0	0	0	2	0	0	0	1
SBA >512	5	4	4	4	2	5	5	2	1

Conclusions

[0242] At first, NMB1870 appears not to be a useful antigen for broad immunisation - its expression levels vary between strains, there is significant sequence variability, and there is no cross-protection between the different variants. However, it has been shown that even those strains which express very low levels of this antigen are susceptible to anti-NMB1870 sera. Furthermore, sequence diversity is limited to three variant forms such that broad immunity can be achieved without the need for a large number of antigens. In addition, it seems that these three proteins may offer immunity against more than just serogroup B meningococcus.

[0243] The different variants of NMB1870 can be expressed together as fusion proteins in order to give single polypeptide chains which are active against more than one variant.

[0244] NMB1870 is immunogenic during infection, is able to induce bactericidal antibodies, and protects infant rats from bacterial challenge.

[0245] Further experimental information on NMB1870 can be found in reference 197.

[0246] It will be understood that the invention is described above by way of example only and modifications may be made whilst remaining within the scope of the invention.

BRIEF DESCRIPTION OF THE SEQUENCE LISTING

[0247]

SEQ ID NO:	Description
1-23	23 different NMB1870 sequences, full-length
24-45	22 different NMB 1870 sequences, with N-terminus cysteines
46	N-terminal amino acid sequence used for expression
47-66	PCR primers
67-69	Partial sequences from Figure 1
70-73 & 86	Sequence motifs for retention or omission from proteins of the invention
74-75	Fur boxes
76	'936' from MC58, with leader peptide processed
77	Example of a 936 _{MC58} -ΔG-NMB1870 _{M1239} hybrid
78	Gonococcus-derived sequence used for chimeric expression
79, 82, 83, 85, 87, 88, 89, 90	Tandem NMB1870 proteins
80, 81, 84	Truncated NMB 1870 sequences
91-94	Hybrid proteins of '936' and NMB1870
95-122	PCR primers
123-141	Full-length NMB1870 sequences
142	Triple tandem NMB 1870 sequence
143	Haji NadA sequence
144	Glycine linker

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	Asp	Lys	Leu	Pro	Glu	Gly	Gly	Arg	Ala	Thr	Tyr	Arg	Gly	Thr	Ala	Phe	
				165						170					175		
40	Gly	Ser	Asp	Asp	Ala	Ser	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	Ser	Pro	Glu	Leu	
			195					200					205				
45	Asn	Val	Asp	Leu	Ala	Ala	Ser	Asp	Ile	Lys	Pro	Asp	Lys	Lys	Arg	His	
		210					215					220					
	Ala	Val	Ile	Ser	Gly	Ser	Val	Leu	Tyr	Asn	Gln	Ala	Glu	Lys	Gly	Ser	
50		225				230					235					240	
	Tyr	Ser	Leu	Gly	Ile	Phe	Gly	Gly	Gln	Ala	Gln	Glu	Val	Ala	Gly	Ser	
				245					250						255		
55	Ala	Glu	Val	Glu	Thr	Ala	Asn	Gly	Ile	Arg	His	Ile	Gly	Leu	Ala	Ala	
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	Lys	Gln															

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<210> 8
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Ala Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys
 35 40 45

Gly Leu Gln Ser Leu Met Leu Asp Gln Ser Val Arg Lys Asn Glu Lys
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Leu Lys Leu Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp
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Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp
 85 90 95

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Phe Ile Arg Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser
 100 105 110

Gly Glu Phe Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Leu
 115 120 125

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Gln Thr Glu Gln Val Gln Asp Ser Glu His Ser Gly Lys Met Val Ala
 130 135 140

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Lys Arg Gln Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe
 145 150 155 160

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

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Gly Ser Asp Asp Ala Gly Gly Lys Leu Ile Tyr Thr Ile Asp Phe Ala
 180 185 190

Ala Lys Gln Gly His Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu
 195 200 205

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Asn Val Asp Leu Ala Ala Ala Tyr Ile Lys Pro Asp Glu Lys His His
 210 215 220

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

Tyr Ser Leu Gly Ile Phe Gly Gly Lys Ala Gln Glu Val Ala Gly Ser
 245 250 255

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Ala Glu Val Lys Thr Val Asn Gly Ile Arg His Ile Gly Leu Ala Ala
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Lys Gln

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Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly
			20					25					30		
Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys
		35					40					45			
Gly	Leu	Arg	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys
	50					55					60				
Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp
65					70					75					80
Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp
				85					90					95	
Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser
			100					105					110		
Gly	Glu	Phe	Gln	Val	Tyr	Lys	Gln	Ser	His	Ser	Ala	Leu	Thr	Ala	Leu
		115					120					125			
Gln	Thr	Glu	Gln	Glu	Gln	Asp	Leu	Glu	His	Ser	Gly	Lys	Met	Val	Ala
	130					135					140				
Lys	Arg	Arg	Phe	Arg	Ile	Gly	Asp	Ile	Ala	Gly	Glu	His	Thr	Ser	Phe
145					150					155					160
Asp	Lys	Leu	Arg	Glu	Gly	Gly	Arg	Ala	Thr	Tyr	Arg	Gly	Thr	Ala	Phe
				165					170					175	
Gly	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala
			180					185					190		
Ala	Lys	Gln	Gly	Tyr	Gly	Lys	Ile	Glu	His	Leu	Lys	Ser	Pro	Glu	Leu
		195					200					205			
Asn	Val	Asp	Leu	Ala	Ala	Ala	Asp	Ile	Lys	Pro	Asp	Glu	Lys	His	His
	210					215					220				
Ala	Val	Ile	Ser	Gly	Ser	Val	Leu	Tyr	Asn	Gln	Asp	Glu	Lys	Gly	Ser
225					230					235					240
Tyr	Ser	Leu	Gly	Ile	Phe	Gly	Gly	Glu	Ala	Gln	Glu	Val	Ala	Gly	Ser
			245					250						255	
Ala	Glu	Val	Lys	Thr	Ala	Asn	Gly	Ile	His	His	Ile	Gly	Leu	Ala	Ala
			260					265					270		
Lys	Gln														

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

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Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly
			20					25					30		
Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys
		35					40					45			
Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys
	50					55					60				
Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp
65					70					75					80
Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp
				85					90					95	
Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser
			100					105					110		
Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	Ala	Val	Val	Ala	Leu
		115					120					125			
Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn
	130					135					140				
Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe
145					150					155					160
Asn	Gln	Leu	Pro	Asp	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser
				165					170					175	
Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	Ala
			180					185					190		
Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	Leu	Lys	Thr	Pro	Glu	Gln	Asn
		195					200					205			
Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala
	210					215					220				
Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	Glu	Glu	Lys	Gly	Thr	Tyr
225					230					235					240
His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala
				245					250					255	
Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys
			260					265					270		
Gln															

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<213> Neisseria meningitidis

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	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly	
				20					25					30			
5	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys	
			35					40					45				
	Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys	
		50					55					60					
10	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp	
	65					70					75					80	
	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp	
					85					90					95		
15	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser	
				100					105					110			
	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	Ala	Val	Val	Ala	Leu	
20			115					120					125				
	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn	
		130					135					140					
25	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe	
	145					150					155					160	
	Asn	Gln	Leu	Pro	Ser	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser	
					165					170					175		
30	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	Ala	
				180					185					190			
	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	Leu	Lys	Thr	Pro	Glu	Gln	Asn	
			195					200					205				
35	Val	Glu	Leu	Ala	Ser	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala	
		210					215					220					
	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Gly	Glu	Glu	Lys	Gly	Thr	Tyr	
40		225				230					235					240	
	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	
					245					250					255		
45	Thr	Val	Lys	Ile	Arg	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	
				260					265					270			
	Gln																
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	<212> PRT																
	<213> Neisseria meningitidis																
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5	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly
				20					25					30		
	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys
			35					40					45			
10	Gly	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys
	50						55					60				
	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp
15	65					70					75					80
	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp
					85					90					95	
20	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser
				100					105					110		
	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	Ala	Val	Val	Ala	Leu
			115					120					125			
25	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn
	130						135					140				
	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe
	145					150					155					160
30	Asn	Gln	Leu	Pro	Ser	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser
					165					170					175	
	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	His	Tyr	Ser	Ile	Asp	Phe	Thr	Lys
35				180					185					190		
	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu	His	Leu	Lys	Thr	Pro	Glu	Gln	Asn
			195					200					205			
40	Val	Glu	Leu	Ala	Ser	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala
	210						215					220				
	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Gly	Glu	Glu	Lys	Gly	Thr	Tyr
	225					230					235					240
45	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala
					245					250					255	
	Thr	Val	Lys	Ile	Arg	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys
				260					265					270		
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<211> 273

55 <212> PRT

<213> Neisseria meningitidis

<400> 13

EP 2 261 239 B1

	Met	Asn	Arg	Thr	Ala	Phe	Cys	Cys	Leu	Ser	Leu	Thr	Ala	Ala	Leu	Ile
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5	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly
				20					25					30		
	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys
			35					40					45			
10	Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys
	50						55					60				
	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp
15	65					70					75					80
	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp
					85					90					95	
20	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser
				100					105					110		
	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	Ala	Val	Val	Ala	Leu
			115					120					125			
25	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn
	130						135					140				
	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe
	145					150					155					160
30	Asn	Gln	Leu	Pro	Ser	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser
					165					170					175	
	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	His	Tyr	Ser	Ile	Asp	Phe	Thr	Lys
35				180					185					190		
	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu	His	Leu	Lys	Thr	Pro	Glu	Gln	Asn
			195					200					205			
40	Val	Glu	Leu	Ala	Ser	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala
	210						215					220				
	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Gly	Glu	Glu	Lys	Gly	Thr	Tyr
	225					230					235					240
45	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala
					245					250					255	
	Thr	Val	Lys	Ile	Arg	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys
				260					265					270		
50	Gln															

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55 <212> PRT

<213> Neisseria meningitidis

<400> 14

EP 2 261 239 B1

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5	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly
				20					25					30		
	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys
			35					40					45			
10	Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys
		50					55					60				
	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp
15	65					70					75					80
	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp
					85					90					95	
20	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser
				100					105					110		
	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	Ala	Val	Val	Ala	Leu
			115					120					125			
25	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn
		130					135					140				
	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe
	145					150					155					160
30	Asn	Gln	Leu	Pro	Gly	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser
					165					170					175	
	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	His	Tyr	Ser	Ile	Asp	Phe	Thr	Lys
35				180					185					190		
	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu	His	Leu	Lys	Thr	Pro	Glu	Gln	Asn
			195					200					205			
40	Val	Glu	Leu	Ala	Ser	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala
		210					215					220				
	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	Glu	Glu	Lys	Gly	Thr	Tyr
	225					230					235					240
45	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala
					245					250					255	
	Thr	Val	Lys	Ile	Arg	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys
50				260					265					270		
	Gln															

<210> 15

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55 <212> PRT

<213> Neisseria meningitidis

<400> 15

EP 2 261 239 B1

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5	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly
				20					25					30		
	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Thr	Pro	Leu	Asp	His	Lys	Asp	Lys
			35					40					45			
10	Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys
		50					55					60				
	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp
15	65					70					75					80
	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp
					85					90					95	
20	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Thr	Ile	Thr	Leu	Ala	Ser
				100					105					110		
	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asn	His	Ser	Ala	Val	Val	Ala	Leu
			115					120					125			
25	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn
		130					135					140				
	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe
30	145					150					155					160
	Asn	Gln	Leu	Pro	Asp	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser
					165					170					175	
35	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	His	Tyr	Ser	Ile	Asp	Phe	Thr	Lys
				180					185					190		
	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu	His	Leu	Lys	Thr	Pro	Glu	Gln	Asn
			195					200					205			
40	Val	Glu	Leu	Ala	Ser	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala
		210					215					220				
	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Gly	Glu	Glu	Lys	Gly	Thr	Tyr
	225					230					235					240
45	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala
					245					250					255	
	Thr	Val	Lys	Ile	Arg	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys
50				260					265					270		
	Gln															

<210> 16

<211> 273

55 <212> PRT

<213> Neisseria meningitidis

<400> 16

EP 2 261 239 B1

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5	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly
				20					25					30		
	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys
			35					40					45			
10	Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys
		50					55					60				
	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp
15	65					70				75						80
	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp
					85					90					95	
20	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Thr	Ile	Thr	Leu	Ala	Ser
				100					105					110		
	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asn	His	Ser	Ala	Val	Val	Ala	Leu
			115					120					125			
25	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn
		130					135					140				
	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe
30	145					150					155					160
	Asn	Gln	Leu	Pro	Asp	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser
					165					170					175	
35	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	His	Tyr	Ser	Ile	Asp	Phe	Thr	Lys
				180					185					190		
	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu	His	Leu	Lys	Thr	Pro	Glu	Gln	Asn
			195					200					205			
40	Val	Glu	Leu	Ala	Ser	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala
		210					215					220				
	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Gly	Glu	Glu	Lys	Gly	Thr	Tyr
	225					230					235					240
45	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala
					245					250					255	
	Thr	Val	Lys	Ile	Arg	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys
50				260					265					270		
	Gln															

<210> 17

<211> 273

55 <212> PRT

<213> Neisseria meningitidis

<400> 17

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	Met	Asn	Arg	Thr	Ala	Phe	Cys	Cys	Leu	Ser	Leu	Thr	Thr	Ala	Leu	Ile
	1				5					10					15	
5	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly
				20					25					30		
	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys
			35					40					45			
10	Gly	Leu	Gln	Ser	Leu	Met	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys
	50						55					60				
	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp
15	65					70					75					80
	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp
					85					90					95	
	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Thr	Ile	Thr	Leu	Ala	Ser
20				100					105					110		
	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asn	His	Ser	Ala	Val	Val	Ala	Leu
			115					120					125			
25	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn
	130						135					140				
	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe
30	145					150					155					160
	Asn	Gln	Leu	Pro	Asp	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser
					165					170					175	
	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	His	Tyr	Ser	Ile	Asp	Phe	Thr	Lys
35				180					185					190		
	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu	His	Leu	Lys	Thr	Pro	Glu	Gln	Asn
			195					200					205			
40	Val	Glu	Leu	Ala	Ser	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala
	210						215					220				
	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Gly	Glu	Glu	Lys	Gly	Thr	Tyr
	225					230					235					240
45	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala
					245					250					255	
	Thr	Val	Lys	Ile	Arg	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys
50				260					265					270		
	Gln															

<210> 18

<211> 281

55 <212> PRT

<213> Neisseria meningitidis

<400> 18

EP 2 261 239 B1

	Met	Asn	Arg	Thr	Ala	Phe	Cys	Cys	Leu	Ser	Leu	Thr	Thr	Ala	Leu	Ile
	1				5					10					15	
5	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Val
				20					25					30		
	Ala	Ala	Asp	Ile	Gly	Thr	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu
			35					40					45			
10	Asp	His	Lys	Asp	Lys	Gly	Leu	Lys	Ser	Leu	Thr	Leu	Glu	Asp	Ser	Ile
	50						55					60				
	Pro	Gln	Asn	Gly	Thr	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	Thr
	65					70				75						80
15	Phe	Lys	Ala	Gly	Asp	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys
				85					90						95	
	Asn	Asp	Lys	Ile	Ser	Arg	Phe	Asp	Phe	Val	Gln	Lys	Ile	Glu	Val	Asp
20				100					105					110		
	Gly	Gln	Thr	Ile	Thr	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln
			115					120					125			
25	Asn	His	Ser	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro
		130					135					140				
	Asp	Lys	Thr	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly
	145					150					155					160
30	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Gly	Gly	Lys	Ala
				165					170						175	
	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu
35				180					185					190		
	His	Tyr	Ser	Ile	Asp	Phe	Thr	Lys	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu
			195					200					205			
40	His	Leu	Lys	Thr	Leu	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu
		210					215					220				
	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr
	225					230					235					240
45	Gly	Ser	Glu	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg
				245						250					255	
	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val
				260					265					270		
50	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	Gln							
			275					280								

<210> 19

<211> 281

<212> PRT

<213> Neisseria meningitidis

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<400> 19

5	Met	Asn	Arg	Thr	Ala	Phe	Cys	Cys	Leu	Phe	Leu	Thr	Thr	Ala	Leu	Ile	1	5	10	15
	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Val	20	25	30	
10	Ala	Ala	Asp	Ile	Gly	Thr	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	35	40	45	
	Asp	His	Lys	Asp	Lys	Gly	Leu	Lys	Ser	Leu	Thr	Leu	Glu	Asp	Ser	Ile	50	55	60	
15	Pro	Gln	Asn	Gly	Thr	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	Thr	65	70	75	80
	Phe	Lys	Ala	Gly	Asp	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	85	90	95	
20	Asn	Asp	Lys	Ile	Ser	Arg	Phe	Asp	Phe	Val	Gln	Lys	Ile	Glu	Val	Asp	100	105	110	
	Gly	Gln	Thr	Ile	Thr	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	115	120	125	
25	Asp	His	Ser	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	130	135	140	
30	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	145	150	155	160
	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Gly	Gly	Lys	Ala	165	170	175	
35	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	180	185	190	
	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	Ala	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	195	200	205	
40	His	Leu	Lys	Thr	Pro	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	210	215	220	
45	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	225	230	235	240
	Gly	Ser	Glu	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	245	250	255	
50	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	260	265	270	
	His	Glu	Ile	Ser	Ile	Ala	Gly	Lys	Gln								275	280		

55 <210> 20
 <211> 281
 <212> PRT
 <213> Neisseria meningitidis

EP 2 261 239 B1

<400> 20

5	Met	Asn	Arg	Thr	Ala	Phe	Cys	Cys	Leu	Phe	Leu	Thr	Thr	Ala	Leu	Ile	1	5	10	15
	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Ser	Gly	Gly	Val	20	25	30	
10	Ala	Ala	Asp	Ile	Gly	Thr	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Thr	Pro	Leu	35	40	45	
	Asp	His	Lys	Asp	Lys	Gly	Leu	Lys	Ser	Leu	Thr	Leu	Glu	Asp	Ser	Ile	50	55	60	
15	Pro	Gln	Asn	Gly	Thr	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	Thr	65	70	75	80
	Phe	Lys	Ala	Gly	Asp	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	85	90	95	
20	Asn	Asp	Lys	Ile	Ser	Arg	Phe	Asp	Phe	Val	Gln	Lys	Ile	Glu	Val	Asp	100	105	110	
	Gly	Gln	Thr	Ile	Thr	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	115	120	125	
25	Asp	His	Ser	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	130	135	140	
30	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	145	150	155	160
	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Gly	Gly	Lys	Ala	165	170	175	
35	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	180	185	190	
	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	Ala	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	195	200	205	
40	His	Leu	Lys	Thr	Pro	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	210	215	220	
45	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	225	230	235	240
	Gly	Ser	Glu	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	245	250	255	
50	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	260	265	270	
	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	Gln								275	280		

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<210> 21

<211> 279

<212> PRT

EP 2 261 239 B1

<213> Neisseria meningitidis

<400> 21

5	Met	Asn	Arg	Thr	Ala	Phe	Cys	Cys	Leu	Phe	Leu	Thr	Thr	Ala	Leu	Ile	1	5	10	15
	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Ile	Ala	Ala	20	25	30	
10	Asp	Ile	Gly	Thr	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	35	40	45	
	Lys	Asp	Lys	Gly	Leu	Lys	Ser	Leu	Thr	Leu	Glu	Asp	Ser	Ile	Pro	Gln	50	55	60	
15	Asn	Gly	Thr	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Phe	Lys	65	70	75	80
20	Ala	Gly	Asp	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	85	90	95	
	Lys	Ile	Ser	Arg	Phe	Asp	Phe	Val	Gln	Lys	Ile	Glu	Val	Asp	Gly	Gln	100	105	110	
25	Thr	Ile	Thr	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	115	120	125	
	Ser	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	130	135	140	
30	Ile	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	145	150	155	160
	Gly	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Gly	Gly	Lys	Ala	Glu	Tyr	165	170	175	
35	His	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	180	185	190	
40	Thr	Ile	Asp	Phe	Ala	Ala	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	Leu	195	200	205	
	Lys	Thr	Pro	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala	210	215	220	
45	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	225	230	235	240
	Glu	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	245	250	255	
50	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	260	265	270	
55	Ile	Gly	Ile	Ala	Gly	Lys	Gln										275			

<210> 22

EP 2 261 239 B1

<211> 281

<212> PRT

<213> Neisseria meningitidis

5 <400> 22

	Met	Asn	Arg	Thr	Thr	Phe	Cys	Cys	Leu	Ser	Leu	Thr	Thr	Ala	Leu	Ile	
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10	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Val	
				20					25					30			
	Ala	Ala	Asp	Ile	Gly	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	
			35					40					45				
15	Asp	His	Lys	Asp	Lys	Gly	Leu	Lys	Ser	Leu	Thr	Leu	Glu	Asp	Ser	Ile	
	50						55					60					
	Pro	Gln	Asn	Gly	Thr	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	Thr	
20	65					70					75					80	
	Phe	Lys	Ala	Gly	Gly	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	
					85					90					95		
25	Asn	Asp	Lys	Ile	Ser	Arg	Phe	Asp	Phe	Val	Gln	Lys	Ile	Glu	Val	Asp	
				100					105					110			
	Gly	Gln	Thr	Ile	Thr	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	
			115					120					125				
30	Asp	His	Ser	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	
	130						135					140					
	Asp	Lys	Thr	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	
35	145					150					155					160	
	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Gly	Gly	Lys	Ala	
					165					170					175		
40	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	
				180					185					190			
	His	Tyr	Thr	Ile	Asp	Phe	Thr	Asn	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu	
			195					200					205				
45	His	Leu	Lys	Thr	Pro	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ser	Ala	Glu	Leu	
	210						215					220					
	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	
	225					230					235					240	
50	Gly	Ser	Glu	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	
					245					250					255		
	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	
55				260				265						270			
	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	Gln								
			275					280									

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<210> 23
 <211> 279
 <212> PRT
 <213> Neisseria meningitidis

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<400> 23

10

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Ser Asp Arg Leu Gln Gln Arg Arg Gly Gly Gly Gly Gly Val Ala Ala
 20 25 30

15

Asp Ile Gly Thr Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His
 35 40 45

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

20

Asn Gly Thr Leu Thr Leu Ser Ala Gln Gly Ala Glu Lys Thr Phe Lys
 65 70 75 80

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

25

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

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

30

Ser Ala Val Val Ala Leu Arg Ile Glu Lys Ile Asn Asn Pro Asp Lys
 130 135 140

35

Ile Asp Ser Leu Ile Asn Gln Arg Ser Phe Leu Val Ser Asp Leu Gly
 145 150 155 160

Gly Glu His Thr Ala Phe Asn Gln Leu Pro Asp Gly Lys Ala Glu Tyr
 165 170 175

40

His Gly Lys Ala Phe Ser Ser Asp Asp Ala Asp Gly Lys Leu Thr Tyr
 180 185 190

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

45

50

55

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	Lys	Thr	Pro	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ser	Ala	Glu	Leu	Lys	Ala
	210						215					220				
5	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Gly
	225					230					235				240	
	Glu	Glu	Lys	Gly	Thr	Tyr	Arg	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln
					245					250					255	
10	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu
				260					265					270		
	Ile	Gly	Ile	Ala	Asp	Lys	Gln									
15				275												
	<210> 24															
	<211> 255															
	<212> PRT															
	<213> Neisseria meningitidis															
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45																
50																
55																

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	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly	Ala	Gly	Leu	
	1				5					10					15		
5	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				
10	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	
15	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	
20				100					105					110			
	Gln	Ile	Gln	Asp	Ser	Glu	His	Ser	Gly	Lys	Met	Val	Ala	Lys	Arg	Gln	
			115					120					125				
25	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	
30	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	
35				180					185					190			
	Leu	Ala	Ala	Ala	Asp	Ile	Lys	Pro	Asp	Gly	Lys	Arg	His	Ala	Val	Ile	
			195					200					205				
40	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	
45	Lys	Thr	Val	Asn	Gly	Ile	Arg	His	Ile	Gly	Leu	Ala	Ala	Lys	Gln		
					245					250					255		

<210> 25

<211> 255

50 <212> PRT

<213> Neisseria meningitidis

<400> 25

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				20					25					30		
	Ser	Leu	Met	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys	Leu	Lys	Leu
			35					40					45			
10	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
15	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
20				100					105					110		
	Gln	Val	Gln	Asp	Ser	Glu	Asp	Ser	Gly	Lys	Met	Val	Ala	Lys	Arg	Gln
			115					120					125			
25	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
30	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
35				180					185					190		
	Leu	Ala	Thr	Ala	Tyr	Ile	Lys	Pro	Asp	Glu	Lys	His	His	Ala	Val	Ile
			195					200					205			
40	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
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<210> 26

<211> 255

50 <212> PRT

<213> Neisseria meningitidis

<400> 26

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EP 2 261 239 B1

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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				
10	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	
15	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	
20				100					105					110			
	Gln	Val	Gln	Asp	Ser	Glu	Asp	Ser	Gly	Lys	Met	Val	Ala	Lys	Arg	Gln	
			115					120					125				
25	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	
30	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	
35				180					185					190			
	Leu	Ala	Thr	Ala	Tyr	Ile	Lys	Pro	Asp	Glu	Lys	Arg	His	Ala	Val	Ile	
			195					200					205				
40	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	
45	Glu	Thr	Ala	Asn	Gly	Ile	His	His	Ile	Gly	Leu	Ala	Ala	Lys	Gln		
					245					250					255		

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<211> 255

50 <212> PRT

<213> Neisseria meningitidis

<400> 27

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EP 2 261 239 B1

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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			
10	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
15	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
20				100					105					110		
	Gln	Glu	Gln	Asp	Pro	Glu	His	Ser	Gly	Lys	Met	Val	Ala	Lys	Arg	Arg
			115					120					125			
25	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
30	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
35				180					185					190		
	Leu	Ala	Thr	Ala	Tyr	Ile	Lys	Pro	Asp	Glu	Lys	His	His	Ala	Val	Ile
			195					200						205		
40	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
45	Glu	Thr	Ala	Asn	Gly	Ile	His	His	Ile	Gly	Leu	Ala	Ala	Lys	Gln	
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<213> Neisseria meningitidis

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EP 2 261 239 B1

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5	Ile	Gly	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys
				20					25					30		
	Asp	Lys	Gly	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn
			35					40					45			
10	Glu	Lys	Leu	Lys	Leu	Ala	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
15																
	Phe	Asp	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu
					85					90					95	
20	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	Val	Gln	Asp	Ser	Glu	Asp	Ser	Gly	Lys	Met
			115					120					125			
25	Val	Ala	Lys	Arg	Gln	Phe	Arg	Ile	Gly	Asp	Ile	Ala	Gly	Glu	His	Thr
		130					135					140				
	Ser	Phe	Asp	Lys	Leu	Pro	Lys	Gly	Gly	Ser	Ala	Thr	Tyr	Arg	Gly	Thr
	145					150					155					160
30																
	Ala	Phe	Gly	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp
					165					170					175	
	Phe	Ala	Val	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	Leu	Lys	Ser	Pro
35				180					185					190		
	Glu	Leu	Asn	Val	Asp	Leu	Ala	Ala	Ala	Tyr	Ile	Lys	Pro	Asp	Lys	Lys
			195					200					205			
40	Arg	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	Gly	Gln	Ala	Gln	Glu	Val	Ala
	225					230					235					240
45																
	Gly	Ser	Ala	Glu	Val	Glu	Thr	Ala	Asn	Gly	Ile	His	His	Ile	Gly	Leu
					245					250					255	
	Ala	Ala	Lys	Gln												
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EP 2 261 239 B1

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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				
10	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	
15	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	
20				100					105					110			
	Gln	Val	Gln	Asp	Ser	Glu	His	Ser	Gly	Lys	Met	Val	Ala	Lys	Arg	Gln	
			115					120					125				
25	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	
30	145					150					155					160	
	Asp	Ala	Ser	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	Ala	Lys	Gln	
					165					170					175		
35	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				
40	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	
45	225					230					235					240	
	Glu	Thr	Ala	Asn	Gly	Ile	Arg	His	Ile	Gly	Leu	Ala	Ala	Lys	Gln		
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<213> Neisseria meningitidis

<400> 30

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EP 2 261 239 B1

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5	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				
10	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	
15	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	
20				100					105					110			
	Gln	Val	Gln	Asp	Ser	Glu	His	Ser	Gly	Lys	Met	Val	Ala	Lys	Arg	Gln	
			115					120					125				
25	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	
30	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	
35				180					185					190			
	Leu	Ala	Ala	Ser	Asp	Ile	Lys	Pro	Asp	Lys	Lys	Arg	His	Ala	Val	Ile	
			195					200					205				
40	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	
45	Glu	Thr	Ala	Asn	Gly	Ile	Arg	His	Ile	Gly	Leu	Ala	Ala	Lys	Gln		
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<213> Neisseria meningitidis

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EP 2 261 239 B1

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				20					25					30			
	Ser	Leu	Met	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys	Leu	Lys	Leu	
			35					40					45				
10	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	
15	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	
20				100					105					110			
	Gln	Val	Gln	Asp	Ser	Glu	His	Ser	Gly	Lys	Met	Val	Ala	Lys	Arg	Gln	
				115					120				125				
25	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	
30	Asp	Ala	Gly	Gly	Lys	Leu	Ile	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			
35	Leu	Ala	Ala	Ala	Tyr	Ile	Lys	Pro	Asp	Glu	Lys	His	His	Ala	Val	Ile	
				195				200					205				
	Ser	Gly	Ser	Val	Leu	Tyr	Asn	Gln	Ala	Glu	Lys	Gly	Ser	Tyr	Ser	Leu	
40		210					215					220					
	Gly	Ile	Phe	Gly	Gly	Lys	Ala	Gln	Glu	Val	Ala	Gly	Ser	Ala	Glu	Val	
	225					230					235					240	
45	Lys	Thr	Val	Asn	Gly	Ile	Arg	His	Ile	Gly	Leu	Ala	Ala	Lys	Gln		
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EP 2 261 239 B1

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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				
10	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
15	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
20				100					105					110		
	Gln	Glu	Gln	Asp	Leu	Glu	His	Ser	Gly	Lys	Met	Val	Ala	Lys	Arg	Arg
			115					120					125			
25	Phe	Arg	Ile	Gly	Asp	Ile	Ala	Gly	Glu	His	Thr	Ser	Phe	Asp	Lys	Leu
	130						135					140				
	Arg	Glu	Gly	Gly	Arg	Ala	Thr	Tyr	Arg	Gly	Thr	Ala	Phe	Gly	Ser	Asp
	145					150					155					160
30	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	Ala	Lys	Gln
					165					170					175	
	Gly	Tyr	Gly	Lys	Ile	Glu	His	Leu	Lys	Ser	Pro	Glu	Leu	Asn	Val	Asp
35				180					185					190		
	Leu	Ala	Ala	Ala	Asp	Ile	Lys	Pro	Asp	Glu	Lys	His	His	Ala	Val	Ile
			195					200					205			
40	Ser	Gly	Ser	Val	Leu	Tyr	Asn	Gln	Asp	Glu	Lys	Gly	Ser	Tyr	Ser	Leu
	210						215					220				
	Gly	Ile	Phe	Gly	Gly	Glu	Ala	Gln	Glu	Val	Ala	Gly	Ser	Ala	Glu	Val
	225					230					235					240
45	Lys	Thr	Ala	Asn	Gly	Ile	His	His	Ile	Gly	Leu	Ala	Ala	Lys	Gln	
					245					250					255	

<210> 33

<211> 254

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<213> Neisseria meningitidis

<400> 33

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EP 2 261 239 B1

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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			
10	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
15	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
20				100					105					110		
	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser
			115					120					125			
25	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
30	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
35				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
40		210					215					220				
	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys
	225					230					235					240
45	Ile	Gly	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	Gln		
					245					250						

<210> 34

<211> 254

50 <212> PRT

<213> Neisseria meningitidis

<400> 34

55	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	Ser	Leu	Gln
				20					25					30		
5	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				
10	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	
15	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
20			115					120					125			
	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu
	130						135					140				
25	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	
30	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
35			195					200					205			
	Gly	Asp	Thr	Arg	Tyr	Gly	Gly	Glu	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala
	210						215					220				
40	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						

45 <210> 35
 <211> 254
 <212> PRT
 <213> Neisseria meningitidis

50 <400> 35

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EP 2 261 239 B1

	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly	Ala	Gly	Leu	
	1				5					10					15		
5	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				
10	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	
15	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	
20				100					105					110			
	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	
			115					120					125				
25	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	
30	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	
35				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	
40		210					215					220					
	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	
	225					230					235					240	
45	Ile	Arg	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	Gln			
					245					250							

<210> 36

<211> 254

50 <212> PRT

<213> Neisseria meningitidis

<400> 36

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EP 2 261 239 B1

	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly	Ala	Gly	Leu	
	1				5					10					15		
5	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				
10	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	
15	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	
20				100					105					110			
	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	
			115					120					125				
25	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	
30	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	
35				180					185					190			
	Ala	Ser	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	
			195					200					205				
40	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	
45	Ile	Arg	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	Gln			
					245					250							

<210> 37

<211> 254

50 <212> PRT

<213> Neisseria meningitidis

<400> 37

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EP 2 261 239 B1

	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly	Ala	Gly	Leu	
	1				5					10					15		
5	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				
10	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	
15	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	
20				100					105					110			
	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	
			115					120					125				
25	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	
	130						135					140					
	Pro	Gly	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	
	145					150					155					160	
30	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	
35				180					185					190			
	Ala	Ser	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	
			195					200					205				
40	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	
45	Ile	Arg	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	Gln			
					245					250							

<210> 38

<211> 254

50 <212> PRT

<213> Neisseria meningitidis

<400> 38

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EP 2 261 239 B1

	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly	Ala	Gly	Leu	
	1				5					10					15		
5	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				
10	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	
15	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	
20				100					105					110			
	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	
			115					120					125				
25	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	
30	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			
35	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	
40		210					215					220					
	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	
	225					230					235					240	
45	Ile	Arg	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	Gln			
					245					250							

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<211> 254

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<213> Neisseria meningitidis

<400> 39

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EP 2 261 239 B1

	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly	Ala	Gly	Leu
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5	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			
10	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
15	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
20				100					105					110		
	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser
			115					120					125			
25	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
30	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
35				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
40		210					215					220				
	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys
	225					230					235					240
45	Ile	Arg	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	Gln		
					245					250						

<210> 40

<211> 254

50 <212> PRT

<213> Neisseria meningitidis

<400> 40

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	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly	Ala	Gly	Leu
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5	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys	Gly	Leu	Gln
				20					25					30		
	Ser	Leu	Met	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys	Leu	Lys	Leu
			35					40					45			
10	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
15	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
20				100					105					110		
	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser
			115					120					125			
25	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
30	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
35				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
40			210				215					220				
	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys
	225					230					235					240
45	Ile	Arg	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	Gln		
					245					250						
	<210> 41															
	<211> 262															
50	<212> PRT															
	<213> Neisseria meningitidis															
	<400> 41															
55	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp
	1				5					10					15	

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	Ile	Gly	Thr	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	
				20					25					30			
5	Asp	Lys	Gly	Leu	Lys	Ser	Leu	Thr	Leu	Glu	Asp	Ser	Ile	Pro	Gln	Asn	
			35					40					45				
	Gly	Thr	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Phe	Lys	Ala	
		50					55					60					
10	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	Val	Gln	Lys	Ile	Glu	Val	Asp	Gly	Gln	Thr	
				85					90						95		
15	Ile	Thr	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asn	His	Ser	
			100					105						110			
	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Thr	
20			115					120					125				
	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	
		130				135						140					
25	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Gly	Gly	Lys	Ala	Glu	Tyr	His	
	145					150					155					160	
	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	His	Tyr	Ser	
				165					170					175			
30	Ile	Asp	Phe	Thr	Lys	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu	His	Leu	Lys	
			180						185					190			
	Thr	Leu	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala	Asp	
35			195					200					205				
	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	Glu	
		210					215					220					
40	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	
	225					230					235					240	
	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	Ile	
				245						250					255		
45	Gly	Ile	Ala	Gly	Lys	Gln											
				260													

<210> 42

<211> 262

50 <212> PRT

<213> Neisseria meningitidis

<400> 42

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EP 2 261 239 B1

	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	
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5	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	Pro	Gln	Asn	
			35					40					45				
10	Gly	Thr	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Phe	Lys	Ala	
		50					55					60					
	Gly	Asp	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	
15	65					70					75					80	
	Ile	Ser	Arg	Phe	Asp	Phe	Val	Gln	Lys	Ile	Glu	Val	Asp	Gly	Gln	Thr	
					85					90					95		
	Ile	Thr	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	
20				100					105					110			
	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	
			115					120					125				
25	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	
		130					135					140					
	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Gly	Gly	Lys	Ala	Glu	Tyr	His	
	145					150					155					160	
30	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	
					165					170					175		
	Ile	Asp	Phe	Ala	Ala	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	Leu	Lys	
35				180					185					190			
	Thr	Pro	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala	Asp	
			195					200					205				
	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	Glu	
40		210					215					220					
	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	
	225					230					235					240	
45	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	Ile	
					245					250					255		
	Ser	Ile	Ala	Gly	Lys	Gln											
				260													

<210> 43

<211> 262

<212> PRT

<213> Neisseria meningitidis

<400> 43

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	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Ser	Gly	Gly	Val	Ala	Ala	Asp	
	1				5					10					15		
5	Ile	Gly	Thr	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Thr	Pro	Leu	Asp	His	Lys	
				20					25					30			
	Asp	Lys	Gly	Leu	Lys	Ser	Leu	Thr	Leu	Glu	Asp	Ser	Ile	Pro	Gln	Asn	
			35					40					45				
10	Gly	Thr	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	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	
15																	
	Ile	Ser	Arg	Phe	Asp	Phe	Val	Gln	Lys	Ile	Glu	Val	Asp	Gly	Gln	Thr	
				85						90					95		
20	Ile	Thr	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	
				100					105					110			
	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	
			115					120					125				
25	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	
		130					135						140				
	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Gly	Gly	Lys	Ala	Glu	Tyr	His	
	145					150					155					160	
30																	
	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	
					165					170					175		
	Ile	Asp	Phe	Ala	Ala	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	Leu	Lys	
35				180					185					190			
	Thr	Pro	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala	Asp	
			195					200					205				
40	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	Glu	
		210					215					220					
	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	
	225					230					235					240	
45																	
	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	Ile	
					245					250					255		
	Gly	Ile	Ala	Gly	Lys	Gln											
				260													
50																	

<210> 44

<211> 260

<212> PRT

<213> Neisseria meningitidis

55

<400> 44

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	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Ile	Ala	Ala	Asp	Ile	Gly	
	1				5					10					15		
5	Thr	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys	
				20					25					30			
	Gly	Leu	Lys	Ser	Leu	Thr	Leu	Glu	Asp	Ser	Ile	Pro	Gln	Asn	Gly	Thr	
			35					40					45				
10	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Phe	Lys	Ala	Gly	Asp	
		50					55					60					
	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Ile	Ser	
15	65					70					75					80	
	Arg	Phe	Asp	Phe	Val	Gln	Lys	Ile	Glu	Val	Asp	Gly	Gln	Thr	Ile	Thr	
					85					90					95		
	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	Ala	Val	
20				100					105					110			
	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	
			115					120					125				
25	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	
		130					135					140					
	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Gly	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	
	145					150					155					160	
30	Ala	Phe	Ser	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	Thr	Pro	
35				180					185					190			
	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	
			195					200					205				
40	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	Glu	Glu	Lys	
		210					215					220					
	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	
	225					230					235					240	
45	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	
					245					250					255		
	Ala	Gly	Lys	Gln													
50				260													

<210> 45

<211> 262

<212> PRT

<213> Neisseria meningitidis

<400> 45

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	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	
	1				5					10					15		
5	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	Pro	Gln	Asn	
			35					40					45				
10	Gly	Thr	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Phe	Lys	Ala	
		50					55						60				
	Gly	Gly	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	
	65					70					75					80	
15	Ile	Ser	Arg	Phe	Asp	Phe	Val	Gln	Lys	Ile	Glu	Val	Asp	Gly	Gln	Thr	
					85					90					95		
	Ile	Thr	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	
20				100					105					110			
	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Thr	
				115				120					125				
25	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	
		130					135						140				
	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Gly	Gly	Lys	Ala	Glu	Tyr	His	
	145					150					155					160	
30	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	His	Tyr	Thr	
					165					170					175		
	Ile	Asp	Phe	Thr	Asn	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu	His	Leu	Lys	
35				180					185					190			
	Thr	Pro	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ser	Ala	Glu	Leu	Lys	Ala	Asp	
			195					200					205				
40	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	Glu	
		210					215					220					
	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	
	225					230					235					240	
45	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	Ile	
					245					250					255		
	Gly	Ile	Ala	Gly	Lys	Gln											
50				260													

<210> 46

<211> 12

<212> PRT

<213> Neisseria gonorrhoeae

<400> 46

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1 5 10

5 <210> 47
<211> 31
<212> DNA
<213> Artificial Sequence

10 <220>
<223> Amplification primer

<400> 47
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15 <210> 48
<211> 27
<212> DNA
<213> Artificial Sequence

20 <220>
<223> Amplification primer

<400> 48
25 ccgctcgag ttgctggcg gcaaggc

<210> 49
<211> 65
<212> DNA
30 <213> Artificial Sequence

<220>
<223> Amplification primer

35 <400> 49

cgcgatccc atatgggccc tgattctgac cgctgcagc agcggagggt cgccgccgac 60
atcgg 65

40 <210> 50
<211> 28
<212> DNA
<213> Artificial Sequence

45 <220>
<223> Amplification primer

<400> 50
50 ccgctcgag ctgttgccg gcatgcc 28

<210> 51
<211> 65
<212> DNA
55 <213> Artificial Sequence

<220>
<223> Amplification primer

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<400> 51

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	gtcgc	65

<210> 52

<211> 28

<212> DNA

10 <213> Artificial Sequence

<220>

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15	<400> 52	
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<210> 53

<211> 37

20 <212> DNA

<213> Artificial Sequence

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25	<400> 53	
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<210> 54

30 <211> 30

<212> DNA

<213> Artificial Sequence

<220>

35 <223> Amplification primer

	<400> 54	
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40 <210> 55

<211> 17

<212> DNA

<213> Artificial Sequence

45 <220>

<223> Amplification primer

	<400> 55	
	gacctgcctc attgatg	17

50 <210> 56

<211> 25

<212> DNA

<213> Artificial Sequence

55 <220>

<223> Amplification primer

<400> 56
 cggtaaatta tcgtgttcgg acggc 25

5 <210> 57
 <211> 21
 <212> DNA
 <213> Artificial Sequence

10 <220>
 <223> Amplification primer

<400> 57
 caaatcgaag tggacgggca g 21

15 <210> 58
 <211> 23
 <212> DNA
 <213> Artificial Sequence

20 <220>
 <223> Amplification primer

<400> 58
 tggtcgattt tgccgtttcc ctg 23

25 <210> 59
 <211> 24
 <212> DNA
 <213> Artificial Sequence

30 <220>
 <223> Amplification primer

<400> 59
 gctctagacc agccaggcgc atac 24

35 <210> 60
 <211> 29
 <212> DNA
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40 <220>
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45 <400> 60
 tcccccgggg acggcathtt gttacagg 29

50 <210> 61
 <211> 28
 <212> DNA
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55 <220>
 <223> Amplification primer

<400> 61
 tcccccgggc gccaaagcaat aaccattg 28

<210> 62
 <211> 28
 <212> DNA
 <213> Artificial Sequence
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 <400> 62
 10 cccgctcgag cagcgatcg aaccatgc 28
 <210> 63
 <211> 27
 <212> DNA
 15 <213> Artificial Sequence
 <220>
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 20 <400> 63
 gctctagatt cttccaag aactctc 27
 <210> 64
 <211> 26
 25 <212> DNA
 <213> Artificial Sequence
 <220>
 <223> Amplification primer
 30 <400> 64
 tccccgggc cggatcatc caccac 26
 <210> 65
 35 <211> 26
 <212> DNA
 <213> Artificial Sequence
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 40 <223> Amplification primer
 <400> 65
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 45 <210> 66
 <211> 28
 <212> DNA
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 50 <220>
 <223> Amplification primer
 <400> 66
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 <210> 67
 <211> 6
 <212> PRT

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<213> Neisseria meningitidis

<400> 67

5 Leu Asn Gln Ile Val Lys
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<210> 68

<211> 20

10 <212> PRT

<213> Neisseria meningitidis

<400> 68

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Leu Thr Ala Cys
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<210> 69

<211> 240

<212> DNA

<213> Neisseria meningitidis

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<400> 69

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ttcggacgac atttgatttt tgcttctttg acctgcctca ttgatgcggt atgcaaaaaa 120
agataccata accaaaatgt ttatatatta tctattctgc gtatgactag gagtaaacct 180
gtgaatcgaa ctgccttctg ctgcctttct ctgaccactg ccctgattct gaccgcctgc 240

<210> 70

35 <211> 5

<212> PRT

<213> Neisseria meningitidis

<400> 70

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Thr Arg Ser Lys Pro
1 5

<210> 71

45 <211> 6

<212> PRT

<213> Neisseria meningitidis

<400> 71

50

Thr Arg Ser Lys Pro Val
1 5

55 <210> 72

<211> 7

<212> PRT

<213> Neisseria meningitidis

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<400> 72

Pro Ser Glu Pro Pro Phe Gly
1 5

5

<210> 73

<211> 4

<212> PRT

<213> Artificial Sequence

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<220>

<223> Gly4 tetrapeptide

<400> 73

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Gly Gly Gly Gly
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<210> 74

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<211> 19

<212> DNA

<213> Neisseria meningitidis

<400> 74

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cataaccaaa atgtttata 19

<210> 75

<211> 19

<212> DNA

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<213> Escherichia coli

<400> 75

gataatgata atcattatc 19

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<210> 76

<211> 179

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<213> Neisseria meningitidis

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<400> 76

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	1				5					10					15	
5	Asp	Arg	Arg	Thr	Thr	Gly	Ala	Gln	Thr	Asp	Asp	Asn	Val	Met	Ala	Leu
				20					25					30		
	Arg	Ile	Glu	Thr	Thr	Ala	Arg	Ser	Tyr	Leu	Arg	Gln	Asn	Asn	Gln	Thr
			35					40					45			
10	Lys	Gly	Tyr	Thr	Pro	Gln	Ile	Ser	Val	Val	Gly	Tyr	Asn	Arg	His	Leu
	50						55					60				
	Leu	Leu	Leu	Gly	Gln	Val	Ala	Thr	Glu	Gly	Glu	Lys	Gln	Phe	Val	Gly
	65					70					75					80
15	Gln	Ile	Ala	Arg	Ser	Glu	Gln	Ala	Ala	Glu	Gly	Val	Tyr	Asn	Tyr	Ile
					85					90					95	
	Thr	Val	Ala	Ser	Leu	Pro	Arg	Thr	Ala	Gly	Asp	Ile	Ala	Gly	Asp	Thr
20				100					105					110		
	Trp	Asn	Thr	Ser	Lys	Val	Arg	Ala	Thr	Leu	Leu	Gly	Ile	Ser	Pro	Ala
			115					120					125			
25	Thr	Gln	Ala	Arg	Val	Lys	Ile	Val	Thr	Tyr	Gly	Asn	Val	Thr	Tyr	Val
	130						135					140				
	Met	Gly	Ile	Leu	Thr	Pro	Glu	Glu	Gln	Ala	Gln	Ile	Thr	Gln	Lys	Val
	145					150					155					160
30	Ser	Thr	Thr	Val	Gly	Val	Gln	Lys	Val	Ile	Thr	Leu	Tyr	Gln	Asn	Tyr
					165					170					175	

Val Gln Arg

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<210> 77

<211> 436

<212> PRT

<213> Artificial Sequence

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<220>

<223> Hybrid meningococcus protein

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<400> 77

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	1				5					10					15	
5	Val	Asp	Arg	Arg	Thr	Thr	Gly	Ala	Gln	Thr	Asp	Asp	Asn	Val	Met	Ala
				20					25					30		
	Leu	Arg	Ile	Glu	Thr	Thr	Ala	Arg	Ser	Tyr	Leu	Arg	Gln	Asn	Asn	Gln
			35					40					45			
10	Thr	Lys	Gly	Tyr	Thr	Pro	Gln	Ile	Ser	Val	Val	Gly	Tyr	Asn	Arg	His
		50					55					60				
	Leu	Leu	Leu	Leu	Gly	Gln	Val	Ala	Thr	Glu	Gly	Glu	Lys	Gln	Phe	Val
15	65					70					75					80
	Gly	Gln	Ile	Ala	Arg	Ser	Glu	Gln	Ala	Ala	Glu	Gly	Val	Tyr	Asn	Tyr
					85					90					95	
20	Ile	Thr	Val	Ala	Ser	Leu	Pro	Arg	Thr	Ala	Gly	Asp	Ile	Ala	Gly	Asp
				100					105					110		
	Thr	Trp	Asn	Thr	Ser	Lys	Val	Arg	Ala	Thr	Leu	Leu	Gly	Ile	Ser	Pro
			115					120					125			
25	Ala	Thr	Gln	Ala	Arg	Val	Lys	Ile	Val	Thr	Tyr	Gly	Asn	Val	Thr	Tyr
		130					135					140				
	Val	Met	Gly	Ile	Leu	Thr	Pro	Glu	Glu	Gln	Ala	Gln	Ile	Thr	Gln	Lys
30	145					150					155					160
	Val	Ser	Thr	Thr	Val	Gly	Val	Gln	Lys	Val	Ile	Thr	Leu	Tyr	Gln	Asn
					165					170					175	
	Tyr	Val	Gln	Arg	Gly	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly
35				180				185						190		
	Thr	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys
			195					200					205			
40	Gly	Leu	Lys	Ser	Leu	Thr	Leu	Glu	Asp	Ser	Ile	Pro	Gln	Asn	Gly	Thr
		210					215					220				
	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Phe	Lys	Ala	Gly	Asp
	225					230					235					240
45	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Ile	Ser
					245					250					255	

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55

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	Arg	Phe	Asp	Phe	Val	Gln	Lys	Ile	Glu	Val	Asp	Gly	Gln	Thr	Ile	Thr
				260					265					270		
5	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asn	His	Ser	Ala	Val
			275					280					285			
	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Thr	Asp	Ser
		290					295					300				
10	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His
	305					310					315					320
	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Gly	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys
				325						330					335	
15	Ala	Phe	Ser	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	His	Tyr	Ser	Ile	Asp
				340					345					350		
	Phe	Thr	Lys	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu	His	Leu	Lys	Thr	Leu
20			355					360					365			
	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys
		370					375					380				
25	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	Glu	Glu	Lys
	385					390					395					400
	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala
				405					410						415	
30	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	Ile	Gly	Ile
				420					425					430		
	Ala	Gly	Lys	Gln												
			435													
35	<210> 78															
	<211> 13															
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	<213> Artificial Sequence															
40	<220>															
	<223> Linker															
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50	<210> 79															
	<211> 508															
	<212> PRT															
	<213> Artificial Sequence															
55	<220>															
	<223> Tandem meningococcus protein															
	<400> 79															

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Val Ala Ala Asp Ile Gly Ala Gly Leu Ala Asp Ala Leu Thr Ala Pro
1 5 10 15

5 Leu Asp His Lys Asp Lys Gly Leu Gln Ser Leu Thr Leu Asp Gln Ser
20 25 30

10

15

20

25

30

35

40

45

50

55

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	Val	Arg	Lys	Asn	Glu	Lys	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	
			35					40					45				
5	Thr	Tyr	Gly	Asn	Gly	Asp	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	
		50					55					60					
	Lys	Val	Ser	Arg	Phe	Asp	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	
	65					70					75					80	
10	Leu	Ile	Thr	Leu	Glu	Ser	Gly	Glu	Phe	Gln	Val	Tyr	Lys	Gln	Ser	His	
					85					90					95		
	Ser	Ala	Leu	Thr	Ala	Phe	Gln	Thr	Glu	Gln	Ile	Gln	Asp	Ser	Glu	His	
				100					105					110			
15	Ser	Gly	Lys	Met	Val	Ala	Lys	Arg	Gln	Phe	Arg	Ile	Gly	Asp	Ile	Ala	
			115					120					125				
	Gly	Glu	His	Thr	Ser	Phe	Asp	Lys	Leu	Pro	Glu	Gly	Gly	Arg	Ala	Thr	
	130						135					140					
20	Tyr	Arg	Gly	Thr	Ala	Phe	Gly	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	
	145					150					155					160	
	Tyr	Thr	Ile	Asp	Phe	Ala	Ala	Lys	Gln	Gly	Asn	Gly	Lys	Ile	Glu	His	
					165					170					175		
25	Leu	Lys	Ser	Pro	Glu	Leu	Asn	Val	Asp	Leu	Ala	Ala	Ala	Asp	Ile	Lys	
				180					185					190			
	Pro	Asp	Gly	Lys	Arg	His	Ala	Val	Ile	Ser	Gly	Ser	Val	Leu	Tyr	Asn	
			195					200					205				
30	Gln	Ala	Glu	Lys	Gly	Ser	Tyr	Ser	Leu	Gly	Ile	Phe	Gly	Gly	Lys	Ala	
		210					215					220					
	Gln	Glu	Val	Ala	Gly	Ser	Ala	Glu	Val	Lys	Thr	Val	Asn	Gly	Ile	Arg	
35	225					230					235					240	
	His	Ile	Gly	Leu	Ala	Ala	Lys	Gln	Gly	Ser	Gly	Pro	Asp	Ser	Asp	Arg	
					245					250					255		
40	Leu	Gln	Gln	Arg	Arg	Val	Ala	Ala	Asp	Ile	Gly	Ala	Gly	Leu	Ala	Asp	
				260					265					270			
	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys	Ser	Leu	Gln	Ser	Leu	
			275					280					285				
45	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys	Leu	Lys	Leu	Ala	Ala	
		290					295					300					
	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp	Ser	Leu	Asn	Thr	Gly	
	305					310					315					320	
50	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp	Phe	Ile	Arg	Gln	Ile	
					325					330					335		
	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser	Gly	Glu	Phe	Gln	Ile	
				340					345					350			
55	Tyr	Lys	Gln	Asp	His	Ser	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	
			355					360					365				

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	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	
	370						375					380					
5	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Asp	
	385					390					395					400	
	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Ala	Gly	
					405					410					415		
10	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	Ala	Lys	Gln	Gly	His	Gly	
				420					425					430			
	Lys	Ile	Glu	His	Leu	Lys	Thr	Pro	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	
			435					440					445				
15	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	
	450						455					460					
	Thr	Arg	Tyr	Gly	Ser	Glu	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	
20	465					470					475					480	
	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	
					485				490						495		
25	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	Gln					
				500					505								

<210> 80

<211> 248

<212> PRT

30 <213> Neisseria meningitidis

<400> 80

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	1				5					10					15		
5	Leu	Asp	His	Lys	Asp	Lys	Gly	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	
				20					25					30			
	Val	Arg	Lys	Asn	Glu	Lys	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	
			35				40						45				
10	Thr	Tyr	Gly	Asn	Gly	Asp	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	
		50					55					60					
	Lys	Val	Ser	Arg	Phe	Asp	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	
	65					70					75					80	
15	Leu	Ile	Thr	Leu	Glu	Ser	Gly	Glu	Phe	Gln	Val	Tyr	Lys	Gln	Ser	His	
					85					90					95		
	Ser	Ala	Leu	Thr	Ala	Phe	Gln	Thr	Glu	Gln	Ile	Gln	Asp	Ser	Glu	His	
20				100					105					110			
	Ser	Gly	Lys	Met	Val	Ala	Lys	Arg	Gln	Phe	Arg	Ile	Gly	Asp	Ile	Ala	
			115					120					125				
25	Gly	Glu	His	Thr	Ser	Phe	Asp	Lys	Leu	Pro	Glu	Gly	Gly	Arg	Ala	Thr	
		130					135					140					
	Tyr	Arg	Gly	Thr	Ala	Phe	Gly	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	
	145					150					155					160	
30	Tyr	Thr	Ile	Asp	Phe	Ala	Ala	Lys	Gln	Gly	Asn	Gly	Lys	Ile	Glu	His	
					165					170					175		
	Leu	Lys	Ser	Pro	Glu	Leu	Asn	Val	Asp	Leu	Ala	Ala	Ala	Asp	Ile	Lys	
35				180					185					190			
	Pro	Asp	Gly	Lys	Arg	His	Ala	Val	Ile	Ser	Gly	Ser	Val	Leu	Tyr	Asn	
			195					200					205				
40	Gln	Ala	Glu	Lys	Gly	Ser	Tyr	Ser	Leu	Gly	Ile	Phe	Gly	Gly	Lys	Ala	
		210					215					220					
	Gln	Glu	Val	Ala	Gly	Ser	Ala	Glu	Val	Lys	Thr	Val	Asn	Gly	Ile	Arg	
	225					230					235					240	
45	His	Ile	Gly	Leu	Ala	Ala	Lys	Gln									
					245												

<210> 81

<211> 247

50 <212> PRT

<213> Neisseria meningitidis

<400> 81

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	Val	Ala	Ala	Asp	Ile	Gly	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	
	1				5					10					15		
5	Leu	Asp	His	Lys	Asp	Lys	Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	
				20					25					30			
	Val	Arg	Lys	Asn	Glu	Lys	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	
			35					40					45				
10	Thr	Tyr	Gly	Asn	Gly	Asp	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	
		50					55					60					
	Lys	Val	Ser	Arg	Phe	Asp	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	
	65					70				75						80	
15	Leu	Ile	Thr	Leu	Glu	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	
					85					90					95		
	Ser	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	
20				100					105					110			
	Ile	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	
			115				120						125				
25	Gly	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Asp	Gly	Lys	Ala	Glu	Tyr	
		130					135					140					
	His	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	
	145					150					155					160	
30	Thr	Ile	Asp	Phe	Ala	Ala	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	Leu	
				165						170					175		
	Lys	Thr	Pro	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala	
35				180					185					190			
	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	
			195					200					205				
40	Glu	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	
		210					215					220					
	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	
	225					230					235					240	
45	Ile	Gly	Ile	Ala	Gly	Lys	Gln										
					245												

<210> 82

<211> 501

50 <212> PRT

<213> Artificial Sequence

<220>

<223> Tandem meningococcus protein

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<400> 82

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5	Leu	Asp	His	Lys	Asp	Lys	Gly	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser
				20					25					30		
	Val	Arg	Lys	Asn	Glu	Lys	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys
			35					40					45			
10	Thr	Tyr	Gly	Asn	Gly	Asp	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp
		50					55					60				
	Lys	Val	Ser	Arg	Phe	Asp	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln
15	65					70				75						80
	Leu	Ile	Thr	Leu	Glu	Ser	Gly	Glu	Phe	Gln	Val	Tyr	Lys	Gln	Ser	His
					85					90					95	
	Ser	Ala	Leu	Thr	Ala	Phe	Gln	Thr	Glu	Gln	Ile	Gln	Asp	Ser	Glu	His
20				100					105					110		
	Ser	Gly	Lys	Met	Val	Ala	Lys	Arg	Gln	Phe	Arg	Ile	Gly	Asp	Ile	Ala
			115					120					125			
25	Gly	Glu	His	Thr	Ser	Phe	Asp	Lys	Leu	Pro	Glu	Gly	Gly	Arg	Ala	Thr
		130					135					140				
	Tyr	Arg	Gly	Thr	Ala	Phe	Gly	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr
	145					150					155					160
30	Tyr	Thr	Ile	Asp	Phe	Ala	Ala	Lys	Gln	Gly	Asn	Gly	Lys	Ile	Glu	His
				165						170					175	
	Leu	Lys	Ser	Pro	Glu	Leu	Asn	Val	Asp	Leu	Ala	Ala	Ala	Asp	Ile	Lys
35				180					185					190		
	Pro	Asp	Gly	Lys	Arg	His	Ala	Val	Ile	Ser	Gly	Ser	Val	Leu	Tyr	Asn
			195					200					205			
	Gln	Ala	Glu	Lys	Gly	Ser	Tyr	Ser	Leu	Gly	Ile	Phe	Gly	Gly	Lys	Ala
40		210					215					220				
	Gln	Glu	Val	Ala	Gly	Ser	Ala	Glu	Val	Lys	Thr	Val	Asn	Gly	Ile	Arg
	225					230					235					240

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	His	Ile	Gly	Leu	Ala	Ala	Lys	Gln	Gly	Ser	Gly	Gly	Gly	Gly	Val	Ala	
					245					250					255		
5	Ala	Asp	Ile	Gly	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	
				260					265					270			
	His	Lys	Asp	Lys	Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	
			275					280					285				
10	Lys	Asn	Glu	Lys	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	
		290					295					300					
	Gly	Asn	Gly	Asp	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	
15	305					310					315					320	
	Ser	Arg	Phe	Asp	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	
					325					330					335		
	Thr	Leu	Glu	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	Ala	
20				340					345					350			
	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	
			355					360					365				
25	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	
		370					375					380					
	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Asp	Gly	Lys	Ala	Glu	Tyr	His	Gly	
	385					390					395					400	
30	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	
					405					410					415		
	Asp	Phe	Ala	Ala	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	Leu	Lys	Thr	
35				420					425					430			
	Pro	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala	Asp	Glu	
			435					440					445				
40	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	Glu	Glu	
		450					455					460					
	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	
	465					470					475					480	
45	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	Ile	Gly	
					485					490					495		
	Ile	Ala	Gly	Lys	Gln												
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<210> 83

<211> 511

<212> PRT

<213> Artificial Sequence

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<220>

<223> Tandem meningococcus protein

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<400> 83

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20																
25																
30																
35																
40																
45																
50																
55																

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	Leu	Asp	His	Lys	Asp	Lys	Gly	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	
				20					25					30			
5	Val	Arg	Lys	Asn	Glu	Lys	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	
			35				40						45				
	Thr	Tyr	Gly	Asn	Gly	Asp	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	
		50					55					60					
10	Lys	Val	Ser	Arg	Phe	Asp	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	
	65					70				75						80	
	Leu	Ile	Thr	Leu	Glu	Ser	Gly	Glu	Phe	Gln	Val	Tyr	Lys	Gln	Ser	His	
					85					90					95		
15	Ser	Ala	Leu	Thr	Ala	Phe	Gln	Thr	Glu	Gln	Ile	Gln	Asp	Ser	Glu	His	
				100					105					110			
	Ser	Gly	Lys	Met	Val	Ala	Lys	Arg	Gln	Phe	Arg	Ile	Gly	Asp	Ile	Ala	
			115					120					125				
20	Gly	Glu	His	Thr	Ser	Phe	Asp	Lys	Leu	Pro	Glu	Gly	Gly	Arg	Ala	Thr	
		130					135					140					
	Tyr	Arg	Gly	Thr	Ala	Phe	Gly	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	
	145					150					155					160	
25	Tyr	Thr	Ile	Asp	Phe	Ala	Ala	Lys	Gln	Gly	Asn	Gly	Lys	Ile	Glu	His	
				165					170						175		
	Leu	Lys	Ser	Pro	Glu	Leu	Asn	Val	Asp	Leu	Ala	Ala	Ala	Asp	Ile	Lys	
				180				185						190			
30	Pro	Asp	Gly	Lys	Arg	His	Ala	Val	Ile	Ser	Gly	Ser	Val	Leu	Tyr	Asn	
			195					200					205				
	Gln	Ala	Glu	Lys	Gly	Ser	Tyr	Ser	Leu	Gly	Ile	Phe	Gly	Gly	Lys	Ala	
35		210					215					220					
	Gln	Glu	Val	Ala	Gly	Ser	Ala	Glu	Val	Lys	Thr	Val	Asn	Gly	Ile	Arg	
	225				230					235						240	
	His	Ile	Gly	Leu	Ala	Ala	Lys	Gln	Gly	Ser	Gly	Pro	Asp	Ser	Asp	Arg	
40				245					250						255		
	Leu	Gln	Gln	Arg	Arg	Val	Ala	Ala	Asp	Ile	Gly	Thr	Gly	Leu	Ala	Asp	
				260					265					270			
45	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys	Gly	Leu	Lys	Ser	Leu	
			275					280					285				
	Thr	Leu	Glu	Asp	Ser	Ile	Pro	Gln	Asn	Gly	Thr	Leu	Thr	Leu	Ser	Ala	
		290					295					300					
50	Gln	Gly	Ala	Glu	Lys	Thr	Phe	Lys	Ala	Gly	Asp	Lys	Asp	Asn	Ser	Leu	
	305					310					315					320	
	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Ile	Ser	Arg	Phe	Asp	Phe	Val	
				325					330						335		
55	Gln	Lys	Ile	Glu	Val	Asp	Gly	Gln	Thr	Ile	Thr	Leu	Ala	Ser	Gly	Glu	
				340					345						350		

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	Phe	Gln	Ile	Tyr	Lys	Gln	Asn	His	Ser	Ala	Val	Val	Ala	Leu	Gln	Ile	
			355					360					365				
5	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Thr	Asp	Ser	Leu	Ile	Asn	Gln	Arg	
		370					375					380					
	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe	Asn	Gln	
	385					390					395					400	
10	Leu	Pro	Gly	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser	Ser	Asp	
					405					410					415		
	Asp	Pro	Asn	Gly	Arg	Leu	His	Tyr	Ser	Ile	Asp	Phe	Thr	Lys	Lys	Gln	
				420					425					430			
15	Gly	Tyr	Gly	Arg	Ile	Glu	His	Leu	Lys	Thr	Leu	Glu	Gln	Asn	Val	Glu	
			435					440					445				
	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	
20		450					455					460					
	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	Glu	Glu	Lys	Gly	Thr	Tyr	His	Leu	
	465					470					475					480	
	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	
25					485					490					495		
	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	Gln		
			500						505					510			
30	<210> 84																
	<211> 250																
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	<213> Neisseria meningitidis																
35	<400> 84																
40																	
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	1				5					10					15	
5	Leu	Asp	His	Lys	Asp	Lys	Gly	Leu	Lys	Ser	Leu	Thr	Leu	Glu	Asp	Ser
				20					25					30		
	Ile	Pro	Gln	Asn	Gly	Thr	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys
			35					40					45			
10	Thr	Phe	Lys	Ala	Gly	Asp	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu
		50					55					60				
	Lys	Asn	Asp	Lys	Ile	Ser	Arg	Phe	Asp	Phe	Val	Gln	Lys	Ile	Glu	Val
	65					70					75					80
15	Asp	Gly	Gln	Thr	Ile	Thr	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys
					85					90					95	
	Gln	Asn	His	Ser	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn
20				100					105					110		
	Pro	Asp	Lys	Thr	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser
			115					120					125			
25	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Gly	Gly	Lys
		130					135					140				
	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Pro	Asn	Gly	Arg
	145					150					155					160
30	Leu	His	Tyr	Ser	Ile	Asp	Phe	Thr	Lys	Lys	Gln	Gly	Tyr	Gly	Arg	Ile
					165					170					175	
	Glu	His	Leu	Lys	Thr	Leu	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu
35				180					185					190		
	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg
			195					200					205			
40	Tyr	Gly	Ser	Glu	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp
		210					215					220				
	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys
	225					230					235					240
45	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	Gln						
					245					250						

<210> 85

<211> 504

50 <212> PRT

<213> Artificial Sequence

<220>

<223> Tandem meningococcus protein

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<400> 85

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	Val	Ala	Ala	Asp	Ile	Gly	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro
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5	Leu	Asp	His	Lys	Asp	Lys	Gly	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser
				20					25					30		
	Val	Arg	Lys	Asn	Glu	Lys	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys
			35				40						45			
10	Thr	Tyr	Gly	Asn	Gly	Asp	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp
		50					55					60				
	Lys	Val	Ser	Arg	Phe	Asp	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln
15	65				70					75						80
	Leu	Ile	Thr	Leu	Glu	Ser	Gly	Glu	Phe	Gln	Val	Tyr	Lys	Gln	Ser	His
					85					90					95	
	Ser	Ala	Leu	Thr	Ala	Phe	Gln	Thr	Glu	Gln	Ile	Gln	Asp	Ser	Glu	His
20				100					105					110		
	Ser	Gly	Lys	Met	Val	Ala	Lys	Arg	Gln	Phe	Arg	Ile	Gly	Asp	Ile	Ala
			115					120					125			
25	Gly	Glu	His	Thr	Ser	Phe	Asp	Lys	Leu	Pro	Glu	Gly	Gly	Arg	Ala	Thr
		130					135					140				
	Tyr	Arg	Gly	Thr	Ala	Phe	Gly	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr
	145					150					155					160
30	Tyr	Thr	Ile	Asp	Phe	Ala	Ala	Lys	Gln	Gly	Asn	Gly	Lys	Ile	Glu	His
					165					170					175	

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	Leu	Lys	Ser	Pro	Glu	Leu	Asn	Val	Asp	Leu	Ala	Ala	Ala	Asp	Ile	Lys
				180					185					190		
5	Pro	Asp	Gly	Lys	Arg	His	Ala	Val	Ile	Ser	Gly	Ser	Val	Leu	Tyr	Asn
			195					200					205			
	Gln	Ala	Glu	Lys	Gly	Ser	Tyr	Ser	Leu	Gly	Ile	Phe	Gly	Gly	Lys	Ala
		210					215					220				
10	Gln	Glu	Val	Ala	Gly	Ser	Ala	Glu	Val	Lys	Thr	Val	Asn	Gly	Ile	Arg
	225					230					235					240
	His	Ile	Gly	Leu	Ala	Ala	Lys	Gln	Gly	Ser	Gly	Gly	Gly	Gly	Val	Ala
				245						250					255	
15	Ala	Asp	Ile	Gly	Thr	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp
				260					265						270	
	His	Lys	Asp	Lys	Gly	Leu	Lys	Ser	Leu	Thr	Leu	Glu	Asp	Ser	Ile	Pro
			275					280					285			
20	Gln	Asn	Gly	Thr	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Phe
		290					295					300				
	Lys	Ala	Gly	Asp	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn
	305					310					315					320
25	Asp	Lys	Ile	Ser	Arg	Phe	Asp	Phe	Val	Gln	Lys	Ile	Glu	Val	Asp	Gly
					325					330					335	
	Gln	Thr	Ile	Thr	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asn
				340					345					350		
30	His	Ser	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp
			355					360					365			
	Lys	Thr	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu
35		370					375					380				
	Gly	Gly	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Gly	Gly	Lys	Ala	Glu
	385					390					395					400
40	Tyr	His	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	His
					405					410					415	
	Tyr	Ser	Ile	Asp	Phe	Thr	Lys	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu	His
				420					425					430		
45	Leu	Lys	Thr	Leu	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys
			435					440					445			
	Ala	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly
		450					455					460				
50	Ser	Glu	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala
	465					470					475					480
	Gln	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His
					485					490					495	
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<213> Artificial Sequence
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<223> Linker

<400> 86
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<213> Artificial Sequence

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<400> 87

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5	Gly	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	
				20					25					30			
	Lys	Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	
			35					40					45				
10	Lys	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	
		50					55					60					
	Asp	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	
	65					70				75						80	
15	Asp	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	
					85					90					95		
	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	Ala	Val	Val	Ala	
20				100					105					110			
	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	
			115					120					125				
25	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	
		130					135					140					
	Phe	Asn	Gln	Leu	Pro	Asp	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	
	145					150					155					160	
30	Ser	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	
					165					170					175		
	Ala	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	Leu	Lys	Thr	Pro	Glu	Gln	
35				180					185					190			
	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	
			195					200					205				
40	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	Glu	Glu	Lys	Gly	Thr	
		210					215					220					
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	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	
	225					230					235					240	
5	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	
					245					250					255		
	Lys	Gln	Gly	Ser	Gly	Pro	Asp	Ser	Asp	Arg	Leu	Gln	Gln	Arg	Arg	Val	
				260					265					270			
10	Ala	Ala	Asp	Ile	Gly	Thr	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	
			275					280					285				
	Asp	His	Lys	Asp	Lys	Gly	Leu	Lys	Ser	Leu	Thr	Leu	Glu	Asp	Ser	Ile	
	290						295					300					
15	Pro	Gln	Asn	Gly	Thr	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	Thr	
	305					310					315					320	
	Phe	Lys	Ala	Gly	Asp	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	
20					325					330					335		
	Asn	Asp	Lys	Ile	Ser	Arg	Phe	Asp	Phe	Val	Gln	Lys	Ile	Glu	Val	Asp	
				340					345					350			
25	Gly	Gln	Thr	Ile	Thr	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	
			355					360					365				
	Asn	His	Ser	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	
		370					375					380					
30	Asp	Lys	Thr	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	
	385					390					395					400	
	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Gly	Gly	Lys	Ala	
					405					410					415		
35	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	
				420					425					430			
	His	Tyr	Ser	Ile	Asp	Phe	Thr	Lys	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu	
40			435					440					445				
	His	Leu	Lys	Thr	Leu	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	
		450					455					460					
45	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	
	465					470					475					480	
	Gly	Ser	Glu	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	
					485					490					495		
50	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	
				500					505					510			
	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	Gln								
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<210> 88
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 <212> PRT

<213> Artificial Sequence

<220>

<223> Tandem meningococcus protein

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<400> 88

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	1				5					10					15		
5	Gly	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	
				20					25					30			
	Lys	Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	
			35					40					45				
10	Lys	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	
		50					55					60					
	Asp	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	
	65					70				75						80	
15	Asp	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	
					85					90					95		
	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	Ala	Val	Val	Ala	
				100					105					110			
20	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	
			115					120					125				
	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	
25		130					135					140					
	Phe	Asn	Gln	Leu	Pro	Asp	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	
	145					150					155					160	
30	Ser	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	
					165					170					175		
	Ala	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	Leu	Lys	Thr	Pro	Glu	Gln	
				180					185					190			
35	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	
			195					200					205				
	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	Glu	Glu	Lys	Gly	Thr	
		210					215						220				
40	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	
	225					230					235					240	
	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	
45					245					250					255		
	Lys	Gln	Gly	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly	Thr	Gly	
				260					265					270			
50	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys	Gly	Leu	
			275					280					285				
	Lys	Ser	Leu	Thr	Leu	Glu	Asp	Ser	Ile	Pro	Gln	Asn	Gly	Thr	Leu	Thr	
		290					295					300					
55	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Phe	Lys	Ala	Gly	Asp	Lys	Asp	
	305					310					315					320	

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	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Ile	Ser	Arg	Phe	
					325					330					335		
5	Asp	Phe	Val	Gln	Lys	Ile	Glu	Val	Asp	Gly	Gln	Thr	Ile	Thr	Leu	Ala	
				340					345					350			
	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asn	His	Ser	Ala	Val	Val	Ala	
			355					360					365				
10	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Thr	Asp	Ser	Leu	Ile	
		370					375					380					
	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	
	385					390					395					400	
15	Phe	Asn	Gln	Leu	Pro	Gly	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	
				405					410						415		
	Ser	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	His	Tyr	Ser	Ile	Asp	Phe	Thr	
20			420						425					430			
	Lys	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu	His	Leu	Lys	Thr	Leu	Glu	Gln	
			435					440					445				
25	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	
		450					455					460					
	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	Glu	Glu	Lys	Gly	Thr	
	465				470					475						480	
30	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	
				485						490					495		
	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	
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<213> Artificial Sequence

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<223> Tandem meningococcus protein

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<400> 89

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5	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	Pro	Gln	Asn	Gly
			35					40					45			
10	Thr	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Phe	Lys	Ala	Gly
		50					55					60				
	Asp	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Ile
15	65					70					75					80
20																
25																
30																
35																
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45																
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55																

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	Ser	Arg	Phe	Asp	Phe	Val	Gln	Lys	Ile	Glu	Val	Asp	Gly	Gln	Thr	Ile	
				85						90					95		
5	Thr	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asn	His	Ser	Ala	
				100					105					110			
	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Thr	Asp	
			115					120					125				
10	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	Gly	Gly	Lys	Ala	Glu	Tyr	His	Gly	
	145					150					155					160	
15	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	His	Tyr	Ser	Ile	
					165					170					175		
	Asp	Phe	Thr	Lys	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu	His	Leu	Lys	Thr	
				180					185					190			
20	Leu	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	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					
25	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	Gly	Glu	Lys	Val	His	Glu	Ile	Gly	
					245					250					255		
30	Ile	Ala	Gly	Lys	Gln	Gly	Ser	Gly	Pro	Asp	Ser	Asp	Arg	Leu	Gln	Gln	
				260					265					270			
	Arg	Arg	Val	Ala	Ala	Asp	Ile	Gly	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	
35			275					280					285				
	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys	Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	
	290						295					300					
40	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	
	305					310					315					320	
	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	
					325					330					335		
45	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	
			340					345						350			
	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	
			355					360					365				
50	Asp	His	Ser	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	
	370						375					380					
	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	
	385					390					395					400	
55	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Asp	Gly	Lys	Ala	
					405					410					415		

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	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	
				420					425					430			
5	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	Ala	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	
			435					440				445					
	His	Leu	Lys	Thr	Pro	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	
		450					455					460					
10	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	
	465					470					475					480	
	Gly	Ser	Glu	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	
					485					490					495		
15	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	
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<210> 90

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<212> PRT

25 <213> Artificial Sequence

<220>

<223> Tandem meningococcus protein

30 <400> 90

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5	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	Pro	Gln	Asn	Gly
			35					40					45			
10	Thr	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Phe	Lys	Ala	Gly
		50					55					60				
	Asp	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Ile
	65					70					75					80
15	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	Asn	His	Ser	Ala
20				100					105					110		
	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Thr	Asp
			115					120					125			
25	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	Gly	Gly	Lys	Ala	Glu	Tyr	His	Gly
	145					150					155					160
30	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	His	Tyr	Ser	Ile
					165					170					175	

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	Asp	Phe	Thr	Lys	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu	His	Leu	Lys	Thr
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5	Leu	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	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				
10	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	Gly	Glu	Lys	Val	His	Glu	Ile	Gly
					245					250					255	
15	Ile	Ala	Gly	Lys	Gln	Gly	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile
				260					265						270	
	Gly	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp
			275					280					285			
20	Lys	Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu
		290					295					300				
	Lys	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly
	305					310					315					320
25	Asp	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe
					325					330					335	
	Asp	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu
				340					345					350		
30	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	Ala	Val	Val	Ala
			355					360					365			
	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile
35		370					375					380				
	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala
	385					390					395					400
	Phe	Asn	Gln	Leu	Pro	Asp	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe
40					405					410					415	
	Ser	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala
					420				425					430		
45	Ala	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	Leu	Lys	Thr	Pro	Glu	Gln
			435					440					445			
	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His
		450					455					460				
50	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	Glu	Glu	Lys	Gly	Thr
	465					470					475					480
	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser
					485					490					495	
55	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly
				500					505					510		

Lys Gln

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 <213> Artificial Sequence

10 <220>
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5	Val	Asp	Arg	Arg	Thr	Thr	Gly	Ala	Gln	Thr	Asp	Asp	Asn	Val	Met	Ala
				20					25					30		
	Leu	Arg	Ile	Glu	Thr	Thr	Ala	Arg	Ser	Tyr	Leu	Arg	Gln	Asn	Asn	Gln
			35					40					45			
10	Thr	Lys	Gly	Tyr	Thr	Pro	Gln	Ile	Ser	Val	Val	Gly	Tyr	Asn	Arg	His
		50					55					60				
	Leu	Leu	Leu	Leu	Gly	Gln	Val	Ala	Thr	Glu	Gly	Glu	Lys	Gln	Phe	Val
15	65					70					75					80
	Gly	Gln	Ile	Ala	Arg	Ser	Glu	Gln	Ala	Ala	Glu	Gly	Val	Tyr	Asn	Tyr
					85					90					95	
	Ile	Thr	Val	Ala	Ser	Leu	Pro	Arg	Thr	Ala	Gly	Asp	Ile	Ala	Gly	Asp
20				100					105					110		
	Thr	Trp	Asn	Thr	Ser	Lys	Val	Arg	Ala	Thr	Leu	Leu	Gly	Ile	Ser	Pro
			115					120					125			
25	Ala	Thr	Gln	Ala	Arg	Val	Lys	Ile	Val	Thr	Tyr	Gly	Asn	Val	Thr	Tyr
		130					135					140				
	Val	Met	Gly	Ile	Leu	Thr	Pro	Glu	Glu	Gln	Ala	Gln	Ile	Thr	Gln	Lys
	145					150					155					160
30	Val	Ser	Thr	Thr	Val	Gly	Val	Gln	Lys	Val	Ile	Thr	Leu	Tyr	Gln	Asn
					165					170					175	
	Tyr	Val	Gln	Arg	Gly	Ser	Gly	Pro	Asp	Ser	Asp	Arg	Leu	Gln	Gln	Arg
35				180					185					190		
	Arg	Val	Ala	Ala	Asp	Ile	Gly	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala
			195					200					205			
	Pro	Leu	Asp	His	Lys	Asp	Lys	Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln
40		210					215					220				
	Ser	Val	Arg	Lys	Asn	Glu	Lys	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu
	225					230					235					240
45	Lys	Thr	Tyr	Gly	Asn	Gly	Asp	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn
				245						250					255	
	Asp	Lys	Val	Ser	Arg	Phe	Asp	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly
50				260					265					270		
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	Gln	Leu	Ile	Thr	Leu	Glu	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	
				275				280					285				
5	His	Ser	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	
		290					295					300					
	Lys	Ile	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	
	305					310					315					320	
10	Gly	Gly	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Asp	Gly	Lys	Ala	Glu	
					325					330					335		
	Tyr	His	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	
				340					345					350			
15	Tyr	Thr	Ile	Asp	Phe	Ala	Ala	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	
			355					360					365				
	Leu	Lys	Thr	Pro	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	
20		370					375					380					
	Ala	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	
	385					390					395					400	
25	Ser	Glu	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	
				405					410						415		
	Gln	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	
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30	Glu	Ile	Gly	Ile	Ala	Gly	Lys	Gln									
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<211> 433

35 <212> PRT

<213> Artificial Sequence

<220>

<223> Hybrid meningococcus protein

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<400> 92

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5	Val	Asp	Arg	Arg	Thr	Thr	Gly	Ala	Gln	Thr	Asp	Asp	Asn	Val	Met	Ala
				20					25					30		
	Leu	Arg	Ile	Glu	Thr	Thr	Ala	Arg	Ser	Tyr	Leu	Arg	Gln	Asn	Asn	Gln
			35					40					45			
10	Thr	Lys	Gly	Tyr	Thr	Pro	Gln	Ile	Ser	Val	Val	Gly	Tyr	Asn	Arg	His
		50					55					60				
	Leu	Leu	Leu	Leu	Gly	Gln	Val	Ala	Thr	Glu	Gly	Glu	Lys	Gln	Phe	Val
15	65					70					75				80	
	Gly	Gln	Ile	Ala	Arg	Ser	Glu	Gln	Ala	Ala	Glu	Gly	Val	Tyr	Asn	Tyr
					85					90					95	
	Ile	Thr	Val	Ala	Ser	Leu	Pro	Arg	Thr	Ala	Gly	Asp	Ile	Ala	Gly	Asp
20				100					105					110		
25																
30																
35																
40																
45																
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	Thr	Trp	Asn	Thr	Ser	Lys	Val	Arg	Ala	Thr	Leu	Leu	Gly	Ile	Ser	Pro	
			115					120					125				
5	Ala	Thr	Gln	Ala	Arg	Val	Lys	Ile	Val	Thr	Tyr	Gly	Asn	Val	Thr	Tyr	
			130				135					140					
	Val	Met	Gly	Ile	Leu	Thr	Pro	Glu	Glu	Gln	Ala	Gln	Ile	Thr	Gln	Lys	
			145			150					155					160	
10	Val	Ser	Thr	Thr	Val	Gly	Val	Gln	Lys	Val	Ile	Thr	Leu	Tyr	Gln	Asn	
					165					170					175		
	Tyr	Val	Gln	Arg	Gly	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly	
				180					185					190			
15	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys	
			195					200					205				
	Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys	
			210				215					220					
20	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp	
						230					235					240	
	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp	
					245					250					255		
25	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser	
				260					265					270			
	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	Ala	Val	Val	Ala	Leu	
30			275					280					285				
	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn	
			290				295					300					
35	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe	
					310						315					320	
	Asn	Gln	Leu	Pro	Asp	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser	
					325					330					335		
40	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	Ala	
				340					345					350			
	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	Leu	Lys	Thr	Pro	Glu	Gln	Asn	
			355					360					365				
45	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala	
			370				375					380					
	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	Glu	Glu	Lys	Gly	Thr	Tyr	
50						390					395					400	
	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	
					405					410					415		
	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	
55				420					425					430			
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<400> 93

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5	Val	Asp	Arg	Arg	Thr	Thr	Gly	Ala	Gln	Thr	Asp	Asp	Asn	Val	Met	Ala
				20					25					30		
	Leu	Arg	Ile	Glu	Thr	Thr	Ala	Arg	Ser	Tyr	Leu	Arg	Gln	Asn	Asn	Gln
			35					40					45			
10	Thr	Lys	Gly	Tyr	Thr	Pro	Gln	Ile	Ser	Val	Val	Gly	Tyr	Asn	Arg	His
		50					55					60				
	Leu	Leu	Leu	Leu	Gly	Gln	Val	Ala	Thr	Glu	Gly	Glu	Lys	Gln	Phe	Val
	65					70					75					80
15	Gly	Gln	Ile	Ala	Arg	Ser	Glu	Gln	Ala	Ala	Glu	Gly	Val	Tyr	Asn	Tyr
					85					90					95	
	Ile	Thr	Val	Ala	Ser	Leu	Pro	Arg	Thr	Ala	Gly	Asp	Ile	Ala	Gly	Asp
20				100					105					110		
	Thr	Trp	Asn	Thr	Ser	Lys	Val	Arg	Ala	Thr	Leu	Leu	Gly	Ile	Ser	Pro
			115					120					125			
25	Ala	Thr	Gln	Ala	Arg	Val	Lys	Ile	Val	Thr	Tyr	Gly	Asn	Val	Thr	Tyr
		130					135					140				
	Val	Met	Gly	Ile	Leu	Thr	Pro	Glu	Glu	Gln	Ala	Gln	Ile	Thr	Gln	Lys
	145					150					155					160
30	Val	Ser	Thr	Thr	Val	Gly	Val	Gln	Lys	Val	Ile	Thr	Leu	Tyr	Gln	Asn
					165					170					175	
	Tyr	Val	Gln	Arg	Gly	Ser	Gly	Pro	Asp	Ser	Asp	Arg	Leu	Gln	Gln	Arg
				180					185					190		
35	Arg	Val	Ala	Ala	Asp	Ile	Gly	Thr	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala
			195					200					205			
	Pro	Leu	Asp	His	Lys	Asp	Lys	Gly	Leu	Lys	Ser	Leu	Thr	Leu	Glu	Asp
40		210					215					220				
	Ser	Ile	Pro	Gln	Asn	Gly	Thr	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu
	225					230					235					240
45	Lys	Thr	Phe	Lys	Ala	Gly	Asp	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys
					245					250					255	
	Leu	Lys	Asn	Asp	Lys	Ile	Ser	Arg	Phe	Asp	Phe	Val	Gln	Lys	Ile	Glu
				260					265					270		
50	Val	Asp	Gly	Gln	Thr	Ile	Thr	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr
			275					280					285			
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	Lys	Gln	Asn	His	Ser	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	
	290						295					300					
5	Asn	Pro	Asp	Lys	Thr	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	
	305					310					315					320	
	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Gly	Gly	
				325						330					335		
10	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Pro	Asn	Gly	
				340					345					350			
	Arg	Leu	His	Tyr	Ser	Ile	Asp	Phe	Thr	Lys	Lys	Gln	Gly	Tyr	Gly	Arg	
			355					360					365				
15	Ile	Glu	His	Leu	Lys	Thr	Leu	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	
	370						375					380					
	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	
20	385					390					395					400	
	Arg	Tyr	Gly	Ser	Glu	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	
				405						410					415		
25	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	
			420					425					430				
	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	Gln						
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5	Val	Asp	Arg	Arg	Thr	Thr	Gly	Ala	Gln	Thr	Asp	Asp	Asn	Val	Met	Ala
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	Leu	Arg	Ile	Glu	Thr	Thr	Ala	Arg	Ser	Tyr	Leu	Arg	Gln	Asn	Asn	Gln
			35					40					45			
10	Thr	Lys	Gly	Tyr	Thr	Pro	Gln	Ile	Ser	Val	Val	Gly	Tyr	Asn	Arg	His
		50					55					60				
	Leu	Leu	Leu	Leu	Gly	Gln	Val	Ala	Thr	Glu	Gly	Glu	Lys	Gln	Phe	Val
15	65					70					75					80
	Gly	Gln	Ile	Ala	Arg	Ser	Glu	Gln	Ala	Ala	Glu	Gly	Val	Tyr	Asn	Tyr
					85					90					95	
	Ile	Thr	Val	Ala	Ser	Leu	Pro	Arg	Thr	Ala	Gly	Asp	Ile	Ala	Gly	Asp
20				100					105					110		
	Thr	Trp	Asn	Thr	Ser	Lys	Val	Arg	Ala	Thr	Leu	Leu	Gly	Ile	Ser	Pro
			115					120					125			
25																
30																
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	Ala	Thr	Gln	Ala	Arg	Val	Lys	Ile	Val	Thr	Tyr	Gly	Asn	Val	Thr	Tyr	
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5	Val	Met	Gly	Ile	Leu	Thr	Pro	Glu	Glu	Gln	Ala	Gln	Ile	Thr	Gln	Lys	
	145					150					155					160	
	Val	Ser	Thr	Thr	Val	Gly	Val	Gln	Lys	Val	Ile	Thr	Leu	Tyr	Gln	Asn	
					165					170					175		
10	Tyr	Val	Gln	Arg	Gly	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly	
				180					185						190		
	Thr	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys	
			195					200					205				
15	Gly	Leu	Lys	Ser	Leu	Thr	Leu	Glu	Asp	Ser	Ile	Pro	Gln	Asn	Gly	Thr	
	210						215					220					
	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Phe	Lys	Ala	Gly	Asp	
20	225					230					235					240	
	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Ile	Ser	
					245					250					255		
25	Arg	Phe	Asp	Phe	Val	Gln	Lys	Ile	Glu	Val	Asp	Gly	Gln	Thr	Ile	Thr	
				260					265					270			
	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asn	His	Ser	Ala	Val	
			275					280					285				
30	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Thr	Asp	Ser	
	290						295					300					
	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	
	305					310					315					320	
35	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Gly	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	
					325					330					335		
	Ala	Phe	Ser	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	His	Tyr	Ser	Ile	Asp	
40				340					345					350			
	Phe	Thr	Lys	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu	His	Leu	Lys	Thr	Leu	
			355					360					365				
45	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	
	370					375						380					
	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	Glu	Glu	Lys	
	385					390					395					400	
50	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	
					405					410					415		
	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	
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 cccaagcttc tgttgccg cgatgcc 27
 15
 <210> 107
 <211> 26
 <212> DNA
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 20
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 <223> Amplification primer
 <400> 107
 cgcgatccg gccctgattc tgaccg 26
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 <211> 28
 <212> DNA
 <213> Artificial Sequence
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 <223> Amplification primer
 <400> 108
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 35
 <210> 109
 <211> 25
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 <210> 111
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 <400> 111
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 <210> 112
 15 <211> 28
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 25 <210> 113
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 35 <210> 114
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 <212> DNA
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 <400> 114
 45 cccgctcgag ctgtttgccg gcgatgcc 28
 <210> 115
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 55 <400> 115
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 <210> 116

<211> 27
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5 <220>
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<400> 116
 10 cccaagcttc tgttgccgg cgatgcc 27

<210> 117
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 <212> DNA
 <213> Artificial Sequence

15 <220>
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<400> 117
 20 cgcgatccg gaggggtgg tgtcg 25

<210> 118
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 25 <213> Artificial Sequence

<220>
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30 <400> 118
 cccaagcttc tgttgccgg cgatgcc 27

<210> 119
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 35 <212> DNA
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<220>
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40 <400> 119
 cgcgatccc atatgggcc tgattctgac cg 32

<210> 120
 45 <211> 27
 <212> DNA
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<220>
 50 <223> Amplification primer

<400> 120
 cgcgatccc tgttgccgg cgatgcc 27

55 <210> 121
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<220>

<223> Amplification primer

<400> 121

5 cgcggatccc atatgggccc tgattctgac cg 32

<210> 122

<211> 27

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<220>

<223> Amplification primer

<400> 122

15 cgcggatccc tgtttgcgg cgatgcc 27

<210> 123

<211> 274

20 <212> PRT

<213> Neisseria meningitidis

<400> 123

25 Met Asn Arg Thr Ala Phe Cys Cys Leu Ser Leu Thr Ala Ala Leu Ile
1 5 10 15

30 Leu Thr Ala Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly

35

40

45

50

55

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	20	25	30
5	Ala Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys 35 40 45		
	Ser Leu Gln Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys 50 55 60		
10	Leu Lys Leu Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp 65 70 75 80		
	Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp 85 90 95		
15	Phe Ile Arg Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser 100 105 110		
	Gly Glu Phe Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Leu 115 120 125		
20	Gln Thr Glu Gln Val Gln Asp Ser Glu His Ser Gly Lys Met Val Ala 130 135 140		
	Lys Arg Gln Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe 145 150 155 160		
25	Asp Lys Leu Pro Glu Gly Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe 165 170 175		
	Gly Ser Asp Asp Ala Ser Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala 180 185 190		
30	Ala Lys Gln Gly His Gly Lys Ile Glu His Leu Lys Ser Leu Glu Leu 195 200 205		
	Asn Val Asp Leu Ala Ala Ser Asp Ile Lys Pro Asp Lys Lys Arg His 210 215 220		
35	Ala Val Ile Ser Gly Ser Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser 225 230 235 240		
40	Tyr Ser Leu Gly Ile Phe Gly Gly Gln Ala Gln Glu Val Ala Gly Ser 245 250 255		
	Ala Glu Val Glu Thr Ala Asn Gly Ile Arg His Ile Gly Leu Ala Ala 260 265 270		
45	Lys Gln		

<210> 124

50 <211> 274

<212> PRT

<213> Neisseria meningitidis

<400> 124

55

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	Met	Asn	Arg	Thr	Ala	Phe	Cys	Cys	Phe	Ser	Leu	Thr	Ala	Ala	Leu	Ile	
	1				5					10					15		
5	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly	
				20					25					30			
	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys	
10				35					40					45			
	Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys	
		50					55					60					
15	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp	
	65					70					75					80	
	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp	
					85					90					95		
20	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser	
				100					105					110			
	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	Ala	Leu	Thr	Ala	Leu	
25			115					120					125				
	Gln	Thr	Glu	Gln	Glu	Gln	Asp	Pro	Glu	His	Ser	Gly	Lys	Met	Val	Ala	
		130					135					140					
30	Lys	Arg	Arg	Phe	Lys	Ile	Gly	Asp	Ile	Ala	Gly	Glu	His	Thr	Ser	Phe	
	145					150					155					160	
	Asp	Lys	Leu	Pro	Lys	Asp	Val	Met	Ala	Thr	Tyr	Arg	Gly	Thr	Ala	Phe	
					165					170					175		
35	Gly	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	Ser	Pro	Glu	Leu	
			195					200					205				
40	Asn	Val	Glu	Leu	Ala	Thr	Ala	Tyr	Ile	Lys	Pro	Asp	Glu	Lys	His	His	
		210					215					220					
	Ala	Val	Ile	Ser	Gly	Ser	Val	Leu	Tyr	Asn	Gln	Asp	Glu	Lys	Gly	Ser	
45					225		230				235					240	
	Tyr	Ser	Leu	Gly	Ile	Phe	Gly	Gly	Gln	Ala	Gln	Glu	Val	Ala	Gly	Ser	
				245						250					255		
50	Ala	Glu	Val	Glu	Thr	Ala	Asn	Gly	Ile	His	His	Ile	Gly	Leu	Ala	Ala	
				260					265					270			
	Lys	Gln															

<210> 125

55 <211> 274

<212> PRT

<213> Neisseria meningitidis

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<400> 125

5	Met	Asn	Arg	Thr	Ala	Phe	Cys	Cys	Leu	Ser	Leu	Thr	Thr	Ala	Leu	Ile	
	1				5					10					15		
	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly	
				20					25					30			
10	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys	
			35					40					45				
	Gly	Leu	Gln	Ser	Leu	Met	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys	
15			50					55					60				
	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp	
	65					70					75					80	
20	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp	
					85					90					95		
	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser	
				100					105					110			
25	Gly	Glu	Phe	Gln	Val	Tyr	Lys	Gln	Ser	His	Ser	Ala	Leu	Thr	Ala	Leu	
			115					120					125				
	Gln	Thr	Glu	Gln	Val	Gln	Asp	Ser	Glu	Asp	Ser	Gly	Lys	Met	Val	Ala	
		130					135					140					
30	Lys	Arg	Gln	Phe	Arg	Ile	Gly	Asp	Ile	Ala	Gly	Glu	His	Thr	Ser	Phe	
	145					150					155					160	
	Asp	Lys	Leu	Pro	Lys	Asp	Val	Met	Ala	Thr	Tyr	Arg	Gly	Thr	Ala	Phe	
35					165					170					175		
	Gly	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	
				180					185					190			
40	Ala	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	Leu	Lys	Ser	Pro	Glu	Leu	
			195					200					205				
	Asn	Val	Glu	Leu	Ala	Ala	Ala	Tyr	Ile	Lys	Pro	Asp	Glu	Lys	His	His	
		210					215					220					
45	Ala	Val	Ile	Ser	Gly	Ser	Val	Leu	Tyr	Asn	Gln	Asp	Glu	Lys	Gly	Ser	
	225					230					235					240	
	Tyr	Ser	Leu	Gly	Ile	Phe	Gly	Gly	Gln	Ala	Gln	Glu	Val	Ala	Gly	Ser	
				245						250					255		
50	Ala	Glu	Val	Glu	Thr	Ala	Asn	Gly	Ile	Gln	His	Ile	Gly	Leu	Ala	Ala	
				260					265					270			
55	Lys	Gln															

<210> 126

<211> 274

<212> PRT

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<213> Neisseria meningitidis

<400> 126

5	Met	Asn	Arg	Thr	Thr	Phe	Cys	Cys	Leu	Ser	Leu	Thr	Ala	Ala	Leu	Ile
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	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly
10				20					25					30		
	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys
			35					40					45			
	Gly	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys
15		50					55					60				
	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp
20	65					70					75				80	
	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp
					85					90					95	
	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asn	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser
25				100					105					110		
	Gly	Glu	Phe	Gln	Val	Tyr	Lys	Gln	Ser	His	Ser	Ala	Leu	Thr	Ala	Leu
			115					120					125			
30	Gln	Thr	Glu	Gln	Val	Gln	Asp	Ser	Glu	His	Ser	Arg	Lys	Met	Val	Ala
		130					135					140				
	Lys	Arg	Gln	Phe	Arg	Ile	Gly	Asp	Ile	Ala	Gly	Glu	His	Thr	Ser	Phe
	145					150				155						160
35	Asp	Lys	Leu	Pro	Lys	Gly	Asp	Ser	Ala	Thr	Tyr	Arg	Gly	Thr	Ala	Phe
					165					170					175	
	Gly	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala
40				180					185					190		
	Ala	Lys	Gln	Gly	Tyr	Gly	Lys	Ile	Glu	His	Leu	Lys	Ser	Pro	Glu	Leu
			195					200					205			
45	Asn	Val	Asp	Leu	Ala	Ala	Ala	Tyr	Ile	Lys	Pro	Asp	Glu	Lys	His	His
	210						215					220				
	Ala	Val	Ile	Ser	Gly	Ser	Val	Leu	Tyr	Asn	Gln	Asp	Glu	Lys	Gly	Ser
	225					230					235					240
50	Tyr	Ser	Leu	Gly	Ile	Phe	Gly	Gly	Gln	Ala	Gln	Glu	Val	Ala	Gly	Ser
				245						250					255	
	Ala	Glu	Val	Lys	Thr	Ala	Asn	Gly	Ile	Arg	His	Ile	Gly	Leu	Ala	Ala
				260					265					270		
55	Lys	Gln														

<210> 127

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<211> 274
 <212> PRT
 <213> Neisseria meningitidis

5 <400> 127

	Met	Asn	Arg	Thr	Ala	Phe	Cys	Cys	Leu	Ser	Leu	Thr	Ala	Ala	Leu	Ile	
	1				5					10					15		
10	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly	
				20					25					30			
	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys	
			35					40					45				
15	Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys	
	50						55					60					
	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp	
20	65					70					75					80	
	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp	
					85					90					95		
25	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser	
				100					105					110			
	Gly	Glu	Phe	Gln	Val	Tyr	Lys	Gln	Ser	His	Ser	Ala	Leu	Thr	Ala	Phe	
30			115					120					125				
	Gln	Thr	Glu	Gln	Ile	Gln	Asp	Ser	Glu	His	Ser	Gly	Lys	Met	Val	Ala	
		130					135					140					
	Lys	Arg	Gln	Phe	Arg	Ile	Gly	Asp	Ile	Ala	Gly	Glu	His	Thr	Ser	Phe	
35	145					150					155					160	
	Asp	Lys	Leu	Pro	Glu	Gly	Gly	Arg	Ala	Thr	Tyr	Arg	Gly	Thr	Ala	Phe	
					165					170					175		
40	Gly	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	
				180					185					190			
	Ala	Lys	Gln	Gly	Asn	Gly	Lys	Ile	Glu	His	Leu	Lys	Ser	Pro	Glu	Leu	
45			195					200					205				
	Asn	Val	Asp	Leu	Ala	Ala	Ala	Asp	Ile	Lys	Pro	Asp	Gly	Lys	Arg	His	
		210					215					220					
	Ala	Val	Ile	Ser	Gly	Ser	Val	Leu	Tyr	Asn	Gln	Ala	Glu	Lys	Gly	Ser	
50	225					230					235					240	
	Tyr	Ser	Leu	Gly	Ile	Phe	Gly	Gly	Lys	Ala	Gln	Glu	Val	Ala	Gly	Ser	
				245						250					255		
55	Ala	Glu	Val	Lys	Thr	Val	Asn	Gly	Ile	Arg	His	Ile	Gly	Leu	Ala	Ala	
				260					265					270			
	Lys	Gln															

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<210> 128
 <211> 274
 <212> PRT
 <213> Neisseria meningitidis

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<400> 128

10

Met Asn Arg Thr Ala Phe Cys Cys Leu Ser Leu Thr Thr Ala Leu Ile
 1 5 10 15

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

15

Thr Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys
 35 40 45

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

20

Leu Thr Leu Ser Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp
 65 70 75 80

Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp
 85 90 95

25

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

30

35

40

45

50

55

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	100							105					110				
5	Gly	Glu	Phe	Gln	Val	Tyr	Lys	Gln	Ser	His	Ser	Ala	Leu	Thr	Ala	Leu	
			115					120					125				
	Gln	Thr	Glu	Gln	Val	Gln	Asp	Ser	Glu	Asp	Ser	Gly	Lys	Met	Val	Ala	
		130					135					140					
10	Lys	Arg	Gln	Phe	Arg	Ile	Gly	Asp	Ile	Ala	Gly	Glu	His	Thr	Ser	Phe	
	145					150					155					160	
	Asp	Lys	Leu	Pro	Lys	Gly	Gly	Ser	Ala	Thr	Tyr	Arg	Gly	Thr	Ala	Phe	
					165					170					175		
15	Gly	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	Ser	Pro	Glu	Leu	
			195					200					205				
20	Asn	Val	Glu	Leu	Ala	Thr	Ala	Tyr	Ile	Lys	Pro	Asp	Glu	Lys	His	His	
		210					215					220					
	Ala	Val	Ile	Ser	Gly	Ser	Val	Leu	Tyr	Asn	Gln	Asp	Glu	Lys	Gly	Ser	
25	225					230					235					240	
	Tyr	Ser	Leu	Gly	Ile	Phe	Gly	Gly	Gln	Ala	Gln	Glu	Val	Ala	Gly	Ser	
				245						250					255		
30	Ala	Glu	Val	Glu	Thr	Ala	Asn	Gly	Ile	His	His	Ile	Gly	Leu	Ala	Ala	
				260					265					270			
	Lys	Gln															

35 <210> 129
 <211> 274
 <212> PRT
 <213> Neisseria meningitidis
 40 <400> 129

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	Met	Asn	Arg	Thr	Ala	Phe	Cys	Cys	Phe	Ser	Leu	Thr	Ala	Ala	Leu	Ile
	1				5					10					15	
5	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly
				20					25					30		
	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys
			35					40					45			
10	Gly	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys
	50						55					60				
	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp
15	65					70					75					80
	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp
					85					90					95	
20	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Lys	Leu	Ile	Thr	Leu	Glu	Ser
				100					105					110		
	Gly	Glu	Phe	Gln	Val	Tyr	Lys	Gln	Ser	His	Ser	Ala	Leu	Thr	Ala	Leu
25				115				120					125			
	Gln	Thr	Glu	Gln	Val	Gln	Asp	Ser	Glu	Asp	Ser	Gly	Lys	Met	Val	Ala
		130					135					140				
30	Lys	Arg	Gln	Phe	Arg	Ile	Gly	Asp	Ile	Ala	Gly	Glu	His	Thr	Ser	Phe
	145					150					155					160
	Asp	Lys	Leu	Pro	Lys	Gly	Gly	Ser	Ala	Thr	Tyr	Arg	Gly	Thr	Ala	Phe
					165					170					175	
35	Gly	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	Ser	Pro	Glu	Leu
			195					200					205			
40	Asn	Val	Glu	Leu	Ala	Thr	Ala	Tyr	Ile	Lys	Pro	Asp	Glu	Lys	Arg	His
	210						215					220				
	Ala	Val	Ile	Ser	Gly	Ser	Val	Leu	Tyr	Asn	Gln	Asp	Glu	Lys	Gly	Ser
45	225					230					235					240
	Tyr	Ser	Leu	Gly	Ile	Phe	Gly	Gly	Gln	Ala	Gln	Glu	Val	Ala	Gly	Ser
					245					250					255	
50	Ala	Glu	Val	Glu	Thr	Ala	Asn	Gly	Ile	His	His	Ile	Gly	Leu	Ala	Ala
				260					265					270		
	Lys	Gln														
55	<210>	130														
	<211>	274														
	<212>	PRT														
	<213>	Neisseria meningitidis														

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<400> 130

5	Met	Asn	Arg	Thr	Ala	Phe	Cys	Cys	Leu	Ser	Leu	Thr	Ala	Ala	Leu	Ile	1	5	10	15
	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly	20	25	30	
10	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys	35	40	45	
	Gly	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys	50	55	60	
15	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp	65	70	75	80
	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp	85	90	95	
20	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser	100	105	110	
	Gly	Glu	Phe	Gln	Val	Tyr	Lys	Gln	Ser	His	Ser	Ala	Leu	Thr	Ala	Leu	115	120	125	
25	Gln	Thr	Glu	Gln	Val	Gln	Asp	Ser	Glu	Asp	Ser	Gly	Lys	Met	Val	Ala				
30			130				135				140									
	Lys	Arg	Gln	Phe	Arg	Ile	Gly	Asp	Ile	Ala	Gly	Glu	His	Thr	Ser	Phe	145	150	155	160
35	Asp	Lys	Leu	Pro	Lys	Gly	Gly	Ser	Ala	Thr	Tyr	Arg	Gly	Thr	Ala	Phe	165	170	175	
	Ser	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	180	185	190	
40	Ala	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	Leu	Lys	Ser	Pro	Glu	Leu	195	200	205	
	Asn	Val	Glu	Leu	Ala	Thr	Ala	Tyr	Ile	Lys	Pro	Asp	Glu	Lys	Arg	His	210	215	220	
45	Ala	Val	Ile	Ser	Gly	Ser	Val	Leu	Tyr	Asn	Gln	Asp	Glu	Lys	Gly	Ser	225	230	235	240
	Tyr	Ser	Leu	Gly	Ile	Phe	Gly	Gly	Gln	Ala	Gln	Glu	Val	Ala	Gly	Ser	245	250	255	
50	Ala	Glu	Val	Glu	Thr	Ala	Asn	Gly	Ile	Gln	His	Ile	Gly	Leu	Ala	Ala	260	265	270	
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<210> 131

<211> 273

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<212> PRT

<213> Neisseria meningitidis

<400> 131

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

Ala Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys
35          40          45

15
Ser Leu Gln Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys
50          55          60

Leu Lys Leu Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp
65          70          75          80

20
Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp
85          90          95

Phe Ile Arg Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser
100         105         110

25
Gly Glu Phe Gln Ile Tyr Lys Gln Asp His Ser Ala Val Val Ala Leu
115         120         125

Gln Ile Glu Lys Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu Ile Asn
130         135         140

Gln Arg Ser Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr Ala Phe
145         150         155         160

35
Asn Gln Leu Pro Val Asp Lys Ala Glu Tyr His Gly Lys Ala Phe Ser
165         170         175

40
Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala
180         185         190

Lys Gln Gly His Gly Lys Ile Glu His Leu Lys Thr Pro Glu Gln Asn
195         200         205

45
Val Glu Leu Ala Ser Ala Glu Leu Lys Ala Asp Glu Lys Ser His Ala
210         215         220

Val Ile Leu Gly Asp Thr Arg Tyr Gly Ser Glu Glu Lys Gly Thr Tyr
225         230         235         240

His Leu Ala Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly Ser Ala
245         250         255

55
Thr Val Lys Ile Gly Glu Lys Val His Glu Ile Gly Ile Ala Gly Lys
260         265         270

Gln

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<210> 132
 <211> 273
 <212> PRT
 <213> Neisseria meningitidis

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<400> 132

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55

Met	Asn	Arg	Thr	Ala	Phe	Cys	Cys	Leu	Ser	Leu	Thr	Ala	Ala	Leu	Ile
1				5					10					15	
Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly
			20					25					30		
Ala	Arg	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys
		35					40					45			
Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys
	50					55					60				
Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp
65					70					75				80	
Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp
				85					90					95	
Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser
			100					105					110		
Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	Ala	Val	Val	Ala	Leu
		115					120					125			
Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn
	130					135					140				
Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe
145					150					155					160
Asn	Gln	Leu	Pro	Asp	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser

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[illegible]

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	Met	Asn	Arg	Thr	Ala	Phe	Cys	Cys	Leu	Ser	Leu	Thr	Thr	Ala	Leu	Ile
	1				5					10					15	
5	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly
				20					25					30		
	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys
			35					40					45			
10	Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys
	50						55					60				
	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp
	65					70					75					80
15	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp
					85					90					95	
	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser
20				100					105					110		
	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	Ala	Val	Val	Ala	Leu
			115					120					125			
25	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn
	130						135					140				
	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe
	145					150					155					160
30	Asn	Gln	Leu	Pro	Gly	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser
					165					170					175	
	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	Ala
35					180					185					190	
	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	Leu	Lys	Thr	Pro	Glu	Gln	Asn
			195					200					205			
40	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala
	210						215					220				
	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	Glu	Glu	Lys	Gly	Thr	Tyr
	225					230					235					240
45	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala
					245					250					255	
	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys
50				260					265					270		
	Gln															
55	<210>	134														
	<211>	273														
	<212>	PRT														
	<213>	Neisseria meningitidis														

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<400> 134

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	1				5					10					15		
	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly	
				20					25					30			
10	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys	
			35					40					45				
	Gly	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys	
		50					55					60					
15	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp	
	65					70					75					80	
	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp	
					85					90					95		
20	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser	
				100					105					110			
	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	Ala	Val	Val	Ala	Leu	
25			115					120					125				
	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn	
		130					135					140					
30	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe	
	145					150					155					160	
	Asn	Gln	Leu	Pro	Asp	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser	
				165					170						175		
35	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	Ala	
				180					185					190			
	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	Leu	Lys	Thr	Pro	Glu	Gln	Asn	
40				195					200					205			
	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala	
		210					215					220					
45	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	Glu	Glu	Lys	Gly	Thr	Tyr	
	225					230					235					240	
	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	
50					245					250					255		
	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	
				260					265					270			
55	Gln																

<210> 135
 <211> 273
 <212> PRT

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<213> Neisseria meningitidis

<400> 135

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	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	Asp	Ile	Gly
10				20					25					30		
	Thr	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys
			35					40					45			
	Gly	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys
15		50					55					60				
	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp
	65					70					75					80
	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp
20					85					90					95	
	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser
				100					105					110		
	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	Ala	Val	Val	Ala	Leu
25				115				120					125			
	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn
30			130				135					140				
	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe
	145				150						155					160
	Asn	Gln	Leu	Pro	Ser	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser
35					165					170					175	
	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	Ala
				180					185					190		
	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	Leu	Lys	Thr	Pro	Glu	Gln	Asn
40			195					200					205			
	Val	Glu	Leu	Ala	Ser	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala
45			210					215					220			
	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Gly	Glu	Glu	Lys	Gly	Thr	Tyr
	225					230					235					240
	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala
50					245					250					255	
	Thr	Val	Lys	Ile	Arg	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys
				260					265					270		
55	Gln															

<210> 136

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<211> 273

<212> PRT

<213> Neisseria meningitidis

5 <400> 136

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				20					25					30			
	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys	
			35					40					45				
15	Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys	
		50					55					60					
	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp	
20	65					70					75					80	
	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp	
					85					90					95		
25	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser	
				100					105					110			
	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asp	His	Ser	Ala	Val	Val	Ala	Leu	
			115					120					125				
30	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn	
		130					135					140					
	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe	
35	145					150					155					160	
	Asn	Gln	Leu	Pro	Ser	Gly	Lys	Ala	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser	
				165						170					175		
40	Phe	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	Ala	
				180					185					190			
	Lys	Gln	Gly	His	Gly	Lys	Ile	Glu	His	Leu	Lys	Thr	Pro	Glu	Gln	Asn	
			195					200					205				
45	Val	Glu	Leu	Ala	Ser	Ala	Glu	Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala	
		210					215					220					
	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Gly	Glu	Glu	Lys	Gly	Thr	Tyr	
50																	
	225					230					235					240	
	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	
				245						250					255		
55	Thr	Val	Lys	Ile	Arg	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	
				260					265					270			
	Gln																

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<210> 137
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 <212> PRT
 <213> Neisseria meningitidis

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<400> 137

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

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Ala Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys
 35 40 45

Gly Leu Gln Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys
 50 55 60

20

Leu Lys Leu Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp
 65 70 75 80

Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp
 85 90 95

25

Phe Ile Arg Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser
 100 105 110

Gly Glu Phe Gln Ile Tyr Lys Gln Asp His Ser Ala Val Val Ala Leu
 115 120 125

30

Gln Ile Glu Lys Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu Ile Asn
 130 135 140

Gln Arg Ser Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr Ala Phe
 145 150 155 160

35

Asn Gln Leu Pro Ser Gly Lys Ala Glu Tyr His Gly Lys Ala Phe Ser
 165 170 175

Ser Asp Asp Pro Asn Gly Arg Leu His Tyr Ser Ile Asp Phe Thr Lys
 180 185 190

40

Lys Gln Gly Tyr Gly Arg Ile Glu His Leu Lys Thr Pro Glu Gln Asn
 195 200 205

45

Val Glu Leu Ala Ser Ala Glu Leu Lys Ala Asp Glu Lys Ser His Ala
 210 215 220

Val Ile Leu Gly Asp Thr Arg Tyr Gly Gly Glu Glu Lys Gly Thr Tyr
 225 230 235 240

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His Leu Ala Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly Ser Ala

55

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				245					250					255				
			Thr	Val	Lys	Ile	Arg	Glu	Lys	Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys
5						260					265				270			
			Gln															
			<210>	138														
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50																		
55																		

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	Met	Asn	Arg	Thr	Thr	Phe	Cys	Cys	Leu	Ser	Leu	Thr	Ala	Ala	Leu	Ile	
	1				5					10					15		
5	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Val	
				20					25					30			
	Ala	Ala	Asp	Ile	Gly	Thr	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	
			35					40					45				
10	Asp	His	Lys	Asp	Lys	Gly	Leu	Lys	Ser	Leu	Thr	Leu	Glu	Asp	Ser	Ile	
	50						55					60					
	Pro	Gln	Asn	Gly	Thr	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	Thr	
	65					70				75						80	
15	Phe	Lys	Ala	Gly	Asp	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	
				85					90						95		
	Asn	Asp	Lys	Ile	Ser	Arg	Phe	Asp	Phe	Val	Gln	Lys	Ile	Glu	Val	Asp	
20				100					105					110			
	Gly	Gln	Thr	Ile	Thr	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	
			115					120					125				
25	Asn	His	Ser	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	
	130						135					140					
	Asp	Lys	Ile	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	
	145					150				155						160	
30	Leu	Gly	Gly	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Gly	Asp	Lys	Ala	
					165				170						175		
	Glu	Tyr	His	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	
				180					185					190			
35	His	Tyr	Thr	Ile	Asp	Phe	Thr	Asn	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu	
			195					200					205				
	His	Leu	Lys	Thr	Pro	Glu	Leu	Asn	Val	Asp	Leu	Ala	Ser	Ala	Glu	Leu	
40			210				215					220					
	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	
	225					230				235						240	
45	Gly	Ser	Glu	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	
					245				250						255		
	Ala	Gln	Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	
50					260				265						270		
	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	Gln								
			275					280									

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 <212> PRT
 <213> Neisseria meningitidis

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<400> 139

5	Met	Asn	Arg	Thr	Ala	Phe	Cys	Cys	Leu	Ser	Leu	Thr	Thr	Ala	Leu	Ile	1	5	10	15
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10	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	Lys	Asp	Lys	35	40	45	
	Gly	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Arg	Lys	Asn	Glu	Lys	50	55	60	
15	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly	Asn	Gly	Asp	65	70	75	80
	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser	Arg	Phe	Asp	85	90	95	
20	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr	Leu	Glu	Ser	100	105	110	
	Gly	Glu	Phe	Gln	Val	Tyr	Lys	Gln	Ser	His	Ser	Ala	Leu	Thr	Ala	Phe	115	120	125	
25	Gln	Thr	Glu	Gln	Ile	Gln	Asp	Ser	Glu	His	Ser	Gly	Lys	Met	Val	Ala	130	135	140	
	Lys	Arg	Gln	Phe	Arg	Ile	Gly	Asp	Ile	Ala	Gly	Glu	His	Thr	Ser	Phe	145	150	155	160
30	Asp	Lys	Leu	Pro	Glu	Gly	Gly	Arg	Ala	Thr	Tyr	Arg	Gly	Thr	Ala	Phe	165	170	175	
35	Gly	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	180	185	190	
	Ala	Lys	Gln	Gly	Asn	Gly	Lys	Ile	Glu	His	Leu	Lys	Ser	Pro	Glu	Leu	195	200	205	
40	Asn	Val	Asp	Leu	Ala	Ala	Ala	Asp	Ile	Lys	Pro	Asp	Gly	Lys	Arg	His	210	215	220	
	Ala	Val	Ile	Ser	Gly	Ser	Val	Leu	Tyr	Asn	Gln	Ala	Glu	Lys	Gly	Ser	225	230	235	240
45	Tyr	Ser	Leu	Gly	Ile	Phe	Gly	Gly	Lys	Ala							245	250		

50 <210> 140
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 <212> PRT
 <213> Neisseria meningitidis

55 <400> 140

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	Met	Asn	Arg	Thr	Thr	Phe	Cys	Cys	Leu	Ser	Leu	Thr	Ala	Ala	Leu	Ile
	1				5					10					15	
5	Leu	Thr	Ala	Cys	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Val
				20					25					30		
	Ala	Ala	Asp	Ile	Gly	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu
			35					40					45			
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15	Phe	Lys	Ala	Gly	Asp	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys
					85					90					95	
	Asn	Asp	Lys	Ile	Ser	Arg	Phe	Asp	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp
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			115					120					125			
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	130						135					140				
	Glu	His	Ser	Gly	Lys	Met	Val	Ala	Lys	Arg	Gln	Phe	Arg	Ile	Gly	Asp
	145					150					155					160
30	Ile	Val	Gly	Glu	His	Thr	Ser	Phe	Gly	Lys	Leu	Pro	Lys	Asp	Val	Met
					165					170					175	
	Ala	Thr	Tyr	Arg	Gly	Thr	Ala	Phe	Gly	Ser	Asp	Asp	Ala	Gly	Gly	Lys
				180					185					190		
35	Leu	Thr	Tyr	Thr	Ile	Asp	Phe	Ala	Ala	Lys	Gln	Gly	His	Gly	Lys	Ile
			195					200					205			
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	Ile	Lys	Pro	Asp	Glu	Lys	His	His	Ala	Val	Ile	Ser	Gly	Ser	Val	Leu
	225					230					235					240
45	Tyr	Asn	Gln	Ala	Glu	Lys	Gly	Ser	Tyr	Ser	Leu	Gly	Ile	Phe	Gly	Gly
					245					250					255	
	Gln	Ala	Gln	Glu	Val	Ala	Gly	Ser	Ala	Glu	Val	Glu	Thr	Ala	Asn	Gly
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<211> 275

55 <212> PRT

<213> Neisseria meningitidis

<400> 141

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	Asp Lys Ser Leu Gln Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn	50	55	60
15	Glu Lys Leu Lys Leu Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn	65	70	75
	Gly Asp Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg	85	90	95
20	Phe Asp Phe Ile Arg Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu	100	105	110
	Glu Ser Gly Glu Phe Gln Ile Tyr Lys Gln Asp His Ser Ala Val Val	115	120	125
25	Ala Leu Gln Ile Glu Lys Ile Asn Asn Pro Asp Lys Ile Asp Ser Leu	130	135	140
	Ile Asn Gln Arg Ser Phe Leu Val Ser Gly Leu Gly Gly Glu His Thr	145	150	155
30	Ala Phe Asn Gln Leu Pro Gly Gly Lys Ala Glu Tyr His Gly Lys Ala	165	170	175
	Phe Ser Ser Asp Asp Pro Asn Gly Arg Leu His Tyr Ser Ile Asp Phe	180	185	190
	Thr Lys Lys Gln Gly Tyr Gly Arg Ile Glu His Leu Lys Thr Pro Glu	195	200	205
40	Gln Asn Val Glu Leu Ala Ser Ala Glu Leu Lys Ala Asp Glu Lys Ser	210	215	220
	His Ala Val Ile Leu Gly Asp Thr Arg Tyr Gly Gly Glu Glu Lys Gly	225	230	235
45	Thr Tyr His Leu Ala Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly	245	250	255
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<220>

<223> Tandem meningococcus protein

<400> 142

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	Ser	Arg	Phe	Asp	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile
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				340					345					350			
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				500					505					510			
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	Asp	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Ile	
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10	Lys Gly Thr Tyr His	Leu Ala Leu Phe Gly	Asp Arg Ala Gln Glu Ile
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	Val	Asn	Glu	Asn	Lys	Gln	Asn	Val	Asp	Ala	Lys	Val	Lys	Ala	Ala	Glu
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25	Leu	Ala	Asp	Thr	Asp	Ala	Ala	Leu	Asp	Ala	Thr	Thr	Asn	Ala	Leu	Asn
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	Lys	His	Ala	Glu	Ala	Phe	Asn	Asp	Ile	Ala	Asp	Ser	Leu	Asp	Glu	Thr
			180						185					190		
35	Asn	Thr	Lys	Ala	Asp	Glu	Ala	Val	Lys	Thr	Ala	Asn	Glu	Ala	Lys	Gln
			195					200					205			
40	Thr	Ala	Glu	Glu	Thr	Lys	Gln	Asn	Val	Asp	Ala	Lys	Val	Lys	Ala	Ala
45																
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55																

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5	Glu Thr Ala Ala Gly Lys Ala Glu Ala Ala Ala Gly Thr Ala Asn Thr					
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	Ala Ala Asp Lys Ala Glu Ala Val Ala Ala Lys Val Thr Asp Ile Lys					
		245		250		255
10	Ala Asp Ile Ala Thr Asn Lys Asp Asn Ile Ala Lys Lys Ala Asn Ser					
		260		265		270
	Ala Asp Val Tyr Thr Arg Glu Glu Ser Asp Ser Lys Phe Val Arg Ile					
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15	Asp Gly Leu Asn Ala Thr Thr Glu Lys Leu Asp Thr Arg Leu Ala Ser					
		290		295		300
	Ala Glu Lys Ser Ile Thr Glu His Gly Thr Arg Leu Asn Gly Leu Asp					
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20	Arg Thr Val Ser Asp Leu Arg Lys Glu Thr Arg Gln Gly Leu Ala Glu					
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	Gln Ala Ala Leu Ser Gly Leu Phe Gln Pro Tyr Asn Val Gly Arg Phe					
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	Asn Val Thr Ala Ala Val Gly Gly Tyr Lys Ser Glu Ser Ala Val Ala					
		355		360		365
30	Ile Gly Thr Gly Phe Arg Phe Thr Glu Asn Phe Ala Ala Lys Ala Gly					
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 <400> 144

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Claims

1. A composition comprising (a) a first protein which is able to induce bactericidal antibodies, comprising an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 24, and (b) a second protein which is able to induce bactericidal antibodies, comprising an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 41; wherein the first and second proteins have less than 75% sequence identity to each other.

2. The composition of claim 1, comprising (c) a third protein which is able to induce bactericidal antibodies, comprising an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 33; wherein the first and second proteins have less than 75% sequence identity to each other, the first and third proteins have less than 75% sequence identity to each other, and the second and third proteins have less than 75% sequence identity to each other.
3. A composition, for instance of claim 2, comprising (a) a first protein, comprising an amino acid sequence having at least 92% sequence identity to SEQ ID NO: 24, and (b) a second protein, comprising an amino acid sequence having at least 92% sequence identity to SEQ ID NO: 33; and (c) a third protein comprising an amino acid sequence having at least 92% sequence identity to SEQ ID NO: 41.
4. The composition of any preceding claim, wherein one or more of the proteins is a lipoprotein.
5. The composition of claim 4, wherein the lipoprotein(s) is/are expressed in *E.coli*.
6. The composition of claim 5, wherein the lipoprotein(s) is/are expressed not as a fusion protein.
7. The composition of claim 5, wherein the lipoprotein(s) is/are expressed as a fusion protein.
8. The composition of claim 7, wherein the fusion protein includes SEQ ID NO: 46 and/or the *H.influenzae* P4 lipoprotein leader sequence.
9. A composition comprising a hybrid protein of formula $\text{NH}_2\text{-A-}[\text{-X-L-}]_n\text{-B-COOH}$, wherein: n is 2 or more; L is an optional linker amino acid sequence; A is an optional N-terminal amino acid sequence; B is an optional C-terminal amino acid sequence; and the X moieties include (a) a first protein which can induce bactericidal anti-meningococcal antibodies after administration to a host animal, comprising an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 24, and (b) a second protein which can induce bactericidal anti-meningococcal antibodies after administration to a host animal, comprising an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 41; wherein the first and second proteins have less than 75% sequence identity to each other.
10. The composition of claim 9, wherein n is 3 or more and the X moieties further include (c) a third protein which can induce bactericidal anti-meningococcal antibodies after administration to a host animal, comprising an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 33; wherein the first and second proteins have less than 75% sequence identity to each other, the first and third proteins have less than 75% sequence identity to each other, and the second and third proteins have less than 75% sequence identity to each other.
11. The composition of any preceding claim, including fewer than 15 antigens.
12. The composition of any preceding claim, comprising a Neisserial antigen other than a NMB1870 protein.
13. The composition of any preceding claim, comprising a vesicle prepared from *N.meningitidis*.
14. The composition of claim 12, comprising a saccharide antigen from *N.meningitidis* serogroups A, C, W135 and Y.
15. The composition of any preceding claim, comprising a saccharide antigen from *Haemophilus influenzae* type B and/or an antigen from *Streptococcus pneumoniae*.
16. The composition of claim 14 or claim 15, wherein the saccharide antigen(s) is/are conjugated to one or more carrier proteins.
17. The composition of any preceding claim, for use as a medicament.
18. The composition for use according to claim 17, for protecting a mammal, preferably a human, against a Neisserial infection.
19. The use of a first protein which is able to induce bactericidal antibodies and comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 24, and a second protein which is able to induce bactericidal antibodies and comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 41, in the manufacture of a medicament for preventing meningococcal infection in a mammal, wherein the first and second

proteins have less than 75% sequence identity to each other.

Patentansprüche

1. Zusammensetzung, umfassend (a) ein erstes Protein, das fähig ist bakterizide Antikörper zu induzieren, umfassend eine Aminosäuresequenz mit wenigstens 85% Sequenzidentität zu SEQ ID NO: 24, und (b) ein zweites Protein, das fähig ist bakterizide Antikörper zu induzieren, umfassend eine Aminosäuresequenz mit wenigstens 85% Sequenzidentität zu SEQ ID NO: 41; wobei die ersten und zweiten Proteine weniger als 75% Sequenzidentität zueinander haben.
2. Zusammensetzung gemäß Anspruch 1, umfassend (c) ein drittes Protein, das fähig ist bakterizide Antikörper zu induzieren, umfassend eine Aminosäuresequenz mit wenigstens 85% Sequenzidentität zu SEQ ID NO: 33; wobei die ersten und zweiten Proteine weniger als 75% Sequenzidentität zueinander haben, die ersten und dritten Proteine weniger als 75% Sequenzidentität zueinander haben und die zweiten und dritten Proteine weniger als 75% Sequenzidentität zueinander haben.
3. Zusammensetzung, zum Beispiel gemäß Anspruch 2, umfassend (a) ein erstes Protein, umfassend eine Aminosäuresequenz mit wenigstens 92% Sequenzidentität zu SEQ ID NO: 24, und (b) ein zweites Protein, umfassend eine Aminosäuresequenz mit wenigstens 92% Sequenzidentität zu SEQ ID NO: 33; und (c) ein drittes Protein, umfassend eine Aminosäuresequenz mit wenigstens 92% Sequenzidentität zu SEQ ID NO: 41.
4. Zusammensetzung gemäß einem der vorhergehenden Ansprüche, wobei eines oder mehrere der Proteine ein Lipoprotein ist.
5. Zusammensetzung gemäß Anspruch 4, wobei das/die Lipoprotein(e) in *E. coli* exprimiert wird/werden.
6. Zusammensetzung gemäß Anspruch 5, wobei das/die Lipoprotein(e) nicht als ein Fusionsprotein exprimiert wird/werden.
7. Zusammensetzung gemäß Anspruch 5, wobei das/die Lipoprotein(e) als ein Fusionsprotein exprimiert wird/werden.
8. Zusammensetzung gemäß Anspruch 7, wobei das Fusionsprotein SEQ ID NO: 46 und/oder die *H. influenzae* P4-Lipoprotein Leader-Sequenz einschließt.
9. Zusammensetzung, umfassend ein Hybrid-Protein der Formel $\text{NH}_2\text{-A-}[\text{-X-L-}]_n\text{-B-COOH}$, wobei: n 2 oder mehr ist; L eine optionale Linker-Aminosäuresequenz ist; A eine optionale N-terminale Aminosäuresequenz ist; B eine optionale C-terminale Aminosäuresequenz ist; und die X-Reste (a) ein erstes Protein, das bakterizide anti-Meningokokken-Antikörper nach der Verabreichung an ein Wirtstier induzieren kann, umfassend eine Aminosäuresequenz mit wenigstens 85% Sequenzidentität zu SEQ ID NO: 24, und (b) ein zweites Protein, das bakterizide anti-Meningokokken-Antikörper nach Verabreichung an ein Wirtstier induzieren kann, umfassend eine Aminosäuresequenz mit wenigstens 85% Sequenzidentität zu SEQ ID NO: 41, einschließen; wobei die ersten und zweiten Proteine weniger als 75% Sequenzidentität zueinander haben.
10. Zusammensetzung gemäß Anspruch 9, wobei n 3 oder mehr ist und die X-Reste ferner (c) ein drittes Protein, das bakterizide anti-Meningokokken-Antikörper nach Verabreichung an ein Wirtstier induzieren kann, umfassend eine Aminosäuresequenz mit wenigstens 85% Sequenzidentität zu SEQ ID NO: 33, einschließen; wobei die ersten und zweiten Proteine weniger als 75% Sequenzidentität zueinander haben, die ersten und dritten Proteine weniger als 75% Sequenzidentität zueinander haben und die zweiten und dritten Proteine weniger als 75% Sequenzidentität zueinander haben.
11. Zusammensetzung gemäß einem der vorhergehenden Ansprüche, die weniger als 15 Antigene einschließt.
12. Zusammensetzung gemäß einem der vorhergehenden Ansprüche, umfassend ein Neisseria-Antigen, das nicht ein NMB1870-Protein ist.
13. Zusammensetzung gemäß einem der vorhergehenden Ansprüche, umfassend ein aus *N. meningitidis* hergestelltes Vesikel.

14. Zusammensetzung gemäß Anspruch 12, umfassend ein Saccharid-Antigen aus den *N. meningitidis*-Serogruppen A, C, W135 und Y.
15. Zusammensetzung gemäß einem der vorhergehenden Ansprüche, umfassend ein Saccharid-Antigen aus *Haemophilus influenzae*-Typ B und/oder ein Antigen aus *Streptococcus pneumoniae*.
16. Zusammensetzung gemäß Anspruch 14 oder Anspruch 15, wobei das/die Saccharid-Antigen(e) an ein oder mehrere Trägerprotein(e) konjugiert ist/sind.
17. Zusammensetzung gemäß einem der vorhergehenden Ansprüche zur Verwendung als Medikament.
18. Zusammensetzung zur Verwendung gemäß Anspruch 17 zum Schutz eines Säugetiers, bevorzugt eines Menschen, vor einer Neisseria-Infektion.
19. Verwendung eines ersten Proteins, das fähig ist bakterizide Antikörper zu induzieren und eine Aminosäuresequenz mit wenigstens 85% Sequenzidentität zu SEQ ID NO: 24 umfasst, und eines zweiten Proteins, das fähig ist bakterizide Antikörper zu induzieren und eine Aminosäuresequenz mit wenigstens 85% Sequenzidentität zu SEQ ID NO: 41 umfasst, für die Herstellung eines Medikaments zum Verhindern einer Meningokokken-Infektion in einem Säugetier, wobei die ersten und zweiten Proteine weniger als 75% Sequenzidentität zueinander haben.

Revendications

1. Composition comprenant (a) une première protéine qui est capable d'induire des anticorps bactéricides, comprenant une séquence d'acides aminés ayant une identité de séquence d'au moins 85 % avec SEQ ID NO : 24, et (b) une deuxième protéine qui est capable d'induire des anticorps bactéricides, comprenant une séquence d'acides aminés ayant une identité de séquence d'au moins 85 % avec SEQ ID NO : 41 ; dans laquelle les première et deuxième protéines ont une identité de séquence inférieure à 75 % l'une par rapport à l'autre.
2. Composition selon la revendication 1, comprenant (c) une troisième protéine qui est capable d'induire des anticorps bactéricides, comprenant une séquence d'acides aminés ayant une identité de séquence d'au moins 85 % avec SEQ ID NO : 33, dans laquelle les première et deuxième protéines ont une identité de séquence inférieure à 75 % l'une par rapport à l'autre, les première et troisième protéines ont une identité de séquence inférieure à 75 % l'une par rapport à l'autre et les deuxième et troisième protéines ont une identité de séquence inférieure à 75 % l'une par rapport à l'autre.
3. Composition, par exemple selon la revendication 2, comprenant (a) une première protéine comprenant une séquence d'acides aminés ayant une identité de séquence d'au moins 92 % avec SEQ ID NO : 24, et (b) une deuxième protéine, comprenant une séquence d'acides aminés ayant une identité de séquence d'au moins 92 % avec SEQ ID NO : 33 ; et (c) une troisième protéine comprenant une séquence d'acides aminés ayant une identité de séquence d'au moins 92 % avec SEQ ID NO : 41.
4. Composition selon l'une quelconque des revendications précédentes, dans laquelle une ou plusieurs des protéines est une lipoprotéine.
5. Composition selon la revendication 4, dans laquelle la (les) lipoprotéine(s) est/sont exprimées dans *E. coli*.
6. Composition selon la revendication 5, dans laquelle la (les) lipoprotéine(s) est/sont exprimées pas sous la forme d'une protéine de fusion.
7. Composition selon la revendication 5, dans laquelle la (les) lipoprotéine(s) est/sont exprimées sous la forme d'une protéine de fusion.
8. Composition selon la revendication 7, dans laquelle la protéine de fusion comprend SEQ ID NO : 46 et/ou la séquence de tête de la lipoprotéine P4 de *H. influenzae*.
9. Composition comprenant une protéine hybride de formule $\text{NH}_2\text{-A-}[\text{-X-L-}]_n\text{-B-COOH}$, dans laquelle : n vaut 2 ou plus ; L est une séquence d'acides aminés leur facultative ; A est une séquence d'acides aminés N-terminale facultative ;

B est une séquence d'acides aminés C-terminale facultative ; et les fractions X comprennent (a) une première protéine qui peut induire des anticorps anti-méningococciques bactéricides après l'administration à un animal hôte, comprenant une séquence d'acides aminés ayant une identité de séquence d'au moins 85 % avec SEQ ID NO : 24 ; et (b) une deuxième protéine qui peut induire des anticorps anti-méningococciques bactéricides après l'administration à un animal hôte, comprenant une séquence d'acides aminés ayant une identité de séquence d'au moins 85 % avec SEQ ID NO : 41 ; les première et deuxième protéines ayant une identité de séquence inférieure à 75 % l'une envers l'autre.

10. Composition selon la revendication 9, dans laquelle n vaut 3 ou plus, et les fractions X comprennent en outre (c) une troisième protéine qui peut induire des anticorps anti-méningococciques bactéricides après l'administration à un animal hôte, comprenant une séquence d'acides aminés ayant une identité de séquence de 85 % avec SEQ ID NO : 33, dans laquelle les première et deuxième protéines ont une identité de séquence inférieure à 75 % l'une par rapport à l'autre, les première et troisième protéines ont une identité de séquence inférieure à 75 % l'une par rapport à l'autre et les deuxième et troisième protéines ont une identité de séquence de 75 % l'une par rapport à l'autre.

11. Composition selon l'une quelconque des revendications précédentes, comprenant moins de 15 antigènes.

12. Composition selon l'une quelconque des revendications précédentes, comprenant un antigène de *Neisseria* autre qu'une protéine NMB1870.

13. Composition selon l'une quelconque des revendications précédentes, comprenant une vésicule préparée à partir de *N. meningitidis*.

14. Composition selon la revendication 12, comprenant un antigène saccharidique des sérogroupes A, C, W135 et Y de *N. meningitidis*.

15. Composition selon l'une quelconque des revendications précédentes, comprenant un antigène saccharidique d'*Haemophilus influenzae* type B et/ou un antigène de *Streptococcus pneumoniae*.

16. Composition selon la revendication 14 ou 15, dans laquelle l'antigène (les antigènes) saccharidique(s) est/sont conjugué(s) à une ou plusieurs protéines vectrices.

17. Composition selon l'une quelconque des revendications précédentes, pour son utilisation en tant que médicament.

18. Composition pour son utilisation selon la revendication 17, pour la protection d'un mammifère, de préférence d'un être humain, contre une infection par *Neisseria*.

19. Utilisation d'une première protéine qui est capable d'induire des anticorps bactéricides et comprend une séquence d'acides aminés ayant une identité de séquence d'au moins 85 % avec SEQ ID NO : 24, et d'une deuxième protéine qui est capable d'induire des anticorps bactéricides et comprend une séquence d'acides aminés ayant une identité de séquence d'au moins 85 % avec SEQ ID NO : 41, dans la fabrication d'un médicament pour la prévention d'une infection méningococcique chez un mammifère, dans laquelle les première et deuxième protéines ont une identité de séquence inférieure à 75 % l'une par rapport à l'autre.

FIGURE 1



FIGURE 2

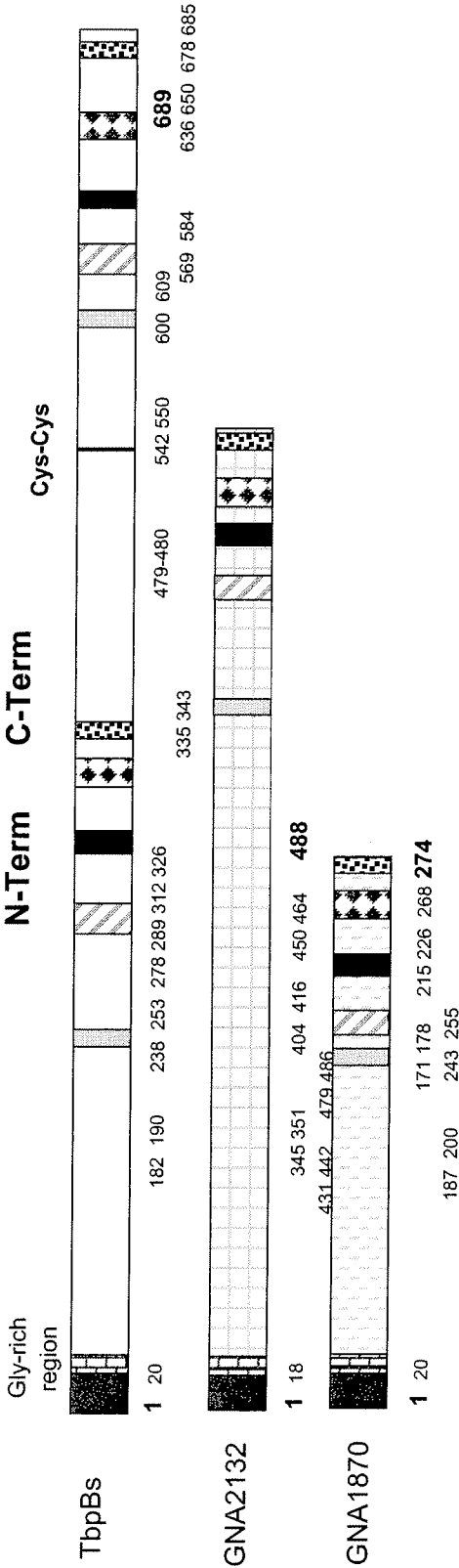


FIGURE 3

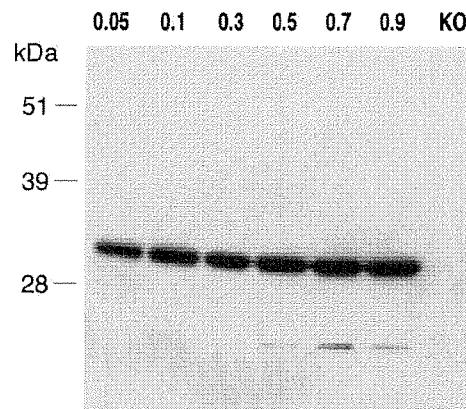


FIGURE 4

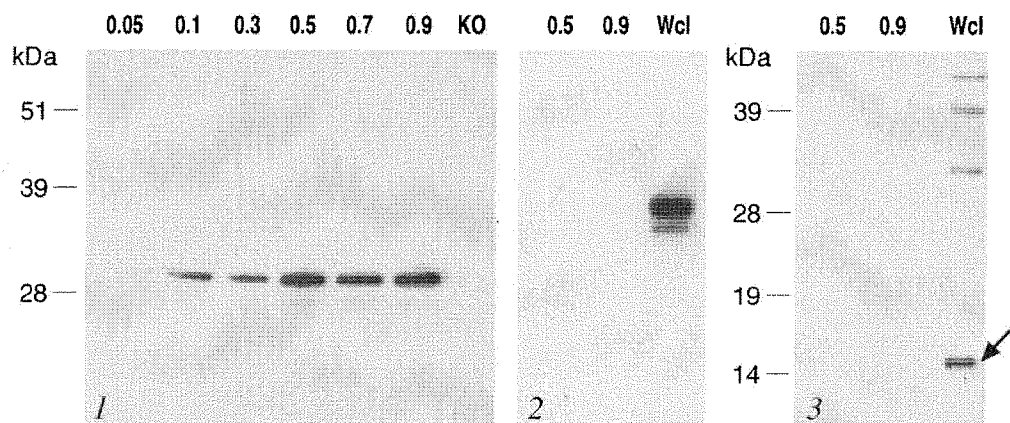


FIGURE 5

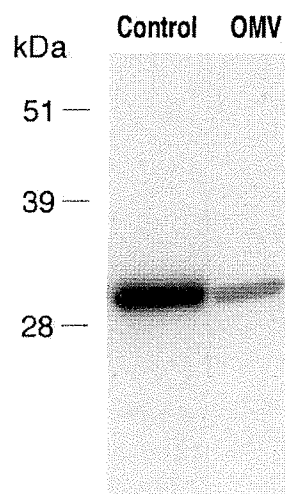


FIGURE 6

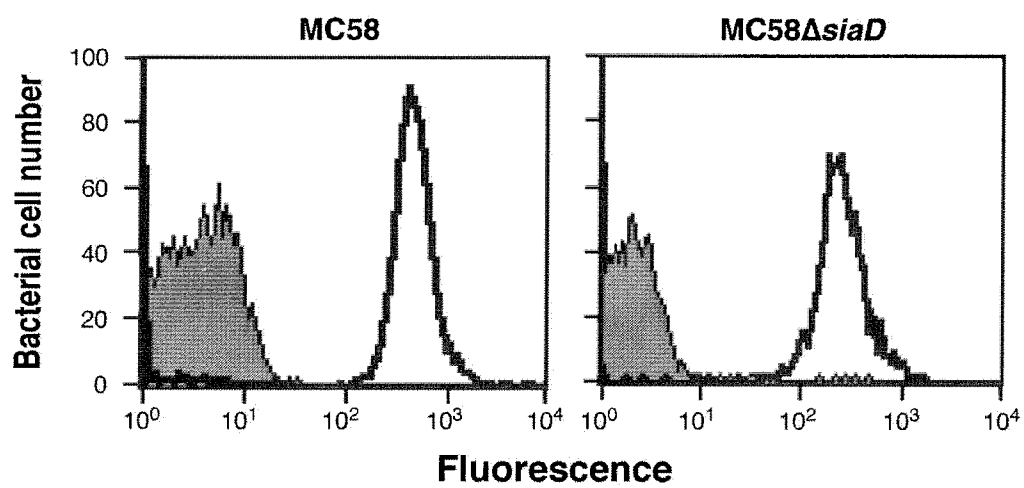


FIGURE 7

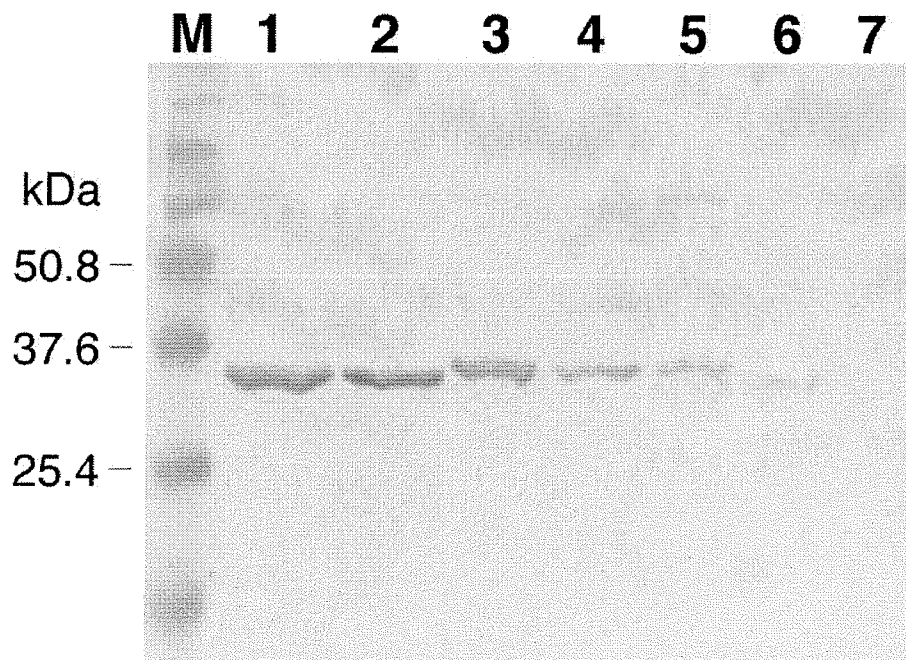


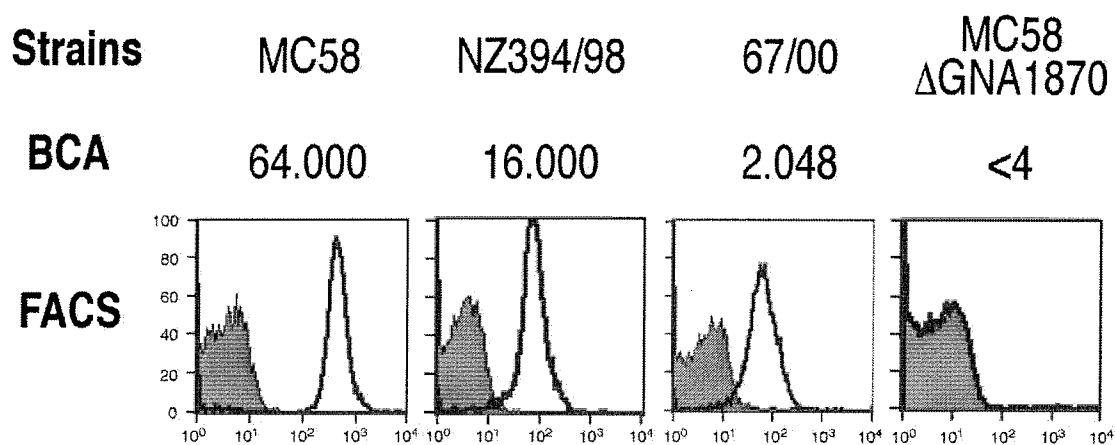
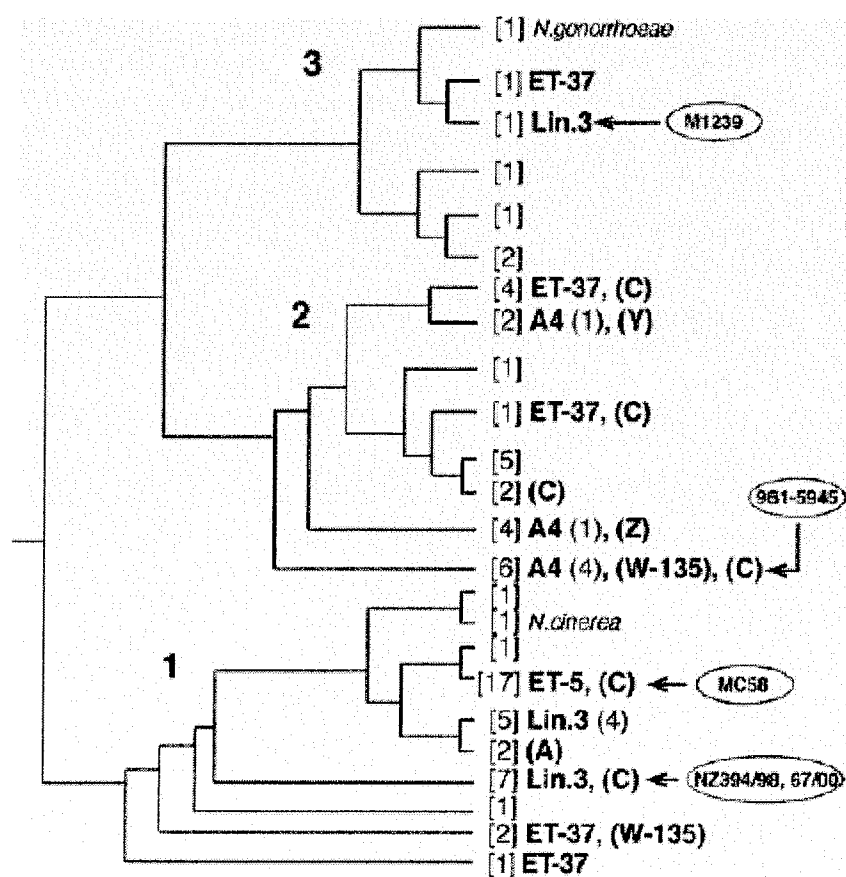
FIGURE 8**FIGURE 9**

FIGURE 10

1

type 1 -19: VNRTAFCCLSLTTALILTACS SGGGGVAADIGAGLADALTAPLDH : 26
 type 2 -19: VNRTAFCCLSLTAAALILTACS SGGGGVAADIGAGLADALTAPLDH : 26
 type 3 -19: VNRTAFCCLSLTTALILTACS SGGGGSGGGGVAAD IGTGLADALTAPLDH : 31

type 1 27: KDKGLQSLTLDQSVRKNEKLKLAQAQAEKTYGNGD ... SLNTGKLKNDKV : 73
 type 2 27: KDKSLQSLTLDQSVRKNEKLKLAQAQAEKTYGNGD ... SLNTGKLKNDKV : 73
 type 3 32: KDKGLKSLTLEDSIPQNGTILTSQAQAEKT KAGDKDNLNTGKLKNDK : 81

type 1 74: SRFDFIRQIEVDGQILITLESGEFQYKQSHSALTAFQTEQIIDSHTSGKM : 123
 type 2 74: SRFDFIRQIEVDGQILITLESGEFQIYKQDHSAVVALQIEKINNPDKIDSL : 123
 type 3 82: SRFDFVQKIEVDGQITITLASGEFQIYKQNHSAVVALQIEKINNPDKIDSL : 131

type 1 124: VAKRQERIGDIAGEHTSFDKLPEGGATYRGTAFGSDDAGGKLYTTIDFA : 173
 type 2 124: INQRSFLVSGLGGEHTAFNQLP.DCKAEYHGKAFSSDDAGGKLYTTIDFA : 172
 type 3 132: INQRSFLVSGLGGEHTAFNQLP.GCKAEYHGKAFSSDDPNGRLHYSIDFT : 180

type 1 174: AKQGNCKIEHLKSPELNVDLAAADIKPDGKRHAVISGSVLYNQAEKGSYS : 223
 type 2 173: AKQGHGKIEHLKTPEQNVELAAAEKKADEKSHAVILCDTRYGSEEKGTYPH : 222
 type 3 181: KKQGYGRIEHLKTLEQNVELAAAEKKADEKSHAVILCDTRYGSEEKGTYPH : 230

type 1 224: LGIFGCKAQEVAGSAEVKTVNGIRHIGLAAKQ : 255
 type 2 223: LALFGDRAQEIAGSATVKIGEKVHEIGIAGKQ : 254
 type 3 231: LALFGDRAQEIAGSATVKIGEKVHEIGIAGKQ : 262

FIGURE 11

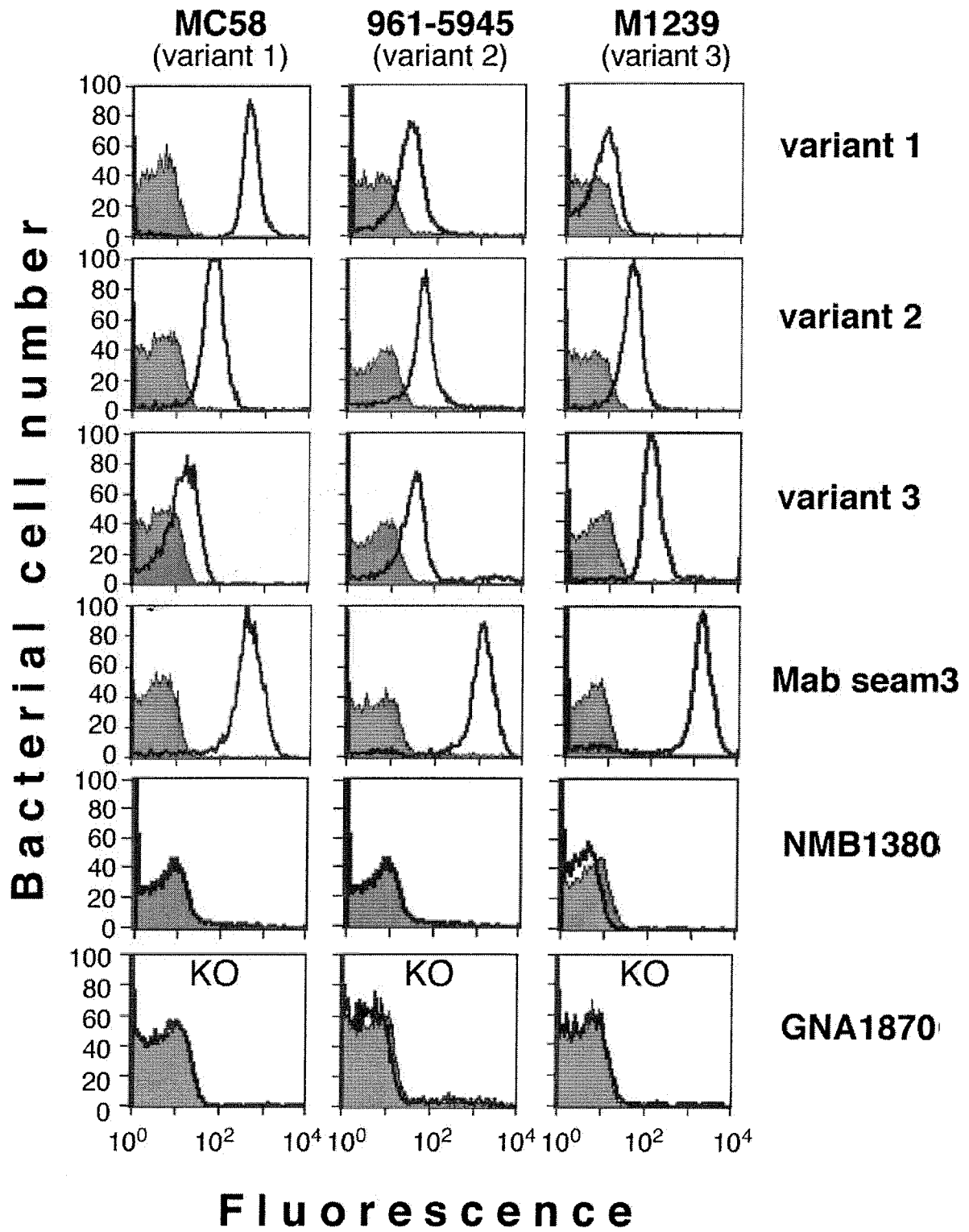


FIGURE 12

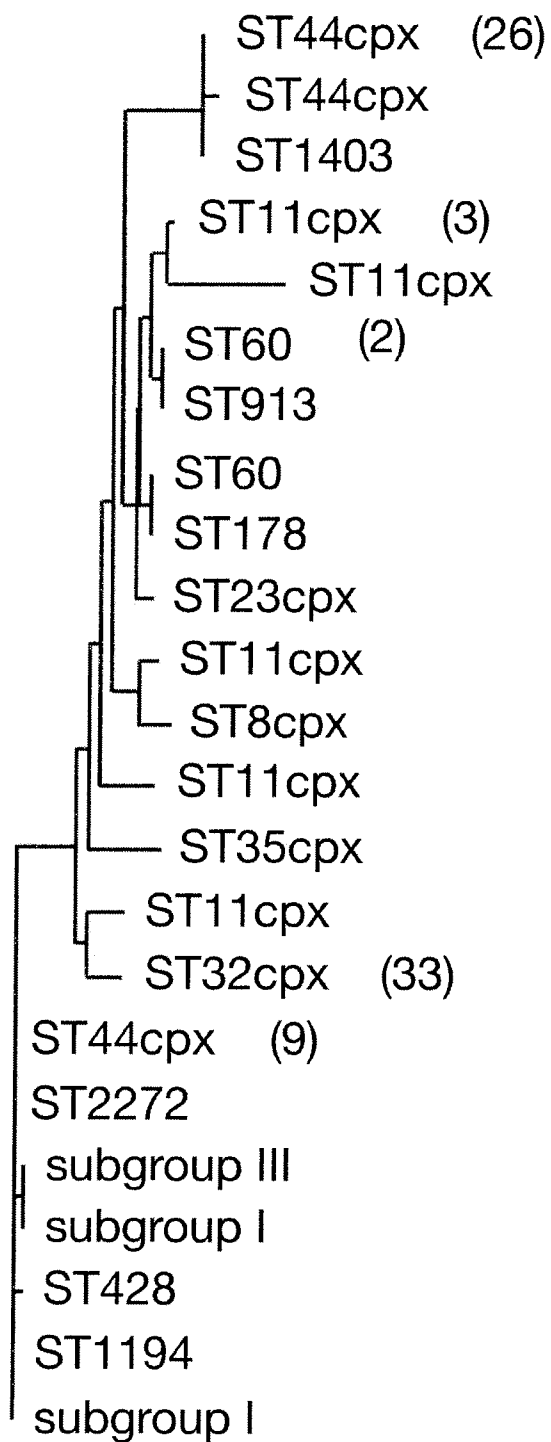


FIGURE 13

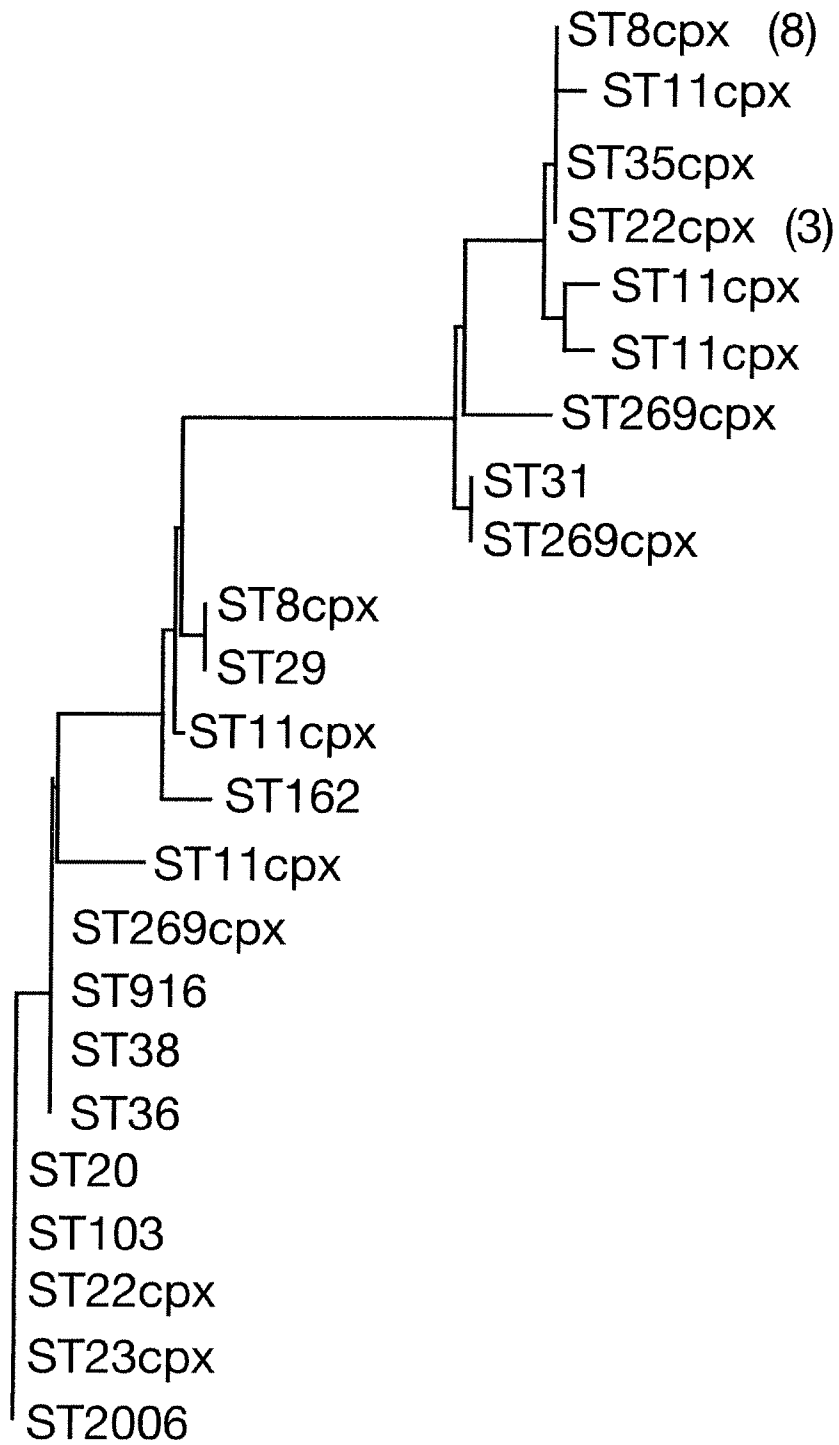
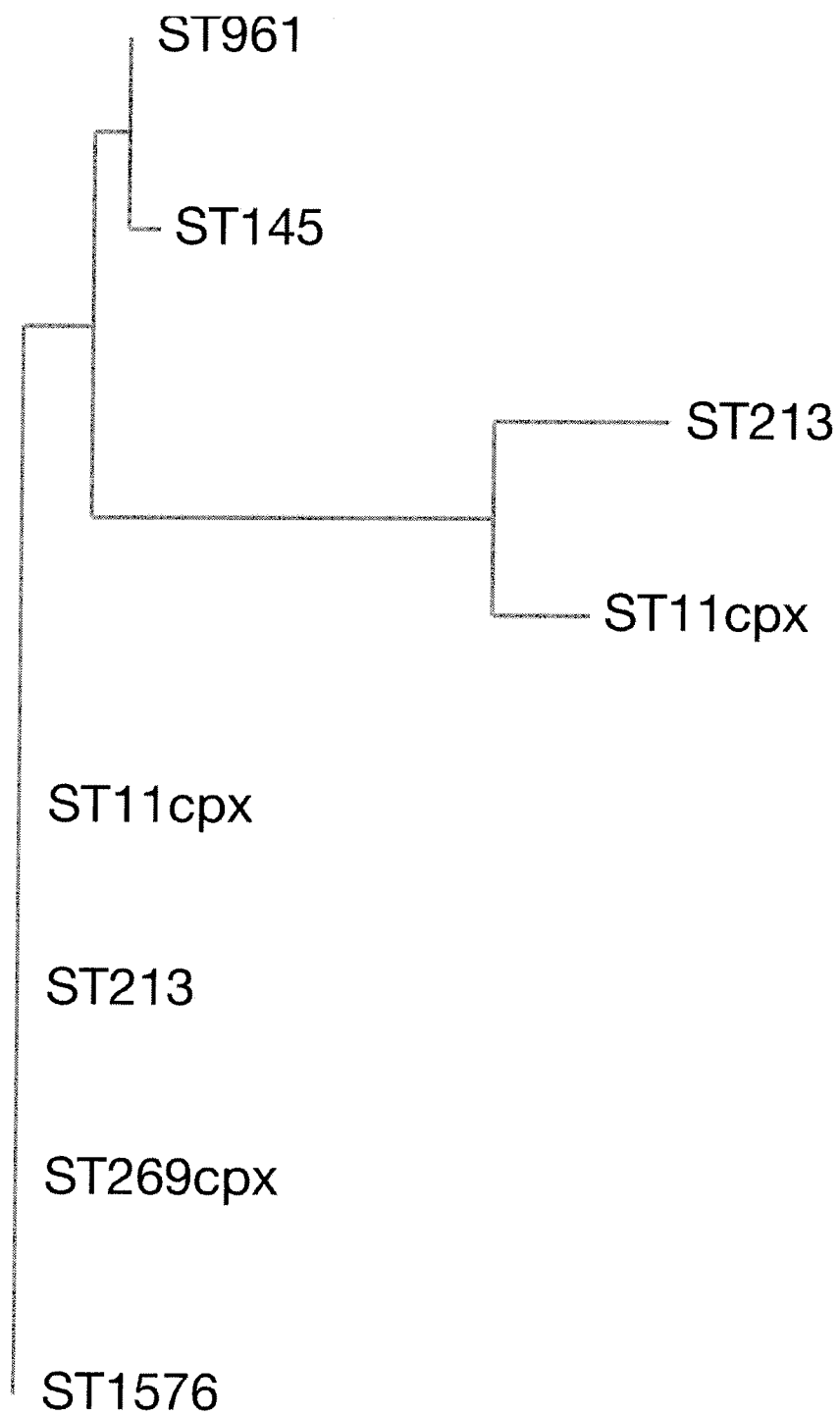


FIGURE 14



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NMB1870 MENINGOCOCCUS-FEHÉRJE TÖBBSZÖRÖS VÁLTOZATAI

Szabadalmi igénypontok

1. Készítmény, amely tartalmaz (a) egy baktericid ellenanyagokat indukálni képes első fehérjét, amely SEQ ID NO: 24 szerinti szekvenciával legalább 85%-ban azonos szekvenciájú aminosav-szekvenciát tartalmaz, és (b) egy baktericid ellenanyagokat indukálni képes második fehérjét, amely SEQ ID NO: 41 szerinti szekvenciával legalább 85%-ban azonos szekvenciájú aminosav-szekvenciát tartalmaz, ahol az első és a második fehérje szekvenciája kevesebb, mint 75%-ban azonos.

2. Az 1. igénypont szerinti készítmény, amely tartalmaz (c) egy baktericid ellenanyagokat indukálni képes második fehérjét, amely SEQ ID NO: 33 szerinti szekvenciával legalább 85%-ban azonos szekvenciájú aminosav-szekvenciát tartalmaz, ahol az első és a második fehérje szekvenciája kevesebb, mint 75%-ban azonos egymással, az első és a harmadik fehérje szekvenciája kevesebb, mint 75%-ban azonos egymással és a második és harmadik fehérje szekvenciája kevesebb, mint 75%-ban azonos egymással.

3. Készítmény, például a 2. igénypont szerinti készítmény, amely tartalmaz (a) a SEQ ID NO: 24 szerinti szekvenciával legalább 92%-ban azonos szekvenciájú aminosav-szekvenciát tartalmazó első fehérjét és (b) a SEQ ID NO: 33 szerinti szekvenciával legalább 92%-ban azonos szekvenciájú aminosav-szekvenciát tartalmazó első fehérjét és (c) a SEQ ID NO: 41 szerinti szekvenciával legalább 92%-ban azonos szekvenciájú aminosav-szekvenciát tartalmazó első fehérjét.

4. Az előző igénypontok bármelyike szerinti készítmény, ahol a fehérjék közül egy vagy több lipoprotein.

5. A 4. igénypont szerinti készítmény, ahol a lipoprotein(ek) *E. coli*-ban expresszált(ak).

6. Az 5. igénypont szerinti készítmény, ahol a lipoprotein(ek) nem fúziós fehérjeként expresszált(ak).

7. Az 5. igénypont szerinti készítmény, ahol a lipoprotein(ek) fúziós fehérjeként expresszált(ak).

8. A 7. igénypont szerinti készítmény, ahol a fúziós fehérje magában foglalja a SEQ ID NO: 46 szerinti szekvenciát és/vagy a *H. influenzae* P4 lipoprotein vezető szekvenciát.

9. Készítmény, amely NH₂-A-[X-L]_n-B-COOH képlet szerinti hibrid fehérjét tartalmaz, ahol n értéke 2 vagy több, L jelentése adott esetben jelenlévő összekötő aminosav-szekvencia, A jelentése adott esetben jelenlévő N-terminális aminosav-szekvencia, B jelentése adott esetben jelenlévő C-terminális aminosav-szekvencia és az X molekuláris részek tartalmaznak (a) gazdaállatnak való beadás után baktericid, meningococcus elleni ellenanyagokat indukálni képes első fehérjét, amely SEQ ID NO: 24 szerinti szekvenciával legalább 85%-ban azonos szekvenciájú aminosav-szekvenciát tartalmaz és (b) gazdaállatnak való beadás után baktericid, meningococcus elleni ellenanyagokat indukálni képes első fehérjét, amely SEQ ID NO: 41 szerinti szekvenciával legalább 85%-ban azonos szekvenciájú aminosav-szekvenciát tartalmaz, ahol az első és a második fehérje szekvenciája kevesebb, mint 75%-ban azonos.

10. A 9. igénypont szerinti készítmény, ahol n értéke 3 vagy több és az X molekularészek tartalmaznak továbbá (c) gazdaállatnak való beadás után baktericid, meningococcus elleni ellenanyagokat indukálni képes első fehérjét, amely SEQ ID NO: 33 szerinti szekvenciával legalább 85%-ban azonos szekvenciájú aminosav-szekvenciát tartalmaz, ahol az első és a második fehérje szekvenciája kevesebb, mint 75%-ban azonos egymással, az első és a harmadik fehérje szekvenciája kevesebb, mint 75%-ban azonos egymással és a második és harmadik fehérje szekvenciája kevesebb, mint 75%-ban azonos egymással.

11. Az előző igénypontok bármelyike szerinti készítmény, amely kevesebb, mint 15 antigént tartalmaz.

12. Az előző igénypontok bármelyike szerinti készítmény, amely NMB1870 fehérjétől különböző *Neisseria*-antigént tartalmaz.

13. Az előző igénypontok bármelyike szerinti készítmény, amely *N.meningitidis*-ből előállított vezikulumot tartalmaz.

14. A 12. igénypont szerinti készítményt, amely *N.meningitidis* A, C, W135 és Y szerocsoportból származó szacharid antigént tartalmaz.

15. Az előző igénypontok bármelyike szerinti készítmény, amely B-típusú *Haemophilus influenzae*-ből származó szacharid antigént és/vagy *Streptococcus pneumoniae*-ből származó antigént tartalmaz.

16. A 14. vagy 15. igénypont szerinti készítmény, ahol a szacharid antigen(ek) egy vagy több hordozófehérjével konjugált(ak).

17. Az előző igénypontok bármelyike szerinti készítmény gyógyszerként történő alkalmazásra.

18. A 17. igénypont szerinti készítmény az ott meghatározott alkalmazásra, emlős, előnyösen ember *Neisseria*-fertőzéssel szembeni védelmére.

19. Baktericid ellenanyagokat indukálni képes első fehérje, amely SEQ ID NO: 24 szerinti szekvenciával legalább 85%-ban azonos szekvenciájú aminosav-szekvenciát tartalmaz, és baktericid ellenanyagokat indukálni képes második fehérje, amely SEQ ID NO: 41 szerinti szekvenciával legalább 85%-ban azonos szekvenciájú aminosav-szekvenciát tartalmaz, alkalmazása emlősben meningococcus-fertőzés megelőzésére szolgáló gyógyszer előállításában, ahol az első és a második fehérje szekvenciája kevesebb, mint 75%-ban azonos.