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DESCRIPTION

TECHNICAL FIELD

[0001] This invention is in the field of protein engineering, relating in particular to the meningococcal factor H binding protein (fHbp), which is known to be a useful vaccine immunogen.

BACKGROUND ART

[0002] *Neisseria meningitidis* is a Gram-negative encapsulated bacterium which colonises the upper respiratory tract of approximately 10% of human population. Conjugate vaccines are available against serogroups A, C, W135 and Y, but the only vaccine which is available for protecting against serogroup B in a two-dose regimen is the BEXSERO™ product which was approved in 2013.

[0003] One of the protective immunogens in BEXSERO™ is fHbp, which has also been known as protein '741' (SEQ ID NO: 2536 in ref. 1; SEQ ID 1 herein), 'NMB1870', 'GNA1870' [2-4, 'P2086', 'LP2086' or 'ORF2086' [5-7]. The 3D structure of this protein is known [8,9], and the protein has two β -barrels connected by a short linker. Many publications have reported on the protective efficacy of this protein in meningococcal vaccines e.g. see references 10-14. The fHbp lipoprotein is expressed in various strains across all serogroups. fHbp sequences have been grouped into three variants [2] (referred to herein as v1, v2 and v3), and it has been found in general that serum raised against a given variant is bactericidal against strains which express that variant, 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 (except for some v2 and v3 cross-reactivity).

[0004] To increase inter-family cross-reactivity the fHbp sequence has been engineered to contain specificities for all three variants [15]. Protein engineering has also been used to remove fHbp's interaction with siderophores [16] and with factor H [17-25]. Disruption of the interaction with fH has been reported for all three variants and is postulated to provide a superior vaccine immunogen [22,26]. For v2 polypeptides, however, references 23 and 24 report an inherent instability which is also seen in mutants with disrupted fH-binding. The instability appears to arise from the N-terminal β -barrel domain, and reference 23 warns that any substitutions in this barrel might promote instability. Reference 35 discloses specific modified v2 fHbp polypeptides having increased stability over a wild type v2 polypeptide and less fH binding.

[0005] It is an object of the invention to provide further fHbp v2 and v3 mutants, but having enhanced stability.

DISCLOSURE OF THE INVENTION

[0006] Full-length fHbp from strain 2996 in v2 has the following amino acid sequence (SEQ ID NO: 2):

MNRTAFCCLSLTAALILTACSSGGGGVAADIGAGLADALTAPLDHKDKSLQSLTLDQSVRKNEKLKLAA
 QGAEKTYGNGDSLNTGKLKNDKVSFRDFIRQIEVDGQLITLESCEFQIYKQDHSVVALQIEKINNPDK
 IDSLINQRSFLVSGLGGEHTAFNQLPDGKAEYHGKAFSSDDAGGKLTYTIDFAAKQGHGKIEHLKTPEQ
 NVELAAAEKKADEKSHAVILGDTRYGSEEKGTYHLALFGDRAQEIAGSATVKIGEKEVHEIGIAGKQ

[0007] The mature lipoprotein lacks the first 19 amino acids of SEQ ID NO: 2 (underlined; provides SEQ ID NO: 4), and the Δ G form of SEQ ID NO: 2 lacks the first 26 amino acids (SEQ ID NO: 5).

[0008] Full-length fHbp from strain M1239 in v3 has the following amino acid sequence (SEQ ID NO: 3):

MNRTAFCCLSLTTALILTACSSGGGGSGGGGVAADIGTGLADALTAPLDHKDKGLKSLTLEDSEI
 PQNGTLTLSAQGAEKTFKAGDKDNSLNTGKLKNDKISRFDVQKIEVDGQTITLASGEFQIYKQNHSA
 VVALQIEKINNPDKTDSLINQRSFLVSGLGGEHTAFNQLPGGKAEYHGKAFSSDDPNRLHYSIDFTK
 KQGYGRIEHLKTLEQNVELAAAEKKADEKSHAVILGDTRYGSEEKGTYHLALFGDRAQEIAGSATVKI
 GEKEVHEIGIAGKQ

[0009] The mature lipoprotein lacks the first 19 amino acids of SEQ ID NO: 3 (underlined; provides SEQ ID NO: 40), and the Δ G form of SEQ ID NO: 3 lacks the first 31 amino acids (SEQ ID NO: 17).

[0010] The inventors have identified residues within SEQ ID NO: 2 and SEQ ID NO: 3 which can be modified to increase the polypeptide's stability. These residues are generally present across v2 and v3 sequences and so their modification can provide v2 and v3 fHbp sequences with enhanced stability. Moreover, the inventors have shown that, as well as increasing stability, mutation of these residues can advantageously decrease binding to human factor H (fH). In addition, however, the mutations disclosed herein can be combined with other mutations *e.g.* to decrease binding to human factor H (fH), for which several mutations are already known in the art.

[0011] Thus, in general the invention provides a mutant v2 or v3 fHbp which has increased stability relative to a wild-type fHbp (*e.g.* relative to SEQ ID NOs: 2 or 3) and which, optionally, has lower affinity for human factor H than a wild-type fHbp (*e.g.* relative to SEQ ID NOs: 2 or 3). The increase in stability and the optional reduction in fH affinity preferably result from the same mutation(s), but in some instances they may be due to the separate effect of combined mutations. Mutant fHbp proteins with both increased stability and reduced fH affinity may be preferred.

[0012] In a first aspect the invention provides a polypeptide comprising a mutant fHbp v2 amino acid sequence, wherein: (a) the amino acid sequence has at least *k*% sequence identity to SEQ ID NO: 5, and/or comprises a fragment of SEQ ID NO: 5; but (b) the amino acid sequence differs

from SEQ ID NO: 5 at residue 32 by the substitution S32V. In a preferred embodiment, the amino acid sequence further differs from SEQ ID NO: 5 at residues L123, V124, S125, G126, L127, and/or G128.

[0013] Where feature (a) relates to a fragment, the fragment includes the residue corresponding to residue 32 from SEQ ID NO: 5. A fragment of (a) is at least 7 amino acids long e.g. 7, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 24, 26, 28, 40, 45, 50, 55, 60 contiguous amino acids or more from SEQ ID NO: 5. The fragment will typically include at least one epitope from SEQ ID NO: 5. Epitope identification and mapping is established for fHbp [11; 27-31]. Sharing at least 30 contiguous amino acids with SEQ ID NO: 5 will be typical, and usually a mutant fHbp v2 amino acid sequence will include several (e.g. 2, 3, 4, 5 or more) fragments from SEQ ID NO: 5. Overall, a mutant fHbp v2 amino acid sequence has at least $k\%$ sequence identity to and may include several fragments of SEQ ID NO: 5.

[0014] The value of k is at least 80, and may be e.g. 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or more. For instance, it may be 90 (*i.e.* the mutant fHbp v2 amino acid sequence has at least 90% identity to SEQ ID NO: 5) or 95.

[0015] The polypeptide can, after administration to a host animal, elicit antibodies which can recognise a wild-type meningococcal polypeptide consisting of SEQ ID NO: 4. These antibodies may be bactericidal (see below). These antibodies can include some antibodies which do not recognise a v1 or a v3 polypeptide (e.g. a wild-type meningococcal polypeptide consisting of SEQ ID NO: 46 and a wild-type meningococcal polypeptide consisting of SEQ ID NO: 40), although they may also include some antibodies which cross-react with v1 and/or v3 polypeptides.

[0016] The polypeptide has, under the same experimental conditions, a higher stability than the same polypeptide but without the sequence difference/s of (b) e.g. higher stability than a wild-type meningococcal polypeptide consisting of SEQ ID NO: 4. The stability enhancement can be assessed using differential scanning calorimetry (DSC) e.g. as discussed in references 32 & 33. DSC has previously been used to assess the stability of v2 fHbp [24]. Suitable conditions for DSC to assess stability can use 20 μ M of polypeptide in a buffered solution (e.g. 25mM Tris) with a pH between 6 and 8 (e.g. 7-7.5) with 100-200mM NaCl (e.g. 150mM).

[0017] In some instances, the polypeptide of the invention may be truncated relative to SEQ ID NO: 5. Compared to the wild-type mature sequence, SEQ ID NO: 5 is already truncated at the N-terminus up to and including the poly-glycine sequence (compare SEQ ID NOs: 4 and 5), but SEQ ID NO: 5 can be truncated at the C-terminus and/or further truncated at the N-terminus.

[0018] The increase in stability is ideally at least 5°C e.g. at least 10°C, 15°C, 20°C, 25°C, 30°C, 35°C or more. These temperatures refer to the increase in thermal transition midpoint (T_m) as assessed by DSC. Wild-type fHbp shows two DSC peaks during unfolding (one for the N-terminal domain and one for the C-terminal domain) and, where a polypeptide of the invention includes both such domains, the increase refers to the stability of the N-terminal domain, which can occur even below 40°C with wild-type v2 sequences [24] (whereas C-terminal domains can

have a T_m of 80°C or more). Thus the mutant fHbp v2 amino acid sequence of the invention preferably has a N-terminal domain with a T_m of at least 45°C e.g. $\geq 50^\circ\text{C}$, $\geq 55^\circ\text{C}$, $\geq 60^\circ\text{C}$, $\geq 65^\circ\text{C}$, $\geq 70^\circ\text{C}$, $\geq 75^\circ\text{C}$, or even $\geq 80^\circ\text{C}$.

[0019] In a second embodiment, the invention provides a polypeptide comprising a mutant fHbp v3 amino acid sequence, wherein: (a) the amino acid sequence has at least $j\%$ sequence identity to SEQ ID NO: 17, and/or comprises a fragment of SEQ ID NO: 17; but (b) the amino acid sequence differs from SEQ ID NO: 17 at residue S32 by the substitution S32V. In a preferred embodiment, the amino acid sequence further differs from SEQ ID NO: 17 at residue L126.

[0020] Where feature (a) relates to a fragment, the fragment includes the residue corresponding to residue 32 from SEQ ID NO: 17. A fragment of (a) is at least 7 amino acids long e.g. 7, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 24, 26, 28, 40, 45, 50, 55, 60 contiguous amino acids or more from SEQ ID NO: 17. The fragment will typically include at least one epitope from SEQ ID NO: 17. Epitope identification and mapping is established for fHbp [11; 27-31]. Sharing at least 30 contiguous amino acids with SEQ ID NO: 17 will be typical, and usually a mutant fHbp v3 amino acid sequence will include several (e.g. 2, 3, 4, 5 or more) fragments from SEQ ID NO: 17. Overall, a mutant fHbp v3 amino acid sequence has at least $j\%$ sequence identity to and may include several fragments of SEQ ID NO: 17.

[0021] The value of j is at least 80, and may be e.g. 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or more. For instance, it may be 90 (i.e. the mutant fHbp v3 amino acid sequence has at least 90% identity to SEQ ID NO: 17) or 95.

[0022] The polypeptide can, after administration to a host animal, elicit antibodies which can recognise a wild-type meningococcal polypeptide consisting of SEQ ID NO: 40. These antibodies may be bactericidal (see below). These antibodies can include some antibodies which do not recognise a v1 or a v2 polypeptide (e.g. a wild-type meningococcal polypeptide consisting of SEQ ID NO: 46 and a wild-type meningococcal polypeptide consisting of SEQ ID NO: 4), although they may also include some antibodies which cross-react with v1 and/or v2 polypeptides.

[0023] The polypeptide has, under the same experimental conditions, a higher stability than the same polypeptide but without the sequence difference/s of (b) e.g. higher stability than a wild-type meningococcal polypeptide consisting of SEQ ID NO: 40. The stability enhancement can be assessed using differential scanning calorimetry (DSC) e.g. as discussed in references 32 & 33 DSC has previously been used to assess the stability of v3 fHbp [23]. Suitable conditions for DSC to assess stability can use 20µM of polypeptide in a buffered solution (e.g. 25mM Tris) with a pH between 6 and 8 (e.g. 7-7.5) with 100-200mM NaCl (e.g. 150mM).

[0024] In some instances, the polypeptide of the invention may be truncated relative to SEQ ID NO: 17. Compared to the wild-type mature sequence, SEQ ID NO: 17 is already truncated at the N-terminus up to and including the poly-glycine sequence (compare SEQ ID NOs: 40 and 17), but SEQ ID NO: 17 can be truncated at the C-terminus and/or further truncated at the N-

terminus.

[0025] The increase in stability is ideally at least 5°C e.g. at least 10°C, 15°C, 20°C, 25°C, 30°C, 35°C or more. These temperatures refer to the increase in thermal transition midpoint (T_m) as assessed by DSC. Wild-type fHbp shows two DSC peaks during unfolding (one for the N-terminal domain and one for the C-terminal domain) and, where a polypeptide of the invention includes both such domains, the increase refers to the stability of the N-terminal domain, which can occur at around 60°C or less with wild-type v3 sequences [24] (whereas C-terminal domains can have a T_m of 80°C or more). Thus the mutant fHbp v3 amino acid sequence of the invention preferably has a N-terminal domain with a T_m of at least 65°C e.g. $\geq 70^\circ\text{C}$, $\geq 75^\circ\text{C}$, or even $\geq 80^\circ\text{C}$.

Mutations relative to SEQ ID NO: 5

[0026] Polypeptides of the first aspect of the invention comprise an amino acid sequence which has at least k% identity to SEQ ID NO: 5, and/or comprise a fragment of SEQ ID NO: 5. In comparison to SEQ ID NO: 5, however, this amino sequence differs at residue 32 by the substitution S32V, and optionally further differs from SEQ ID NO: 5 at one or more of residues L123, V124, S125, G126, L127, G128, e.g. at 2, 3, 4, 5 or more of these 6 residues. These residues are numbered according to SEQ ID NO: 5; to match the nascent wild-type sequence (SEQ ID NO: 2), the numbering should change +26 (*i.e.* Ser-32 of SEQ ID NO: 5 is Ser-58 of SEQ ID NO: 2), and to match the mature wild-type sequence (SEQ ID NO: 4) the numbering should change +7 (which also permits easy comparison with ref. 25).

[0027] In addition to the S32V mutation, preferred residues for further mutation are , L123, V124, S125, G126, L127, and/or G128. Mutations at these residues give proteins having good stability compared to wild-type v2.

[0028] The specified residue can be deleted, but preferably it is substituted by a different amino acid. When a substitution is made, the replacement amino acid in some instances may be a simple amino acid such as glycine or alanine. In other instances, the replacement amino acid is a conservative substitution e.g. it is made within the following four groups: (1) acidic *i.e.* aspartate, glutamate; (2) basic *i.e.* lysine, arginine, histidine; (3) non-polar *i.e.* alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan; and (4) uncharged polar *i.e.* glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine. In other instances the substitution is non-conservative. In some instances the substitution may not use alanine.

[0029] Preferred substitutions at the specified residues for further mutations are as follows: L123R; V124I; S125G or S125T; G126D; L127I; G128A.

[0030] Also described herein is a mutant fHbp v2 amino acid sequence which includes a substitution at E240; this substitution will not be with alanine if only E240 is mutated, although it can be alanine if a further amino acid listed in (b) is substituted e.g. if residues E240 and H239

are both mutated. Ideally, E240 is not mutated on its own, and so a mutant fHbp v2 amino acid sequence with a substitution at E240 should also include a substitution at a second residue e.g. at both E240 and H239 (see mutants #1 and #11).

[0031] Also described herein is a mutant fHbp v2 amino acid sequence which includes a substitution at F122; this substitution will not be with alanine if only F122 is mutated, although it can be alanine if a further amino acid listed in (b) is substituted e.g. if residues F122 and S151 are both mutated. Ideally, F122 is not mutated on its own, and so a mutant fHbp v2 amino acid sequence with a substitution at F122 should also include a substitution at a second residue. When F122 is substituted it is preferred that S151 is also substituted e.g. both are substituted with cysteine, to permit formation of a disulfide bridge (see mutant #10).

[0032] Where the mutant fHbp v2 amino acid sequence includes a substitution at L123, substitution with arginine is preferred. When L123 is substituted: (i) S32 is substituted, as seen in mutant #3, and optionally S125 is also substituted, as seen in mutants #20 and #22; or (ii) S32 is substituted and one or more of residues 124-128 is/are also substituted.

[0033] Where the mutant fHbp v2 amino acid sequence includes a substitution at V124, substitution with isoleucine is preferred. When V124 is substituted it is preferred that one or more of residues 124-128 is/are also substituted.

[0034] Where the mutant fHbp v2 amino acid sequence includes a substitution at L127, substitution with isoleucine is preferred. When L127 is substituted it is preferred that one or more of residues 124-128 is/are also substituted.

[0035] The mutant fHbp v2 amino acid sequence includes a substitution at S32, and is substituted with valine. Ideally, however, S32 is not mutated on its own, and so a mutant fHbp v2 amino acid sequence with a substitution at S32 should also include a substitution at a second residue. When S32 is substituted it is preferred that (i) L123 is also substituted e.g. as seen in mutant #3, and optionally S125 is also substituted, as seen in mutants #20 and #22; or (ii) S125 is also substituted e.g. as seen in mutants #19 and #21.

[0036] Also described herein is a mutant fHbp v2 amino acid sequence which includes a substitution at 1113; this substitution will not be with alanine if only I113 is mutated, although it can be alanine if a further amino acid listed in (b) is substituted. If I113 is mutated on its own, substitution with serine is preferred e.g. as seen in mutant #7.

[0037] Also described herein is a mutant fHbp v2 amino acid sequence which includes a substitution at V33; this substitution is preferably not with isoleucine. Where the herein described mutant fHbp v2 amino acid sequence includes a substitution at 1113, this preferably is not with threonine or with alanine. Where the herein described mutant fHbp v2 amino acid sequence includes a substitution at S151, this preferably is not with phenylalanine. Where the herein described mutant fHbp v2 amino acid sequence includes a substitution at both H239 and E240, this preferably is not to R239 and Q240.

[0038] The disclosure describes mutant fHbp v2 amino acid sequences where more than one substitution may be made; these substitutions may be selected from groups 2A to 2O as follows:

2A: residues 239 and 240 *e.g.* mutant #1.

2B: residues 32 and 123 *e.g.* mutant #3.

2C: residues 125 and 126 *e.g.* mutant #5.

2D: residues 100, 125 and 126 *e.g.* mutant #6.

2E: residues 33 and 39 *e.g.* mutant #8.

2F: residues 41 and 69 *e.g.* mutant #9.

2G: residues 122 and 151 *e.g.* mutant #10.

2H: residues 100, 125, 126, 239 and 240 *e.g.* mutant #11.

2I: residues 32 and 125 *e.g.* mutants #19 and #21.

2J: residues 32, 123 and 125 *e.g.* mutants #20 and #22.

2K: residues 33 and 39, both substituted by Cys *e.g.* mutant #8.

2L: residues 41 and 69, both substituted by Cys *e.g.* mutant #9.

2M: residues 122 and 151, both substituted by Cys *e.g.* mutant #10.

2N: residues 123, 124, 125, 126, 127 and 128 *e.g.* mutant #12.

2O: residues 32, 123, 124, 125, 126, 127 and 128.

[0039] Group 2B provides the most preferred mutations, and in particular S32V and L123R (*e.g.* SEQ ID NOs: 20 and 45). Group 2O is another preferred set of mutations, which combines 2B, 2C and three further mutations (*e.g.* to give SEQ ID NO: 58).

[0040] The amino acid residues noted for mutation in a v2 sequence are numbered relative to SEQ ID NO: 5 which is from strain 2996. The corresponding amino acid residues in a v2 fHbp from any other strain can be readily identified by sequence alignment *e.g.* being the amino acid which, when aligned to SEQ ID NO: 5 using a pairwise alignment algorithm (*e.g.* the Needleman-Wunsch global alignment algorithm, as detailed below), aligns with the amino acid mentioned herein. Often the amino acid will be the same as seen in SEQ ID NO: 5 (*e.g.* residue 32 will be serine), but the alignment will easily identify if this is not the case.

[0041] In addition to the mutation(s) noted above, which aim to increase stability, a polypeptide of the invention can include one or more further mutation(s) *e.g.* to disrupt the polypeptide's interaction with siderophores or, more preferably, to disrupt the polypeptide's ability to bind to fH.

[0042] References 19 and 25 report that the interaction between fH and v2 fHbp can be disrupted by mutations at residues R80, D211, E218, E248, T220+H222 (double mutation), and G236. Numbered according to SEQ ID NO: 5, these residues are R73, D203, E210, E240, T213+H215, and G228. Of these positions, polypeptides mutated at D203, E210 or T213+H215 may be preferred because reference 25 reports no impairment of important epitopes in these mutants. The specific substitutions studied in reference 25 were R73A, D203A, E210A, T213A+H215A, G228I, and E240A; these substitutions can be suitable for use according to the invention.

[0043] Reference 24 reports that the interaction between fH and v2 fHbp can be disrupted by mutations at residues R145, S193, F194, L195, A265, E267, K268, V272, I273, L274, E283, T286, H288, F292, T304, and E313 and E283+T304 (double mutation). Numbered according to SEQ ID NO: 5, these residues are R73, S121, F122, L123, A192, E194, K195, V199, I200, L201, E210, T213, H215, F219, T231, and E240 and E210+T231. Four of these overlap with reference 25 (E210, T213, H215, E240). The specific substitutions studied in reference 24 used alanine (except for A265P and T304E), and these substitutions can be suitable for use according to the invention.

[0044] Reference 24 reports that certain substitutions in v2 can increase affinity for fH, and these should be avoided if the intention is to disrupt binding to fH e.g. E85 in SEQ ID NO: 5 (residue 157 in ref. 24).

[0045] Residues which interact with siderophores can be mutated, using the guidance in references 16 and 34 e.g. by aligning SEQ ID NO: 5 herein with SEQ ID NO: 4 of reference 16 to identify residues which can interact with siderophores e.g. with catecholates, hydroxamates or carboxylates.

[0046] Further residues which can be mutated include, but are not limited to, S23, L24, D30, Q31, R34, D95, and/or L102 e.g. using the mutations suggested in reference 35.

[0047] The polypeptide of the first aspect of the invention can comprise any of SEQ ID NOs: 18 to 36. Similarly, taking into account the ' Δ G' mutation (*i.e.* truncation of the nascent N-terminus up to and including the native poly-Gly sequence), the polypeptide of the first aspect of the invention can comprise any of SEQ ID NOs: 18 to 36 excluding amino acids 1-26 thereof. For example, the polypeptide of the first aspect can comprise SEQ ID NO: 45, or can comprise SEQ ID NO: 58.

[0048] Considering the possibility of further point mutations (e.g. to disrupt interactions with siderophores and/or fH) the polypeptide of the first aspect can comprise any of SEQ ID NOs: 19, 20, 33, 34, 35, and 36 (or any of SEQ ID NOs: 19, 20, 33, 34, 35, and 36 excluding amino acids 1-26 thereof, such as SEQ ID NO: 45) but modified by up to 5 single amino acid changes (*i.e.* 1, 2, 3, 4 or 5 single amino acid substitutions, deletions and/or insertions) provided that the modified sequence can, after administration to a host animal, elicit antibodies which bind to a meningococcal fHbp polypeptide consisting of the amino acid sequence of SEQ ID NO: 2. Such

amino acid changes should not reverse the mutations in these sequences relative to the wild-type sequence e.g. SEQ ID NO: 45 should not be mutated at residue V32 or R123.

SEQ ID NOs: 60 is a further example of v2 mutant, namely the mature form of mutant #3 for strain 8047. Mutations relative to SEQ ID NO: 17

[0049] Polypeptides of the second aspect of the invention comprise an amino acid sequence which has at least j% identity to SEQ ID NO: 17, and/or comprise a fragment of SEQ ID NO: 17. In comparison to SEQ ID NO: 17, however, this amino sequence differs at residue 32 by the substitution S32V, and optionally further differs from SEQ ID NO: 17 at residue L126. These residues are numbered according to SEQ ID NO: 17; to match the nascent wild-type sequence (SEQ ID NO: 3), the numbering should change +31 (*i.e.* Ser-32 of SEQ ID NO: 17 is Ser-63 of SEQ ID NO: 3), and to match the mature wild-type sequence (SEQ ID NO: 40) the numbering should change +12.

[0050] The specified residue can be deleted, but preferably it is substituted by a different amino acid. When a substitution is made, the replacement amino acid in some instances may be a simple amino acid such as glycine or alanine. In other instances, the replacement amino acid is a conservative substitution e.g. it is made within the following four groups: (1) acidic *i.e.* aspartate, glutamate; (2) basic *i.e.* lysine, arginine, histidine; (3) non-polar *i.e.* alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan; and (4) uncharged polar *i.e.* glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine. In other embodiments the substitution is non-conservative. In some instances the substitution may not use alanine.

[0051] A preferred substitution at the specified residue for further mutations is L126R.

[0052] Also described herein is a mutant fHbp v3 amino acid sequence which includes a substitution at E243; this substitution will not be with alanine if only E243 is mutated, although it can be alanine if a further amino acid listed in (b) is substituted e.g. if residues E243 and H242 are both mutated. Ideally, E243 is not mutated on its own, and so a mutant fHbp v3 amino acid sequence with a substitution at E243 should also include a substitution at a second residue e.g. at both E243 and H242.

[0053] Also described herein is a mutant fHbp v3 amino acid sequence which includes a substitution at F125; this substitution will not be with alanine if only F125 is mutated, although it can be alanine if a further amino acid listed in (b) is substituted e.g. if residues F125 and S154 are both mutated. Ideally, F125 is not mutated on its own, and so a mutant fHbp v3 amino acid sequence with a substitution at F125 should also include a substitution at a second residue. When F125 is substituted it is preferred that S154 is also substituted e.g. both are substituted with cysteine, to permit formation of a disulfide bridge.

[0054] Where the mutant fHbp v3 amino acid sequence includes a substitution at L126, this substitution can be alanine if residues L126 and S32 are both mutated. Substitution with arginine

is preferred. When L126 is substituted S32 is substituted, and optionally S128 is also substituted.

[0055] Also described herein is a mutant fHbp v3 amino acid sequence which includes a substitution at V127; it is preferred that this substitution will not be with alanine if only V127 is mutated, although it can be alanine if a further amino acid listed in (b) is substituted e.g. if one or more of residues 126-131 are also mutated. If V127 is mutated on its own, substitution with isoleucine is preferred. Ideally, however, V127 is not mutated on its own, and so a mutant fHbp v3 amino acid sequence with a substitution at V127 should also include a substitution at a second residue. When V127 is substituted it is preferred that one or more of residues 127-131 is/are also substituted.

[0056] Also described herein is a mutant fHbp v3 amino acid sequence includes a substitution at L130, it is preferred that this substitution will not be with alanine if only L130 is mutated, although it can be alanine if a further amino acid listed in (b) is substituted e.g. if one or more of residues 126-131 are also mutated. If L130 is mutated on its own, substitution with isoleucine is preferred. Ideally, however, L130 is not mutated on its own, and so a mutant fHbp v3 amino acid sequence with a substitution at L130 should also include a substitution at a second residue. When L130 is substituted it is preferred that one or more of residues 127-131 is/are also substituted.

[0057] The mutant fHbp v3 amino acid sequence includes a substitution at S32. Substitution with valine. Ideally, however, S32 is not mutated on its own, and so a mutant fHbp v3 amino acid sequence with a substitution at S32 should also include a substitution at a second residue. When S32 is substituted it is preferred that L126 is also substituted, and additionally S128 may also be substituted.

[0058] Also described herein is a mutant fHbp v3 amino acid sequence which includes a substitution at T113; this substitution will not be with alanine if only T113 is mutated, although it can be alanine if a further amino acid listed in (b) is substituted. If T113 is mutated on its own, substitution with serine is preferred.

[0059] Also described herein is a mutant fHbp v3 amino acid sequence which includes a substitution at 133; this preferably is not with valine. Also described herein is a mutant fHbp v3 amino acid sequence which includes a substitution at T116; this preferably is not with isoleucine. Also described herein is a mutant fHbp v3 amino acid sequence which includes a substitution at G129; this preferably is not with serine. Also described herein is a mutant fHbp v3 amino acid sequence which includes a substitution at both H242 and E243; this preferably is not to R242 and Q243.

[0060] The disclosure describes mutant fHbp v3 amino acid sequences where more than one substitution may be made; these may be selected from groups 3A to 30 as follows:

3A: residues 242 and 243.

3B: residues 32 and 126.

3C: residues 128 and 129.

3D: residues 103, 128 and 129.

3E: residues 33 and 39.

3F: residues 41 and 72.

3G: residues 125 and 154.

3H: residues 103, 128, 129, 242 and 243.

3I: residues 32 and 128.

3J: residues 32, 126 and 128.

3K: residues 33 and 39, both substituted by Cys.

3L: residues 41 and 72, both substituted by Cys.

3M: residues 125 and 154, both substituted by Cys.

3N: residues 126, 127, 128, 129, 130 and 131.

3O: residues 32, 126, 127, 128, 129, 130 and 131.

[0061] Group 3B provides the most preferred mutations, and in particular S32V and L126R (*e.g.* comprising SEQ ID NO: 44). Group 3O is another preferred mutation, which combines 3B, 3C and three further mutations (*e.g.* to give SEQ ID NO: 61).

[0062] The amino acid residues noted for mutation in a v3 sequence are numbered relative to SEQ ID NO: 17 which is from strain M1239. The corresponding amino acid residues in a v3 fHbp from any other strain can be readily identified by sequence alignment *e.g.* being the amino acid which, when aligned to SEQ ID NO: 17 using a pairwise alignment algorithm (*e.g.* the Needleman-Wunsch global alignment algorithm, as detailed below), aligns with the amino acid mentioned herein. Often the amino acid will be the same as seen in SEQ ID NO: 17 (*e.g.* residue 32 will be serine), but the alignment will easily identify if this is not the case.

[0063] In addition to the mutation(s) noted above, which aim to increase stability, a polypeptide of the invention can include one or more further mutation(s) *e.g.* to disrupt the polypeptide's interaction with siderophores or, more preferably, to disrupt the polypeptide's ability to bind to fH.

[0064] Reference 24 reports that the interaction between fH and v3 fHbp can be disrupted by mutations at residues Q107, 1147, L156, A157, L195, V196, V272, E283, T286, T304, V311, E313 and E283+T304 (double mutation). Numbered according to SEQ ID NO: 17, these

residues are: Q35, 178, L87, A88, L126, V127, V202, E213, T216, T234, V241, E243 and E213+T234. The specific substitutions studied in reference 24 used alanine (except for A157E and T231E), and these substitutions can be suitable for use according to the invention. Residues T216 and E243 are also reported in reference 23. Reference 36 reports that the interaction between fH and v3 fHbp can be disrupted by mutations at residues H288 and G318 (H218 and G248 numbered according to SEQ ID NO: 17), and these substitutions can be suitable for use according to the invention e.g. H218R, G248D.

[0065] Ref. 24 reports that certain substitutions in v3 can increase affinity for fH, and these should be avoided if the intention is to disrupt binding to fH e.g. P44 in SEQ ID NO: 17 (residue 106 in ref. 24)

[0066] Residues which interact with siderophores can be mutated, using the guidance in references 16 and 34 e.g. by aligning SEQ ID NO: 17 herein with SEQ ID NO: 4 of reference 16 to identify residues which can interact with siderophores e.g. with catecholates, hydroxamates or carboxylates.

[0067] The modified v3 polypeptide of the invention can comprise SEQ ID NO: 44. Considering the possibility of further point mutations (e.g. to disrupt interactions with siderophores and/or fH) the polypeptide of the first embodiment can comprise SEQ ID NO: 44 but modified by up to 5 single amino acid changes (i.e. 1, 2, 3, 4 or 5 single amino acid substitutions, deletions and/or insertions) provided that the modified sequence can, after administration to a host animal, elicit antibodies which bind to a meningococcal fHbp polypeptide consisting of the amino acid sequence of SEQ ID NO: 40. Such amino acid changes should not reverse the mutations in these sequences relative to the wild-type sequence e.g. SEQ ID NO: 44 should not be mutated at residue V32 or R126.

Polypeptides

[0068] Polypeptides of the invention 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.

[0069] Polypeptides of the invention are ideally at least 100 amino acids long e.g. 150aa, 175aa, 200aa, 225aa, or longer. They include a mutant fHbp v2 and/or v3 amino acid sequence, and the mutant fHbp v2 or v3 amino acid sequence should similarly be at least 100 amino acids long e.g. 150aa, 175aa, 200aa, 225aa, or longer.

[0070] The fHbp is naturally a lipoprotein in *N.meningitidis*. It has also been found to be lipidated when expressed in *E.coli* with its native leader sequence or with heterologous leader sequences. Polypeptides of the invention may have a N-terminus cysteine residue, which may be lipidated e.g. comprising a palmitoyl group, usually forming tripalmitoyl-S-glyceryl-cysteine. In other

instances the polypeptides are not lipidated.

[0071] Polypeptides are preferably prepared in substantially pure or substantially isolated form (*i.e.* substantially free from other Neisserial or host cell polypeptides). In general, the polypeptides are provided in a non-naturally occurring environment *e.g.* they are separated from their naturally-occurring environment. In certain instances, the polypeptide may be present in a composition that is enriched for the polypeptide as compared to a starting material. Thus purified polypeptide may be provided, whereby purified means that the polypeptide is present in a composition that is substantially free of other expressed polypeptides, whereby substantially free is meant that more than 50% (*e.g.* $\geq 75\%$, $\geq 80\%$, $\geq 90\%$, $\geq 95\%$, or $\geq 99\%$) of total polypeptide in the composition is a polypeptide of the invention.

[0072] Polypeptides can take various forms (*e.g.* native, fusions, glycosylated, non-glycosylated, lipidated, disulfide bridges, *etc.*).

[0073] SEQ ID NOs 4, 5, 17 and 40 do not include a N-terminus methionine. If a polypeptide of the invention is produced by translation in a biological host then a start codon is required, which will provide a N-terminus methionine in most hosts. Thus a polypeptide of the invention will, at least at a nascent stage, include a methionine residue upstream of said SEQ ID NO sequence.

[0074] Cleavage of nascent sequences means that the mutant fHbp v2 or v3 amino acid sequence might itself provide the polypeptide's N-terminus. In other instances, however, a polypeptide of the invention can include a N-terminal sequence upstream of the mutant fHbp v2 or v3 amino acid sequence. In some instances the polypeptide may have a single methionine at the N-terminus immediately followed by the mutant fHbp v2 or v3 amino acid sequence; in other instances a longer upstream sequence may be used. Such an upstream sequence may 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.* a histidine tag *i.e.* His_{*n*} where *n* = 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 *e.g.* the native upstream sequences present in SEQ ID NO: 2 or SEQ ID NO: 3.

[0075] A polypeptide of the invention may also include amino acids downstream of the final amino acid of the mutant fHbp v2 or v3 amino acid sequence. Such C-terminal extensions may 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 a histidine tag *i.e.* His_{*n*} where *n* = 4, 5, 6, 7, 8, 9, 10 or more), or sequences which enhance polypeptide stability. Other suitable C-terminal amino acid sequences will be apparent to those skilled in the art.

[0076] In some instances, the invention can exclude polypeptides which include a histidine tag (*cf.* refs. 24 & 25), and in particular a hexahistidine tag at the C-terminus.

[0077] The term "polypeptide" 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 labelling component. Also included within the definition are, for example, polypeptides 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. Polypeptides can occur as single chains or associated chains.

[0078] Polypeptides of the invention may be attached or immobilised to a solid support.

[0079] Polypeptides 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.

[0080] As disclosed in reference 164, fHbp can be split into three domains, referred to as A, B and C. Taking SEQ ID NO: 1, the three domains are (A) 1-119, (B) 120-183 and (C) 184-274:

MNRTAFCCLSLTALILTACSSGGGGVAADIGAGLADALTAPLDHKDKGLQSLTLDQSVRKNEKIKLA
 AQGAEKTYGNGDSLNTGKLKNDKVSREFDFIRQIEVDGQLITLESGEFQVYKQSHSALTAFQTEQIQDS
EHSCKMVAKRQFRIGDIAGEHTSFDKLEGGGRATYRGTAFGSDDAGGKLTYTIDFAAKQGNKIEHLK
 SPELNVDLAAADIKPDGKRHAVISGSVLYNQAEGSYSLGIFGGKAQEVAGSAEVKTVNGIRHIGLAA
 KQ

[0081] The mature form of domain 'A', from Cys-20 at its N-terminus to Lys-119, is called 'A_{mature}'.

[0082] Multiple fHbp sequences are known and these can readily be aligned using standard methods. By such alignments the skilled person can identify (a) domains 'A' (and 'A_{mature}'), 'B' and 'C' in any given fHbp sequence by comparison to the coordinates in the MC58 sequence, and (b) single residues in multiple fHbp sequences *e.g.* for identifying substitutions. For ease of reference, however, the domains are defined below:

- Domain 'A' in a given fHbp sequence is the fragment of that sequence which, when aligned to SEQ ID NO: 1 using a pairwise alignment algorithm, starts with the amino acid aligned to Met-1 of SEQ ID NO: 1 and ends with the amino acid aligned to Lys-119 of SEQ ID NO: 1.
- Domain 'A_{mature}' in a given fHbp sequence is the fragment of that sequence which, when aligned to SEQ ID NO: 1 using a pairwise alignment algorithm, starts with the amino acid aligned to Cys-20 of SEQ ID NO: 1 and ends with the amino acid aligned to Lys-119 of SEQ ID NO: 1.
- Domain 'B' in a given fHbp sequence is the fragment of that sequence which, when aligned to SEQ ID NO: 1 using a pairwise alignment algorithm, starts with the amino acid aligned to Gln-120 of SEQ ID NO: 1 and ends with the amino acid aligned to Gly-183 of SEQ ID NO: 1.
- Domain 'C' in a given fHbp sequence is the fragment of that sequence which, when

aligned to SEQ ID NO: 1 using a pairwise alignment algorithm, starts with the amino acid aligned to Lys-184 of SEQ ID NO: 1 and ends with the amino acid aligned to Gln-274 of SEQ ID NO: 1.

[0083] The preferred pairwise alignment algorithm for defining the domains is the Needleman-Wunsch global alignment algorithm [158], using default parameters (e.g. with Gap opening penalty = 10.0, and with Gap extension penalty = 0.5, using the EBLOSUM62 scoring matrix). This algorithm is conveniently implemented in the *needle* tool in the EMBOSS package [159].

[0084] In some instances, a mutant fHbp v2 or v3 amino acid sequence of the invention can be truncated to remove its domain A. In general, however, it is preferred that the mutant fHbp v2 or v3 amino acid sequence should include both a N-terminal β -barrel and a C-terminal β -barrel.

[0085] In some instances, a polypeptide can comprise an amino acid sequence as described above, except that up to 10 amino acids (*i.e.* 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10) at the N-terminus and/or up to 10 amino acids (*i.e.* 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10) at the C-terminus may be deleted.

[0086] Polypeptides of the invention typically consist of an artificial amino acid sequence, namely a sequence which is not present in any naturally-occurring meningococci.

[0087] Affinity for factor H can be quantitatively assessed using surface plasmon resonance e.g. as disclosed in references 18 and 21-24 with immobilised human fH. Mutations which provide an affinity reduction (*i.e.* an increase in the dissociation constant, K_D) of at least 10-fold, and ideally at least 100-fold, is preferred (when measured under the same experimental conditions relative to the same polypeptide but without the mutation).

Nucleic acids

[0088] The invention provides nucleic acid encoding a polypeptide of the invention as defined above.

[0089] Nucleic acids of the invention may be prepared in many ways e.g. by chemical synthesis (e.g. phosphoramidite synthesis of DNA) in whole or in part, by digesting longer nucleic acids using nucleases (e.g. restriction enzymes), by joining shorter nucleic acids or nucleotides (e.g. using ligases or polymerases), from genomic or cDNA libraries, *etc.*

[0090] Nucleic acids of the invention can take various forms e.g. single-stranded, double-stranded, vectors, primers, probes, labelled, unlabelled, *etc.*

[0091] Nucleic acids of the invention are preferably in isolated or substantially isolated form.

[0092] 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.*

[0093] Nucleic acid according to the invention may be labelled *e.g.* with a radioactive or fluorescent label.

[0094] The invention also provides vectors (such as plasmids) 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.

Bactericidal responses

[0095] Preferred polypeptides of the invention can elicit antibody responses that are bactericidal against meningococci. Bactericidal antibody responses are conveniently measured in mice and are a standard indicator of vaccine efficacy (*e.g.* see end-note 14 of ref. 37; also ref. 38).

[0096] Polypeptides of the first aspect of the invention can preferably elicit an antibody response which is bactericidal against a *N.meningitidis* strain which expresses a v2 fHbp sequence *e.g.* one or more of strains 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, and/ or L93/4286. Bactericidal responses can for instance be assessed against var2 strain M2091 (ATCC 13091).

[0097] Preferred polypeptides of the first aspect of the invention can elicit antibodies in a mouse which are bactericidal against strain M2091 in a serum bactericidal assay.

[0098] Polypeptides of the second aspect of the invention can preferably elicit an antibody response which is bactericidal against a *N.meningitidis* strain which expresses a v3 fHbp sequence *e.g.* one or more of strains M1239, 16889, gb355 (=M01-240355), m3369, m3813, ngp165. Bactericidal responses can for instance be assessed against var3 strain M01-240355, which is a *Neisseria* MLST reference strains (id 19265 in ref. 39) which has been fully sequenced (see EMBL ID CP002422 [40])

[0099] Preferred polypeptides of the second aspect of the invention can elicit antibodies in a mouse which are bactericidal against strain M01-240355 in a serum bactericidal assay.

[0100] For example, an immunogenic composition comprising these polypeptides can provide a serum bactericidal titer of $\geq 1:4$ using the Goldschneider assay with human complement [41-43], and/or providing a serum bactericidal titer of $\geq 1:128$ using baby rabbit complement.

Immunisation

[0101] Polypeptides of the invention may be used as the active ingredient of immunogenic

compositions, and so the invention provides an immunogenic composition (e.g. a vaccine) comprising a polypeptide of the invention.

[0102] The disclosure also provides 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. The invention provides immunogenic compositions comprising polypeptides of the invention for use in a method for raising an antibody response in a mammal.

[0103] The disclosure also provides a method for protecting a mammal against a Neisserial (e.g. meningococcal) infection, comprising administering to the mammal an immunogenic composition of the invention.

[0104] The disclosure also provide polypeptides of the invention for use as medicaments (e.g. as immunogenic compositions or as vaccines) or as diagnostic reagents. The disclosure also provides the use of nucleic acids or polypeptides of the invention in the manufacture of a medicament for preventing Neisserial (e.g. meningococcal) infection in a mammal.

[0105] The mammal may preferably be a human. The human may be an adult or, preferably, a child. Where the vaccine is for prophylactic use, the human is preferably a child (e.g. a toddler or infant); where the vaccine is for therapeutic use, the human is preferably an adult. A vaccine intended for children may also be administered to adults e.g. to assess safety, dosage, immunogenicity, *etc.*

[0106] The uses and methods may particularly be useful for preventing/treating diseases including, but not limited to, meningitis (particularly bacterial, such as meningococcal, meningitis) and bacteremia. For instance, they are suitable for active immunisation of individuals against invasive meningococcal disease caused by *N.meningitidis* (for example in serogroup B).

[0107] 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 fHbp 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) and then determining standard parameters including serum bactericidal antibodies (SBA) and ELISA titres (GMT). 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.

[0108] 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%.

[0109] 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 about 0.5 ml.

[0110] The invention may be used to elicit systemic and/or mucosal immunity.

[0111] 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.

[0112] The immunogenic composition of the invention may 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. 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. A thorough discussion of suitable carriers is available in ref. 44.

[0113] 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. Compositions suitable for parenteral injection may be most preferred.

[0114] 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 [45]. Compositions of the invention may be isotonic with respect to humans.

[0115] 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. The term "prevention" means that the progression of the disease is reduced and/or eliminated, or that the onset of the disease is eliminated. For example, the immune system of a subject may be primed (e.g. by vaccination) to trigger an immune response and repel infection such that the onset of the disease is eliminated. A vaccinated subject may thus get infected, but is better able to repel the infection than a control subject. This amount varies depending upon the health and physical condition of the individual to be treated, age, the taxonomic group of individuals 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.

[0116] Adjuvants which may be used in compositions of the invention include, but are not limited to insoluble metal salts, oil-in-water emulsions (e.g. MF59 or AS03, both containing squalene), saponins, non-toxic derivatives of LPS (such as monophosphoryl lipid A or 3-O-deacylated MPL), immunostimulatory oligonucleotides, detoxified bacterial ADP-ribosylating toxins, microparticles, liposomes, imidazoquinolones, or mixtures thereof. Other substances that act as immunostimulating agents are disclosed in chapter 7 of ref. 46.

[0117] The use of an aluminium hydroxide and/or aluminium phosphate adjuvant is particularly preferred, and polypeptides are generally adsorbed to these salts. These salts include oxyhydroxides and hydroxyphosphates (e.g. see chapters 8 & 9 of ref. 46). The salts can take any suitable form (e.g. gel, crystalline, amorphous, *etc.*).

Further antigenic components

[0118] Compositions of the invention include mutant v2 and/or v3 fHbp sequence. It can be useful if the composition does not include complex or undefined mixtures of antigens e.g. it may be preferred not to include outer membrane vesicles in the composition. Polypeptides of the invention are preferably expressed recombinantly in a heterologous host and then purified.

[0119] As well as including a fHbp polypeptide, a composition of the invention may also include one or more further neisserial immunogen(s), as a vaccine which targets more than one immunogen per bacterium decreases the possibility of selecting escape mutants. Thus a composition can include a second polypeptide that, when administered to a mammal, elicits an antibody response that is bactericidal against meningococcus. The second polypeptide can be a meningococcal fHbp, but will often not be a fHbp e.g. it may be a NHBA sequence, a NadA sequence, *etc.*

[0120] Any such further neisserial immunogen may be present as a separate polypeptide to the mutant v2 or v3 fHbp of the invention or may be present as a fusion polypeptide with the modified fHbp. For instance, fusion of meningococcal 936 polypeptide and fHbp polypeptides is known [55,56]. Fusion proteins comprising SEQ ID NO: 44 and/or SEQ ID NO: 45 may be particularly preferred, optionally wherein SEQ ID NO: 44 and/or 45 is/are modified by up to 5 single amino acid changes (*i.e.* 1, 2, 3, 4 or 5 single amino acid substitutions, deletions and/or insertions) as described elsewhere herein.

[0121] A composition of the invention may include a NHBA antigen. The NHBA antigen was included in the published genome sequence for meningococcal serogroup B strain MC58 [47] as gene NMB2132 (GenBank accession number GI:7227388; SEQ ID NO: 6 herein). The sequences of NHBA antigen from many strains have been published since then. For example, allelic forms of NHBA can be seen in Figures 5 and 15 of reference 48, and in example 13 and figure 21 of reference 1 (SEQ IDs 3179 to 3184 therein). Various immunogenic fragments of the NHBA antigen have also been reported. Preferred 287 antigens for use with the invention comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 6; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 6, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). Preferred fragments of (b) comprise an epitope from SEQ ID NO: 6. The most useful NHBA antigens of the invention can elicit antibodies which, after administration to a subject, can bind to a meningococcal polypeptide consisting of amino acid sequence SEQ ID NO: 6. Advantageous NHBA antigens for use with the invention can elicit bactericidal anti-meningococcal antibodies after administration to a subject.

[0122] A composition of the invention may include a NadA antigen. The NadA antigen was included in the published genome sequence for meningococcal serogroup B strain MC58 [47] as gene NMB1994 (GenBank accession number GI:7227256; SEQ ID NO: 7 herein). The sequences of NadA antigen from many strains have been published since then, and the protein's activity as a Neisserial adhesin has been well documented. Various immunogenic fragments of NadA have also been reported. Preferred NadA antigens for use with the invention comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 7; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 7, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). Preferred fragments of (b) comprise an epitope from SEQ ID NO: 7. The most useful NadA antigens of the invention can elicit antibodies which, after administration to a subject, can bind to a meningococcal polypeptide consisting of amino acid sequence SEQ ID NO: 7. Advantageous NadA antigens for use with the invention can elicit bactericidal anti-meningococcal antibodies after administration to a subject. SEQ ID NO: 15 is one such fragment.

[0123] A composition of the invention may include a NspA antigen. The NspA antigen was included in the published genome sequence for meningococcal serogroup B strain MC58 [47] as gene NMB0663 (GenBank accession number GI:7225888; SEQ ID NO: 8 herein). The antigen

was previously known from references 49 & 50. The sequences of NspA antigen from many strains have been published since then. Various immunogenic fragments of NspA have also been reported. Preferred NspA antigens for use with the invention comprise an amino acid sequence: (a) having 50% or more identity (e.g. 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 8; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 8, wherein 'n' is 7 or more (e.g. 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). Preferred fragments of (b) comprise an epitope from SEQ ID NO: 8. The most useful NspA antigens of the invention can elicit antibodies which, after administration to a subject, can bind to a meningococcal polypeptide consisting of amino acid sequence SEQ ID NO: 8. Advantageous NspA antigens for use with the invention can elicit bactericidal anti-meningococcal antibodies after administration to a subject.

[0124] Compositions of the invention may include a meningococcal HmbR antigen. The full-length HmbR sequence was included in the published genome sequence for meningococcal serogroup B strain MC58 [47] as gene NMB1668 (SEQ ID NO: 9 herein). The disclosure can use a polypeptide that comprises a full-length HmbR sequence, but it will often use a polypeptide that comprises a partial HmbR sequence. Thus in some embodiments a HmbR sequence used according to the invention may comprise an amino acid sequence having at least *i*% sequence identity to SEQ ID NO: 9, where the value of *i* is 50, 60, 70, 80, 90, 95, 99 or more. In other embodiments a HmbR sequence used according to the invention may comprise a fragment of at least *j* consecutive amino acids from SEQ ID NO: 9, where the value of *j* is 7, 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more. In other embodiments a HmbR sequence used according to the invention may comprise an amino acid sequence (i) having at least *i*% sequence identity to SEQ ID NO: 9 and/or (ii) comprising a fragment of at least *j* consecutive amino acids from SEQ ID NO: 9. Preferred fragments of *j* amino acids comprise an epitope from SEQ ID NO: 9. Such epitopes will usually comprise amino acids that are located on the surface of HmbR. Useful epitopes include those with amino acids involved in HmbR's binding to haemoglobin, as antibodies that bind to these epitopes can block the ability of a bacterium to bind to host haemoglobin. The topology of HmbR, and its critical functional residues, were investigated in reference 51. The most useful HmbR antigens of the invention can elicit antibodies which, after administration to a subject, can bind to a meningococcal polypeptide consisting of amino acid sequence SEQ ID NO: 9. Advantageous HmbR antigens for use with the invention can elicit bactericidal anti-meningococcal antibodies after administration to a subject.

[0125] A composition of the invention may include a NhhA antigen. The NhhA antigen was included in the published genome sequence for meningococcal serogroup B strain MC58 [47] as gene NMB0992 (GenBank accession number GI:7226232; SEQ ID NO: 10 herein). The sequences of NhhA antigen from many strains have been published since e.g. refs 48 & 52, and various immunogenic fragments of NhhA have been reported. It is also known as Hsf. Preferred NhhA antigens for use with the invention comprise an amino acid sequence: (a) having 50% or more identity (e.g. 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 10; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 10, wherein 'n' is 7 or more (e.g. 8, 10, 12, 14, 16,

18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). Preferred fragments of (b) comprise an epitope from SEQ ID NO: 10. The most useful NhhA antigens of the invention can elicit antibodies which, after administration to a subject, can bind to a meningococcal polypeptide consisting of amino acid sequence SEQ ID NO: 10. Advantageous NhhA antigens for use with the invention can elicit bactericidal anti-meningococcal antibodies after administration to a subject.

[0126] A composition of the invention may include an App antigen. The App antigen was included in the published genome sequence for meningococcal serogroup B strain MC58 [47] as gene NMB1985 (GenBank accession number GI:7227246; SEQ ID NO: 11 herein). The sequences of App antigen from many strains have been published since then. Various immunogenic fragments of App have also been reported. Preferred App antigens for use with the invention comprise an amino acid sequence: (a) having 50% or more identity (e.g. 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 11; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 11, wherein 'n' is 7 or more (e.g. 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). Preferred fragments of (b) comprise an epitope from SEQ ID NO: 11. The most useful App antigens of the invention can elicit antibodies which, after administration to a subject, can bind to a meningococcal polypeptide consisting of amino acid sequence SEQ ID NO: 11. Advantageous App antigens for use with the invention can elicit bactericidal anti-meningococcal antibodies after administration to a subject.

[0127] A composition of the invention may include an Omp85 antigen. The Omp85 antigen was included in the published genome sequence for meningococcal serogroup B strain MC58 [47] as gene NMB0182 (GenBank accession number GI:7225401; SEQ ID NO: 12 herein). The sequences of Omp85 antigen from many strains have been published since then. Further information on Omp85 can be found in references 53 and 54. Various immunogenic fragments of Omp85 have also been reported. Preferred Omp85 antigens for use with the invention comprise an amino acid sequence: (a) having 50% or more identity (e.g. 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 12; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 12, wherein 'n' is 7 or more (e.g. 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). Preferred fragments of (b) comprise an epitope from SEQ ID NO: 12. The most useful Omp85 antigens of the invention can elicit antibodies which, after administration to a subject, can bind to a meningococcal polypeptide consisting of amino acid sequence SEQ ID NO: 12. Advantageous Omp85 antigens for use with the invention can elicit bactericidal anti-meningococcal antibodies after administration to a subject.

[0128] A composition of the invention may include a 936 antigen. The 936 antigen was included in the published genome sequence for meningococcal serogroup B strain MC58 [47] as gene NMB2091 (SEQ ID NO: 13 herein). Preferred 936 antigens for use with the invention comprise an amino acid sequence: (a) having 50% or more identity (e.g. 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 13; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 13, wherein 'n' is 7 or more (e.g. 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100,

150, 200, 250 or more). Preferred fragments of (b) comprise an epitope from SEQ ID NO: 13. The most useful 936 antigens of the invention can elicit antibodies which, after administration to a subject, can bind to a meningococcal polypeptide consisting of amino acid sequence SEQ ID NO: 13. The 936 antigen is a good fusion partner for fHbp (e.g. see references 55 & 56).

[0129] A composition may comprise: a polypeptide comprising SEQ ID NO: 14; a polypeptide comprising SEQ ID NO: 15; and a polypeptide of the invention comprising a mutant fHbp v2 amino acid sequence and SEQ ID NO: 13 (*cf.* refs. 55 & 56).

[0130] A composition may comprise: a polypeptide comprising SEQ ID NO: 14; a polypeptide comprising SEQ ID NO: 15; and a polypeptide of the invention comprising a mutant fHbp v3 amino acid sequence and SEQ ID NO: 13 (*cf.* refs. 55 & 56).

[0131] In some instances, a polypeptide of the invention may be combined with a further meningococcal fHbp sequence. In particular, a v2 polypeptide can be combined with a v1 and/or a v3 polypeptide to increase the spectrum of strain coverage [162]. Thus a composition can comprise: (i) a polypeptide of the invention comprising a mutant fHbp v2 amino acid sequence; and (ii) a v1 fHbp polypeptide and/or a v3 fHbp polypeptide. In other embodiments, a polypeptide of the invention can comprise (i) a mutant fHbp v2 amino acid sequence and (ii) a v1 fHbp amino acid sequence and/or a v3 fHbp amino acid sequence. Thus the v1 and/or v3 sequences can be combined with the mutant v2 sequence as separate entities in a composition, or within a fusion polypeptide.

[0132] Similarly, a v3 polypeptide can be combined with a v1 and/or a v2 polypeptide to increase the spectrum of strain coverage [162]. Thus a composition can comprise: (i) a polypeptide of the invention comprising a mutant fHbp v3 amino acid sequence; and (ii) a v1 fHbp polypeptide and/or a v2 fHbp polypeptide. In other embodiments, a polypeptide of the invention can comprise (i) a mutant fHbp v3 amino acid sequence and (ii) a v1 fHbp amino acid sequence and/or a v2 fHbp amino acid sequence. Thus the v1 and/or v2 sequences can be combined with the mutant v3 sequence as separate entities in a composition, or within a fusion polypeptide.

[0133] Moreover, mutant v2 and v3 polypeptides can be combined with each other to increase strain coverage. Thus a composition can comprise: (i) a polypeptide of the invention comprising a mutant fHbp v2 amino acid sequence; (ii) a polypeptide of the invention comprising a mutant fHbp v3 amino acid sequence; and (iii) a fHbp v1 polypeptide. Alternatively, a polypeptide of the invention can comprise (i) a mutant fHbp v2 amino acid sequence (ii) a mutant v3 fHbp amino acid sequence and (iii) a fHbp v1 amino acid sequence. Thus the mutant v2 and v3 sequences can be combined with a v1 sequence as separate entities in a composition, or within a fusion polypeptide. The v1 sequence can be a wild-type sequence or a mutant sequence.

[0134] A v1 fHbp can comprise (a) an amino acid sequence which has at least k% identity to SEQ ID NO: 16, and/or (b) a fragment of SEQ ID NO: 16. Information about 'k' and fragments are given above. The fragment will typically include at least one epitope from SEQ ID NO: 16, and the v1 fHbp polypeptide will include at least one epitope which is not present in the v2 or v3 amino acid sequence of the invention, such that antibodies elicited by the v1 fHbp can recognise

v1 strains. Ideally, the v1 fHbp can elicit antibodies which are bactericidal against v1 strains e.g. against strain MC58 (available from the ATCC as 'BAA-335'). The v1 fHbp can include an amino acid mutation which disrupts its ability to bind to fH.

[0135] A v2 fHbp can comprise (a) an amino acid sequence which has at least $k\%$ identity to SEQ ID NO: 5, and/or (b) a fragment of SEQ ID NO: 5. Information about 'k' and fragments are given above. The fragment will typically include at least one epitope from SEQ ID NO: 5, and the v2 fHbp polypeptide will include at least one epitope which is not present in the v3 amino acid sequence of the invention, such that antibodies elicited by the v2 fHbp can recognise v2 strains. Ideally, the v2 fHbp can elicit antibodies which are bactericidal against v2 strains e.g. against strain M2091 (ATCC 13091). The v2 fHbp can be a polypeptide of the first embodiment.

[0136] A v3 fHbp can comprise (a) an amino acid sequence which has at least $k\%$ identity to SEQ ID NO: 17, and/or (b) a fragment of SEQ ID NO: 17. Information about 'k' and fragments are given above. The fragment will typically include at least one epitope from SEQ ID NO: 17, and the v3 fHbp polypeptide will include at least one epitope which is not present in the v2 amino acid sequence of the invention, such that antibodies elicited by the v3 fHbp can recognise v3 strains. Ideally, the v3 fHbp can elicit antibodies which are bactericidal against v3 strains e.g. against strain M01-240355. The v3 fHbp can be a polypeptide of the second embodiment.

[0137] Thus, for instance, the disclosure can provide a polypeptide comprising, within a single polypeptide chain, each of: (i) a fHbp v1 amino acid sequence; (ii) a mutant fHbp v2 amino acid sequence; and (iii) a mutant fHbp v3 amino acid sequence. The polypeptide can, after administration to a host animal, elicit antibodies which bind to each of: a meningococcal fHbp polypeptide consisting of the amino acid sequence of SEQ ID NO: 46; a meningococcal fHbp polypeptide consisting of the amino acid sequence of SEQ ID NO: 4; and a meningococcal fHbp polypeptide consisting of the amino acid sequence of SEQ ID NO: 40. The sequence of (i) can comprise an amino acid sequence which has at least $k\%$ identity to SEQ ID NO: 16. The sequence of (ii) can comprise an amino acid sequence which has at least $k\%$ identity to SEQ ID NO: 5, but differing from SEQ ID NO: 5 at residue S32 by the substitution S32V and optionally at one or more of the following residues: V33, L39, L41, F69, V100, 1113, F122, L123, V124, S125, G126, L127, G128, S151, H239, and/or E240. The sequence of (iii) can comprise an amino acid sequence which has at least $k\%$ identity to SEQ ID NO: 17, but differing from SEQ ID NO: 17 at residue S32 by the substitution S32V and optionally at one or more of the following residues: 133, L39, L41, F72, V103, T116, F125, L126, V127, S128, G129, L130, G131, S154, H242, and/or E243. Preferably: the sequence of (i) comprises SEQ ID NO: 16, optionally modified by up to 5 single amino acid changes (*i.e.* 1, 2, 3, 4 or 5 single amino acid substitutions, deletions and/or insertions); the sequence of (ii) comprises SEQ ID NO: 45, optionally modified by up to 5 single amino acid changes (*i.e.* 1, 2, 3, 4 or 5 single amino acid substitutions, deletions and/or insertions), provided such amino acid changes do not reverse the mutations in these sequences relative to the wild-type sequence; and the sequence of (iii) comprises SEQ ID NO: 44, optionally modified by up to 5 single amino acid changes, provided such amino acid changes do not reverse the mutations in these sequences relative to the wild-type sequence. Amino acid sequences (i), (ii) and (iii) can be arranged in any order from N- to C-terminus in the polypeptide, but are preferably in the order (ii), then (iii), then (i). For instance,

the disclosure provides a polypeptide of formula -A-B-C- wherein: A comprises SEQ ID NO: 45, optionally modified by up to 3 single amino acid substitutions; B comprises SEQ ID NO: 44, optionally modified by up to 3 single amino acid substitutions; and C comprises SEQ ID NO: 16, optionally modified by up to 3 single amino acid substitutions (e.g. substitution(s) to to disrupt binding to fH). A preferred C comprises SEQ ID NO: 49, where residue Arg-34 is mutated to Ser as reported for the 'R41S' mutation in ref. 21.

[0138] A particularly preferred polypeptide comprises amino acid sequence SEQ ID NO: 47. This sequence includes, from N-terminus to C-terminus: the mutant v2 (SEQ ID NO: 45); the mutant v3 (SEQ ID NO: 44); and the mutant v1 (SEQ ID NO: 49). Between these three mutant fHbp sequences there is in each case a linker sequence, SEQ ID NO: 50. In one instance, the polypeptide comprises amino acid sequence SEQ ID NO: 48, which has a N-terminus methionine, then SEQ ID NO: 37, and then SEQ ID NO: 47.

[0139] SEQ ID NO: 47 (alone, or within SEQ ID NO: 48) can optionally be modified by up to 5 single amino acid changes (*i.e.* 1, 2, 3, 4 or 5 single amino acid substitutions, deletions and/or insertions), provided such amino acid changes do not reverse the mutations in the v1, v2, and v3 sequences relative to the wild-type sequence *i.e.* amino acid residues V32, R123, V285, R379, and S543 of SEQ ID NO: 47 should not be mutated to S32, L123, S285, L379, and R543..

[0140] The mutant fusion can ideally elicit antibodies which bind to each of: a wild-type v1 meningococcal fHbp polypeptide consisting of amino acid sequence SEQ ID NO: 46; a wild-type v2 meningococcal fHbp polypeptide consisting of amino acid sequence SEQ ID NO: 4; and a wild-type v3 meningococcal fHbp polypeptide consisting of amino acid sequence SEQ ID NO: 40.

[0141] In addition to Neisserial polypeptide 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:

- a saccharide antigen from *N.meningitidis* serogroup A, C, W135 and/or Y, such as the saccharide disclosed in ref. 57 from serogroup C (see also ref. 58) or in ref. 59.
- a saccharide antigen from *Streptococcus pneumoniae* [e.g. 60, 61, 62].
- an antigen from hepatitis A virus, such as inactivated virus [e.g. 63, 64].
- an antigen from hepatitis B virus, such as the surface and/or core antigens [e.g. 64, 65].
- a diphtheria antigen, such as a diphtheria toxoid [e.g. chapter 3 of ref. 66] e.g. the CRM₁₉₇ mutant [e.g. 67].
- a tetanus antigen, such as a tetanus toxoid (e.g. chapter 4 of ref. 66).
- 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. 68 & 69).
- a saccharide antigen from *Haemophilus influenzae* B [e.g. 58].
- polio antigen(s) [e.g. 70, 71] such as IPV.
- measles, mumps and/or rubella antigens (e.g. chapters 9, 10 & 11 of ref. 66).
- influenza antigen(s) (e.g. chapter 19 of ref. 66), such as the haemagglutinin and/or

neuraminidase surface proteins.

- an antigen from *Moraxella catarrhalis* [e.g. 72].
- a protein antigen from *Streptococcus agalactiae* (group B streptococcus) [e.g. 73, 74].
- a saccharide antigen from *Streptococcus agalactiae* (group B streptococcus).
- an antigen from *Streptococcus pyogenes* (group A streptococcus) [e.g. 74, 75, 76].
- an antigen from *Staphylococcus aureus* [e.g. 77].

[0142] The composition may comprise one or more of these further antigens.

[0143] Toxic protein antigens may be detoxified where necessary (e.g. detoxification of pertussis toxin by chemical and/or genetic means [69]).

[0144] 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.

[0145] Saccharide antigens are preferably in the form of conjugates. Carrier proteins for the conjugates are discussed in more detail below.

[0146] 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.

[0147] Immunogenic compositions of the invention may be used therapeutically (*i.e.* to treat an existing infection) or prophylactically (*i.e.* to prevent future infection).

[0148] As an alternative to using proteins antigens in the immunogenic compositions of the invention, nucleic acid (which could be RNA, such as a self-replicating RNA, or DNA, such as a plasmid) encoding the antigen may be used.

[0149] In some instances a composition of the invention can comprise in addition to the fHbp sequence, conjugated capsular saccharide antigens from 1, 2, 3 or 4 of meningococcus serogroups A, C, W135 and Y. In other instance, a composition of the invention can comprise in addition to the fHbp sequence, at least one conjugated pneumococcal capsular saccharide antigen.

Meningococcus serogroups Y, W135, C and A

[0150] Current serogroup C vaccines (Menjugate™ [57,78], 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 Menactra™ vaccine contains conjugated capsular saccharide antigens from each of serogroups Y, W135, C and A.

[0151] Compositions of the present invention may include capsular saccharide antigens from one or more of meningococcus serogroups Y, W135, C and 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.

[0152] A typical quantity of each meningococcal saccharide antigen per dose is between 1µg and 20µg e.g. about 1µg, about 2.5µg, about 4µg, about 5µg, or about 10µg (expressed as saccharide).

[0153] 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.

[0154] Capsular saccharides may 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.

[0155] 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 [79].

[0156] If hydrolysis is performed, the hydrolysate will generally be sized in order to remove short-length oligosaccharides [58]. 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.

[0157] Preferred MenC saccharide antigens are disclosed in reference 78, as used in Menjugate™.

[0158] The saccharide antigen may be chemically modified. This is particularly useful for reducing hydrolysis for serogroup A [80]. De-O-acetylation of meningococcal saccharides can be performed. For oligosaccharides, modification may take place before or after depolymerisation.

[0159] 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 [80]. This modification improves resistance to hydrolysis.

Covalent conjugation

[0160] 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.

[0161] Typical carrier proteins are bacterial toxins, such as diphtheria or tetanus toxins, or toxoids or mutants thereof. The CRM₁₉₇ diphtheria toxin mutant [81] is useful, and is the carrier in the PREVNAR™ product. Other suitable carrier proteins include the *N.meningitidis* outer membrane protein complex [82], synthetic peptides [83,84], heat shock proteins [85,86], pertussis proteins [87,88], cytokines [89], lymphokines [89], hormones [89], growth factors [89], artificial proteins comprising multiple human CD4⁺ T cell epitopes from various pathogen-derived antigens [90] such as N19 [91], protein D from *H.influenzae* [92-94], pneumolysin [95] or its non-toxic derivatives [96], pneumococcal surface protein PspA [97], iron-uptake proteins [98], toxin A or B from *C.difficile* [99], recombinant *P.aeruginosa* exoprotein A (rEPA) [100], etc.

[0162] Any suitable conjugation reaction can be used, with any suitable linker where necessary.

[0163] 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 [101,102,etc.]). Other suitable techniques use carbodiimides, hydrazides, active esters, norborane, p-nitrobenzoic acid, N-hydroxysuccinimide, S-NHS, EDC, TSTU, etc.

[0164] Linkages via a linker group may be made using any known procedure, for example, the procedures described in references 103 and 104. 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 [105,106]. Other linkers include B-propionamido [107], nitrophenyl-ethylamine [108], haloacyl halides [109], glycosidic linkages [110], 6-aminocaproic acid [111], ADH [112], C₄ to C₁₂ moieties [113] 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 114 and 115.

[0165] 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.

Outer membrane vesicles

[0166] Some compositions of the invention may not include complex or undefined mixtures of antigens, which are typical characteristics of OMVs. However, the invention can be used in conjunction with OMVs, as fHbp has been found to enhance their efficacy [4], in particular by over-expressing the polypeptides of the invention in the strains used for OMV preparation. See also below.

[0167] This approach may be used in general to improve preparations of *N.meningitidis* serogroup B microvesicles [116], 'native OMVs' [117], blebs or outer membrane vesicles [e.g. refs. 118 to 123, etc.]. These may be prepared from bacteria which have been genetically manipulated [124-127] 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 [128-131]. Vesicles from a non-pathogenic *Neisseria* may be included [132]. OMVs may be prepared without the use of detergents [133,134]. They may express non-Neisserial proteins on their surface [135]. They may be LPS-depleted. They may be mixed with recombinant antigens [118,136]. Vesicles from bacteria with different class I outer membrane protein subtypes may be used e.g. six different subtypes [137,138] 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.

Host cells

[0168] The invention provides a host cell transfected with a plasmid encoding the mutant v2 or v3 polypeptide of the invention. When the host cell is a bacterium, it may be a meningococcus or an *E.coli*. The host cell may constitutively express the polypeptide, but in some instances expression may be under the control of an inducible promoter. The host cell may hyper-express the polypeptide (*cf.* ref.139). Expression of the polypeptide is ideally not phase variable.

[0169] The invention also provides outer membrane vesicles prepared from a bacterium of the invention (particularly from a meningococcus). The disclosure may also provide a process for producing vesicles from a bacterium of the invention. Vesicles prepared from these strains preferably include the polypeptide of the invention, which should be in an immunoaccessible

form in the vesicles *i.e.* an antibody which can bind to purified polypeptide of the invention should also be able to bind to the polypeptide which is present in the vesicles.

[0170] These outer membrane vesicles include any proteoliposomic vesicle obtained by disruption of or blebbing from a meningococcal outer membrane to form vesicles therefrom that include protein components of the outer membrane. Thus the term includes OMVs (sometimes referred to as 'blebs'), microvesicles (MVs [116]) and 'native OMVs' ('NOMVs' [117]).

[0171] MVs and NOMVs are naturally-occurring membrane vesicles that form spontaneously during bacterial growth and are released into culture medium. MVs can be obtained by culturing *Neisseria* in broth culture medium, separating whole cells from the smaller MVs in the broth culture medium (*e.g.* by filtration or by low-speed centrifugation to pellet only the cells and not the smaller vesicles), and then collecting the MVs from the cell-depleted medium (*e.g.* by filtration, by differential precipitation or aggregation of MVs, by high-speed centrifugation to pellet the MVs). Strains for use in production of MVs can generally be selected on the basis of the amount of MVs produced in culture *e.g.* refs. 130 & 131 describe *Neisseria* with high MV production.

[0172] OMVs are prepared artificially from bacteria, and may be prepared using detergent treatment (*e.g.* with deoxycholate), or by non-detergent means (*e.g.* see reference 134). Techniques for forming OMVs include treating bacteria with a bile acid salt detergent (*e.g.* salts of lithocholic acid, chenodeoxycholic acid, ursodeoxycholic acid, deoxycholic acid, cholic acid, ursocholic acid, *etc.*, with sodium deoxycholate [140 & 141] being preferred for treating *Neisseria*) at a pH sufficiently high not to precipitate the detergent [142]. Other techniques may be performed substantially in the absence of detergent [134] using techniques such as sonication, homogenisation, microfluidisation, cavitation, osmotic shock, grinding, French press, blending, *etc.* Methods using no or low detergent can retain useful antigens such as NspA and fHbp [134]. Thus a method may use an OMV extraction buffer with about 0.5% deoxycholate or lower *e.g.* about 0.2%, about 0.1%, <0.05% or zero.

[0173] A useful process for OMV preparation is described in reference 143 and involves ultrafiltration on crude OMVs, rather than instead of high speed centrifugation. The process may involve a step of ultracentrifugation after the ultrafiltration takes place. OMVs can also be purified using the two-stage size filtration process described in ref. 154.

[0174] Vesicles for use with the invention can be prepared from any meningococcal strain. The vesicles will usually be from a serogroup B strain, but it is possible to prepare them from serogroups other than B (*e.g.* reference 142 discloses a process for serogroup A), such as A, C, W135 or Y. The strain may be of any serotype (*e.g.* 1, 2a, 2b, 4, 14, 15, 16, *etc.*), any serosubtype, and any immunotype (*e.g.* L1; L2; L3; L3,3,7; L10; *etc.*). The meningococci may be from any suitable lineage, including hyperinvasive and hypervirulent lineages *e.g.* any of the following seven hypervirulent lineages: subgroup I; subgroup III; subgroup IV-1; ET-5 complex; ET-37 complex; A4 cluster; lineage 3.

[0175] The host cell of the invention may, in addition to encoding a polypeptide of the invention,

may have one or more further modifications. For instance, they may have a modified *fur* gene [144]. Expression of *nspA* expression may be up-regulated with concomitant *porA* and *cps* knockout. Further knockout mutants of *N.meningitidis* for OMV production are disclosed e.g. in reference 150. Reference 145 discloses the construction of vesicles from strains modified to express six different PorA subtypes. Mutant *Neisseria* with low endotoxin levels, achieved by knockout of enzymes involved in LPS biosynthesis, may also be used [146,147]. Mutant *Neisseria* engineered to reduce or switch off expression of at least one gene involved in rendering toxic the lipid A portion of LPS, in particular of *LpxI* gene, can be used with the invention [148]. Similarly, mutant *Neisseria* engineered to reduce or switch off expression of at least one gene involved in the capsular polysaccharide synthesis or export, in particular of *synX* and/or *ctrA* genes can be used with the invention. These or other mutants can all be used with the invention.

[0176] Thus a strain used with the invention may for example express more than one PorA subtype. 6-valent and 9-valent PorA strains have previously been constructed. The strain may express 2, 3, 4, 5, 6, 7, 8 or 9 of PorA subtypes: 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; Pl.7-1,1 and/or Pl.18-1,3,6. Alternatively, a strain may have been down-regulated for PorA expression e.g. in which the amount of PorA has been reduced by at least 20% (e.g. $\geq 30\%$, $\geq 40\%$, $\geq 50\%$, $\geq 60\%$, $\geq 70\%$, $\geq 80\%$, $\geq 90\%$, $\geq 95\%$, etc.), or even knocked out, relative to wild-type levels (e.g. relative to strain H44/76).

[0177] In some instances a strain may hyper-express (relative to the corresponding wild-type strain) certain proteins. For instance, strains may hyper-express NspA, protein 287 [118], fHbp [139] (including fHbp of the invention), TbpA and/or TbpB [136], Cu,Zn-superoxide dismutase, HmbR, etc.

[0178] A gene encoding a polypeptide of the invention may be integrated into the bacterial chromosome or may be present in episomal form e.g. within a plasmid.

[0179] Advantageously for vesicle production, a meningococcus may be genetically engineered to ensure that expression of the polypeptide is not subject to phase variation. Methods for reducing or eliminating phase variability of gene expression in meningococcus are disclosed in reference 149. For example, a gene may be placed under the control of a constitutive or inducible promoter, or by removing or replacing the DNA motif which is responsible for its phase variability.

[0180] In some instances a strain may include one or more of the knockout and/or hyper-expression mutations disclosed in references 122, 124, 128, and 150. For instance, following the guidance and nomenclature in these four documents, useful genes for down-regulation and/or knockout include: (a) Cps, CtrA, CtrB, CtrC, CtrD, FrpB, GalE, HtrB/MsbB, LbpA, LbpB, LpxK, Opa, Opc, PilC, PorB, SiaA, SiaB, SiaC, SiaD, TbpA, and/or TbpB; (b) CtrA, CtrB, CtrC, CtrD, FrpB, GalE, HtrB/MsbB, LbpA, LbpB, LpxK, Opa, Opc, PhoP, PilC, PmrE, PmrF, SiaA, SiaB, SiaC, SiaD, TbpA, and/or TbpB ; (c) ExbB, ExbD, rmpM, CtrA, CtrB, CtrD, GalE, LbpA, LpbB, Opa, Opc, PilC, PorB, SiaA, SiaB, SiaC, SiaD, TbpA, and/or TbpB; or (d) CtrA, CtrB, CtrD, FrpB, Opa, Opc, PilC, PorB, SiaD, SynA, SynB, SynX and/or SynC.

[0181] Where a mutant strain is used, in some instances it may have one or more, or all, of the following characteristics: (i) down-regulated or knocked-out LgtB and/or GalE to truncate the meningococcal LOS; (ii) up-regulated TbpA; (iii) up-regulated NhhA; (iv) up-regulated Omp85; (v) up-regulated LbpA; (vi) up-regulated NspA; (vii) knocked-out PorA; (viii) down-regulated or knocked-out FrpB; (ix) down-regulated or knocked-out Opa; (x) down-regulated or knocked-out Opc; (xii) deleted *cps* gene complex. A truncated LOS can be one that does not include a sialyl-lacto-N-neotetraose epitope e.g. it might be a galactose-deficient LOS. The LOS may have no α chain.

[0182] Depending on the meningococcal strain used for preparing the vesicles, they may or may not include the strain's native fHbp antigen [151].

[0183] In one preferred instance, a meningococcus does not express a functional MltA protein. As discussed in refs. 152 & 153, knockout of MltA (the membrane-bound lytic transglycosylase, also known as GNA33) in meningococcus provides bacteria which spontaneously release large amounts of membrane vesicles into culture medium, from which they can be readily purified. For instance, the vesicles can be purified using the two-stage size filtration process of ref. 154, comprising: (i) a first filtration step in which vesicles are separated from the bacteria based on their different sizes, with the vesicles passing into the filtrate; and (ii) a second filtration step in which the vesicles are retained in the retentate. The MltA mutation (down-regulation or knockout) has been used in 'GMMA' vaccines [155], and can conveniently be combined with further down regulation or knockout of in particular of at least one gene involved in rendering toxic the lipid A portion of LPS, particularly of *lpxI1* and/or of at least one gene involved in the capsular polysaccharide synthesis or export, particularly of *synX* and/or *ctrA* genes. GMMA (Generalized Modules for Membrane Antigens) are genetically detoxified OMV that are produced from meningococcal strains that have been engineered to release GMMA with reduced reactogenicity and increased immunogenicity. GMMA induce less proinflammatory cytokines than OMV when tested in the monocyte activation test (MAT).

[0184] A preferred meningococcal strain for a 'GMMA' vaccine using this approach can express a mutant v2 fHbp and/or a mutant v3 fHbp of the invention, and expression can be driven by strong promoters. Vesicles released by this strain can include the mutant v2 and/or v3 fHbp proteins in immunogenic form, and administration of the vesicles can provide bactericidal antibody response as discussed in reference 155. The strain can also express a v1 fHbp, or a v1 fHbp can instead be provided as a separate recombinant protein in soluble form (and the v1 fHbp can be a wild-type or a mutant sequence e.g. mutated to disrupt its ability to bind to fH, as discussed above). The invention can provide such strains, and can also provide the vesicles which these strains release e.g. as purified from culture media after growth of the strains. A preferred v2 mutant for expression in these strains has a mutation at S32V and additionally L123 as discussed herein, and a preferred v3 mutant for expression in these strains has a mutation at S32 and additionally L126 as discussed herein. Thus vesicles prepared from meningococci expressing these v2 and v3 mutant fHbp sequences are particularly preferred immunogens for use in vaccines of the invention. A useful wild-type v2 sequence for mutagenesis in this way can comprise SEQ ID NO: 51 or SEQ ID NO: 54 (comprising Δ G form

SEQ ID NO: 55), and a useful wild-type v3 sequence for mutagenesis in this way can comprise SEQ ID NO: 52.

[0185] Useful promoters for use in such strains include those disclosed in references 156 and 157. For instance, the promoter can be: (a) the promoter from a porin gene, preferably *porA* or *porB*, particularly from *N.meningitidis*; or (b) a rRNA gene promoter (such as a 16S rRNA gene), particularly from *N.meningitidis*. Where a meningococcal porin promoter is used, it is preferably from *porA*, and even more particularly a -10 region from a meningococcal *porA* gene promoter, and/or a -35 region from a meningococcal *porA* gene promoter (preferably wherein the -10 region and the -35 region are separated by an intervening sequence of 12-20 nucleotides, and wherein the intervening sequence either contains no poly-G sequence or includes a poly-G sequence having no more than eight consecutive G nucleotides). Where a rRNA gene promoter is used, it can comprise more particularly (i) a -10 region from a meningococcal rRNA gene promoter and/or (ii) a -35 region from a meningococcal rRNA gene promoter. It is also possible to use a hybrid of (a) and (b), for instance to have a -10 region from a *porA* promoter and a -35 region from a rRNA promoter (which can be a consensus -35 region). A useful promoter can thus be a promoter which includes either (i) a -10 region from a (particularly meningococcal) rRNA gene and a -35 region from a (particularly meningococcal) *porA* gene, or (ii) a -10 region from a (particularly meningococcal) *porA* gene and a -35 region from a (particularly meningococcal) rRNA gene.

[0186] If LOS is present in a vesicle it is possible to treat the vesicle so as to link its LOS and protein components ("intra-bleb" conjugation [150]).

General

[0187] The term "comprising" encompasses "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. References to "comprising" (or "comprises", etc.) may optionally be replaced by references to "consisting of" (or "consists of", etc.). The term "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention.

[0188] The term "about" in relation to a numerical value x is optional and means, for example, x $\pm$ 10%.

[0189] 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.

[0190] "Sequence identity" can be 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, but is preferably

determined by the Needleman-Wunsch global alignment algorithm [158], using default parameters (e.g. with Gap opening penalty = 10.0, and with Gap extension penalty = 0.5, using the EBLOSUM62 scoring matrix). This algorithm is conveniently implemented in the *needle* tool in the EMBOSS package [159]. Where the application refers to sequence identity to a particular SEQ ID, the identity should be calculated over the entire length of that SEQ ID.

[0191] The term "fragment" in reference to polypeptide sequences means that the polypeptide is a fraction of a full-length protein. Such fragments may possess qualitative biological activity in common with the full-length protein, for example, a fragment may contain or encode one or more epitopes, such as immunodominant epitopes, that allow similar immune response to be raised to the fragment as to the full-length sequence. Polypeptide fragments generally have an amino (N) terminus portion and/or carboxy (C) terminus portion deleted as compared to the native protein, but wherein the remaining amino acid sequence of the fragment is identical to the amino acid sequence of the native protein. Polypeptide fragments may contain, for example: about 7, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 24, 26, 28, 40, 45, 50, 55, 60, 70, 80, 90, 100, 150, 200, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262 contiguous amino acids, including all integers in between, of a reference polypeptide sequence, for example between 50 and 260, 50 and 255, 50 and 250, 50 and 200, 50 and 150 contiguous amino acids of a reference polypeptide sequence. The term fragment explicitly excludes full length fHbp polypeptides and mature lipoproteins thereof.

[0192] 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. The four main hypervirulent clusters are ST32, ST44, ST8 and ST11 complexes.

[0193] In general, the disclosure does not encompass the various fHbp sequences specifically disclosed in references 2, 3, 5, 6, 7, 160, 161, 162, 163, 164, 165, 166, and 167.

BRIEF DESCRIPTION OF THE DRAWINGS

[0194]

Figure 1 shows the different sensitivity of fHbp variants to chymotrypsin cleavage. The arrow shows the position of full-length fHbp proteins.

Figure 2 shows western blot analysis of v2 mutants. Lanes are: (1 & 2) Recombinant purified v2 wild type; (4) v2 wild type lysate; (5) mutant #1; (6) mutant #2; (7) mutant #4; (8) mutant #5; (9)

mutant #7; (10) mutant #8; (11) mutant #12; (12) mutant #14 (13) mutant #15; (14) fHbp var2 NΔG-trx control *i.e.* v2 protein where N-terminal sequence GPDSDDLQQRR (SEQ ID NO: 37) is replaced by GSKDISS (SEQ ID NO: 38). Lanes 2-14 included chymotrypsin. M is molecular markers.

Figure 3 shows further western blot analysis of v2 mutants. Lanes are: (1&2) mutant #3; (3&4) mutant #6; (5&6) mutant #9; (7&8) mutant #10; (9&10) mutant #13; (11&12) Δgono; (13&14) v2 wildtype; (15&16) mutant #22. Odd-numbered lanes are for proteins which were incubated without chymotrypsin, whereas even-numbered lanes were for proteins incubated with chymotrypsin. The 'Δgono' protein is a recombinant v2 where the N-terminal sequence (SEQ ID NO: 37) has been removed.

Figure 4 shows further western blot analysis of v2 mutants. Lanes are: (1&2) mutant #11; (3&4) N-trx; (5-7) mutant #19; (8&9) mutant #20; (10&11) mutant #21. Lanes 2, 4, 7, 9 and 11 proteins which were incubated with chymotrypsin, whereas the other lanes had no chymotrypsin. The 'N-trx' protein is a recombinant v2 where the N-terminal sequence (SEQ ID NO: 37) is replaced by SEQ ID NO: 39.

Figure 5 shows DSC results for wild-type and S58V/L149R mutant v2 fHbp. The C-terminal domain was unaffected by the mutation, but the T_m of the N-terminal domain was increased by >20°C (marked with the arrow). The y-axis shows C_p (kcal/mol/°C), and the x-axis show temperature (°C).

Figure 6 shows the SPR response of wild-type (solid) and mutant (dashed) v2 fHbp.

Figure 7 shows the SPR response of v3 fHbp, either as wild-type (top) or with various mutations.

Figure 8 shows DSC results for the triple fusion protein of SEQ ID NO: 48. The axes are as in Fig.5.

MODES FOR CARRYING OUT THE INVENTION

fHbp mutations

[0195] The v2 fHbp is recognised as being unstable. To analyse the underlying structural reasons for this undesirable property, with a view to engineering the sequence to improve stability, the inventors analysed sequence alignments and 3D structures of fHbp polypeptides. One area of particular interest was the structural interface between the N-terminal and C-terminal domains [168].

[0196] The inventors identified the mutations explained in Table 1. Three of the positions identified for mutation overlap with references 24 and 25, but the invention does not encompass

the polypeptides reported in the prior art *i.e.* where the polypeptides include substitutions solely at these positions by alanine. For instance, the disclosure describes polypeptides where E240 can be substituted with histidine to match v1, and is ideally paired with substitution at residue H239 (mutants #1 and #11). Similarly, if F122 is substituted then it is preferably paired with substitution at S151, both with cysteine to permit formation of a disulfide bridge (mutant #10). Also, if L123 is substituted then it can be substituted with arginine (rather than alanine), or it can be paired with substitution at other residues *e.g.* at S32 (see mutant #3), at S125 (see mutants #20 and #22), or with substitution at residues 124-128 (see mutant #12).

Stability studies

[0197] Unstable proteins tend to be less folded and for this reason prone to cleavage and degradation by proteases. Figure 1 shows that v2 fHbp is more sensitive to chymotrypsin degradation than v1 and v3, and so this test can be used to assess stability of the mutant proteins.

[0198] For Figure 1, wild-type fHbp v1, v2 and v3 were prepared at 0.5mg/μL in 50mM Tris-HCl, 150mM NaCl, pH 8. Chymotrypsin was added at 1:100 (w/w) ratio. Samples were incubated at 24°C, 50mL volume, no shaking. Samples were extracted and boiled for 0, 1, 3, or 6 hours; then run on 12% bis-Tris gel (MES buffer). The left-hand lane, marked *, indicates a sample incubated for 6 hours without protease.

[0199] Cell lysates of *E. coli* expressing the recombinant proteins have been incubated with 1:100 w/w ratio chymotrypsin for 3 hours at 25 °C. The degradation pattern has been analysed by Western blotting following the incubation with an immune polyclonal serum elicited in rabbit against all three fHbp variants. The presence of cleavage products at lower apparent molecular weight (Figures 2-4) is interpreted as an indication of instability, whereas persistence of a band corresponding to an apparent MW of ~30 kDa is interpreted as an indication of increased stability. Mutants #1-6, #12 and #22 all showed increased resistance to chymotrypsin cleavage compared to the wild type v2.

[0200] DSC has been used as an independent approach to assess the effects of mutations on the stability of purified recombinant fHbp v2 proteins. T_m (melting temperature) measured by DSC corresponds to the temperature at which the analysed protein is 50% in the folded state and 50% in the unfolded state. Changes which stabilize the conformation of a protein will increase T_m , whereas destabilizing changes will decrease T_m . As seen in Figure 3D of ref. 24, the DSC profile of wild-type v2 fHbp shows two T_m values: T_{m1} at ~40°C, which corresponds to the melting temperature of the N-terminal domain, and T_{m2} at ~80°C corresponding to the melting temperature of the C-terminal domain. Values of T_{m1} and T_{m2} for analyzed mutants are shown in Table 1. Mutants #2, #4, #5, #12, #19 and #21 showed increased T_m of the N-terminal domain relative to the wild-type protein, and this effect was more marked for mutants #2, #4 and #12.

[0201] Size-exclusion chromatography (SEC) was used to assess the percentage of monomeric protein, and results are also shown in Table 1.

Mutants #2, #3, and #4

[0202] Mutant #3 (group 2B) gave the best overall results in the v2 stability studies. This protein (SEQ ID NO: 20) includes mutations at Ser-58 (S32 in SEQ ID NO: 5) and Leu-149 (L123 in SEQ ID NO: 5), with substitutions by Val and Arg, respectively. The mutant v2 protein (SEQ ID NO: 20, comprising SEQ ID NO: 45) was analysed by DSC and, compared to the wild-type sequence, the T_m of its N-terminus domain is $>20^\circ\text{C}$ higher (Figure 5).

[0203] In a serum bactericidal assay this v2 mutant could compete for binding to human antibodies which had been raised using a wild-type v2 sequence.

[0204] Although the S58V and L149R mutations had been introduced to improve stability, and did indeed achieve this goal, Figure 6 shows that the mutant v2 polypeptide (dotted line) surprisingly showed much reduced binding to fH compared to the wild-type v2 sequence (solid line) when measured by surface plasmon resonance against immobilised fH. The S58V mutation on its own had little impact on fH binding, and the S58V/L149R double mutant showed higher fH binding than fHbp carrying only the L149R mutant.

[0205] When mutant #3 was further combined with the 'E313A' mutation in v2 there was a complete loss of fH binding as assessed by SPR.

[0206] The equivalent mutations were introduced into a v3 sequence (SEQ ID NO: 17), to give v3 mutant SEQ ID NO: 44. The effects of the individual S58V and L149R mutations on fH binding were studied in v3 (*i.e.* the v3 equivalents of v2 mutants #2 and #4). Thus, numbered according to SEQ ID NO: 17, mutation S32V or L126R was introduced into the v3 sequence. These two mutants were compared to two different wild-type v3 sequences, and also to the 'E313A' mutant which is known to disrupt fH binding in v3 [23].

[0207] As shown in Figure 7, wild-type v3 binds fH (top two lines). The S58V mutation, which was designed to improve stability, reduced the SPR peak value by about 2-fold. Most surprisingly, the L149R mutation (again, designed to improve stability) reduced fH affinity to a similar level to the known E313A mutant (bottom two lines).

[0208] The S58V and L149R mutations in v3 were also studied by DSC, and were found to increase the N-terminal T_m by 5.5°C (S58V) or by 6.7°C (L149R) relative to wild-type. The T_m of both mutants was higher than seen in the v2 double mutant (63.5°C - see Table 1). The L149R v3 mutant also showed a higher T_m value for its C-terminal domain, whereas there was almost no shift here for the S58V v3 mutant. SPR showed that fH binding by mutant #2 was reduced by about a half, but for mutant #4 fH affinity was reduced to a similar level to the known E313A mutant (as also seen with v2). When the two mutations were combined (*i.e.* mutant #3) the T_m

increase compared to wild-type was 11.2°C. When the 'E313A' mutation was added to mutant #3 fH binding was almost completely eliminated, although the T_m of the N-terminal domain also decreased by 2.9°C when compared to mutant #3 (while remaining 8.3°C higher than v3 wild-type). The 'E313A' mutation alone was much less stable than wild-type, showing a T_m decrease of 6.3°C.

[0209] Thus mutation #2 can be used alone, or in combination with mutant #4 (*i.e.* mutant #3), optionally with further mutations, to stabilise v2 or v3 fHbp but also to disrupt fH affinity.

[0210] A serum bactericidal assay was used for assessing the immunogenic efficacy of mutants #3 and #4 in v2 and v3. In addition, the 'E313A' mutant was also tested in v2 and v3, either alone or in combination with the #3 mutations. Wild-type v2 and v3 fHbp were also tested for comparison. The proteins were administered at 20µg/dose with an aluminium hydroxide adjuvant and the resulting sera were tested for bactericidal activity against a panel of seven strains (four v2 strains, three v3 strains) including strains which express the same fHbp as the starting wild-type fHbp sequences (*i.e.* v2 sequence 2.16 and v3 sequence 3.42).

[0211] Results for the v2 proteins were as follows (SEQ ID is for the ΔG form; * = homologous fHbp):

Protein	SEQ ID	SBA against v2 strains				SBA against v3 strains		
		v2.16*	v2.19	v2.21	v2.24	v3.42*	v3.28	v3.30
w.t.	5	32768	32	32	1024	>32768	<16	32
#4	21	32768	<16	<16	128	1024	<16	16
#3	45	4096	32	<16	<16	>32768	128	<16
#3+E313A	57	4096	16	<16	<16	>32768	<16	<16
E313A	56	128	16	<16	<16	4096	<16	<16

[0212] Results for the v3 proteins were as follows:

Protein	SEQ ID	SBA against v3 strains			SBA against v2 strains			
		v3.42*	v3.28	v3.30	v2.16*	v2.19	v2.21	v2.24
w.t.	17	>32768	512	1024	1024	32	64	256
#4	53	1024	<16	16	<16	16	<16	128
#3	44	4096	32	16	4096	<16	16	16
#3+E313A	43	256	<16	16	64	<16	<16	16
E313A	41	4096	32	256	8192	32	32	128

Combination of mutants #2 and #12

[0213] Mutants #2 and #12 each showed improvements in v2 stability, so these two mutants were combined into a single fHbp (SEQ ID NO: 58, ΔG form). Compared to mutant #12 the N-terminal T_m of this combined mutant increased by a further 4.2°C, giving the highest T_m of any of the tested mutant v2 proteins. Furthermore, it showed a strongly reduced fH binding (SPR peak value reduced about 8x).

Mutant fusion protein

[0214] Mutant v2 and v3 sequences were fused via a GS GGGG linker (SEQ ID NO: 50), also with a mutant v1 sequence, to give SEQ ID NO: 48. This sequence includes the S58V and L149R mutations for both v2 and v3, and the R41S mutation [21] for v1. SEQ ID NO: 47 includes, from N-terminus to C-terminus: v2 mutant #3 (SEQ ID NO: 45); v3 mutant #3 (SEQ ID NO: 44); and v1 'R41S' mutant (SEQ ID NO: 49), connected by the glycine-rich linker sequence, SEQ ID NO: 50. The fusion protein can conveniently be expressed by adding a N-terminus sequence of Met-[SEQ ID NO: 37]-, thus providing a mature protein SEQ ID NO: 48.

[0215] This fusion protein thus takes advantage of the observation that mutant #3 provides for both v2 and v3 a large increase in stability (T_m) and a large decrease in fH affinity. For v1 the R41S mutation has little effect on thermal stability but strongly reduces fH binding.

[0216] DSC studies of the triple fusion protein (Figure 8) show that the three N-terminal transitions fall together in a broad peak centred at 68°C. The three C-termini transitions also fall together. UPLC showed that the protein was 94.9% pure, and HPLC analysis showed <1.5% oligomers.

Mutant proteins expressed in 'GMMA' membrane vesicles

[0217] A v1 meningococcal strain was prepared with knockouts of *mltA*, *lpxL1* and *synX* to provide a genetic background for hyper-expressing v2 and v3 fHbp lipoproteins under the control of the 'ST2' promoter [157] in a 'GMMA' vaccine. The v2 genes were integrated into the genome at the deleted *lpxL1* locus whereas the v3 genes were integrated at the *synX* locus. In addition, the native v1 *fHbp* gene was deleted so that v2 and v3 could be studied without interference.

[0218] Mutants #3 and #4 were tested for v2, and mutant #4 was tested for v3. In addition, a strain with both of the v2 and v3 #4 mutants was prepared. For these bacteria fHbp expression and fH binding were assessed by FACS.

[0219] For strains expressing only v2 fHbp FACS showed that the various proteins were expressed at similar levels, at levels 2 logs higher than the background $\Delta fHbp$ strain. In terms of fH binding, however, mutants #3 and #4 showed much less binding, with binding in mutant #4 being only slightly above background. These results mirror the SPR data obtained with

recombinant v2 proteins.

[0220] For the strain expressing v3 mutant #4 FACS showed full expression of fHbp, but its fH binding was abolished (matching the fH binding seen with the 'H222R' mutation [19,25]).

[0221] For the strain expressing mutant #4 from v2 and v3, both fHbp proteins could be detected by FACS but fH binding was only slightly above that seen in the background $\Delta fHbp$ strain.

[0222] Western blot analysis was used to test the stability of fHbp expression in these bacteria when growing in liquid culture for 6 days. Expression of mutant v2 proteins remained stable over time, even when v3 was co-expressed. Expression of mutant v3 proteins also remained stable, except in the strain expressing both the v2 and v3 mutant, where v3 expression declined over time.

SEQUENCE LISTING

[0223]

>SEQ ID NO: 1 [MC58, v1]

```
MNRTAFCCLSLTALILTACSSGGGGVAADIGAGLADALTAPLDHKDKGLQSLTLDQSVRKNEKLKLAQAQAEKT
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GDIAGEHTSFDKLP EGGRATYRGTAFGSDDAGGKLTYTIDFAAKQGNGKIEHLKSP ELNVDLAAADIKPDGKRHA
VISGSVLYNQA EKGSYSLGIFGGKAQEVAGSAEVKTVNGIRHIGLA AKQ
```

>SEQ ID NO: 2 [2996, v2]

```
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SGLGGEHTAFNQLPDGKA EYHGKAFSSDDAGGKLTYTIDFAAKQGHGKIEHLKTPEQNVELAAAE LKADEKSHAV
ILGDTRYGSEEKGTYHLALFGDRAQE IAGSATVKIGEKVHEIGIAGKQ
```

>SEQ ID NO: 3 [M1239, v3]

```
MNRTAFCCLSLTALILTACSSGGGGSGGGGVAADIGTGLADALTAPLDHKDKGLKSLTLED SIPQNGTLTLSAQ
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INQRSFLVSGLGGEHTAFNQLPGGKA EYHGKAFSSDDPNGR LHYSIDFTKKQGYGRIEHLKTLEQNVELAAAE LK
ADEKSHAVILGDTRYGSEEKGTYHLALFGDRAQE IAGSATVKIGEKVHEIGIAGKQ
```

>SEQ ID NO: 4 [2996 mature]

```
CSSGGGGVAADIGAGLADALTAPLDHKDKSLQSLTLDQSVRKNEKLKLAQAQAEKTYNGDSLNTGKLKNDKVS R
FDFIRQIEVDGQLITLESGEFQIYKQDHS AVVALQIEKINNPKIDS LINQRSFLVSGLGGEHTAFNQLPDGKA E
YHGKAFSSDDAGGKLTYTIDFAAKQGHGKIEHLKTPEQNVELAAAE LKADEKSHAVILGDTRYGSEEKGTYHLAL
FGDRAQE IAGSATVKIGEKVHEIGIAGKQ
```

>SEQ ID NO: 5 [2996 AG]

```
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EVDGQLITLESGEFQIYKQDHS AVVALQIEKINNPKIDS LINQRSFLVSGLGGEHTAFNQLPDGKA EYHGKAFS
SDDAGGKLTYTIDFAAKQGHGKIEHLKTPEQNVELAAAE LKADEKSHAVILGDTRYGSEEKGTYHLALFGDRAQE
IAGSATVKIGEKVHEIGIAGKQ
```

>SEQ ID NO: 6 [NHBA]

```
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DGMQGD DPSAGGQNAGNTAAQGANQAGNNQAAGSSDPIPASNPAPANGGSNFRV DLANGVLIDGPSQNTLTHC
KGDSCSGNNFLDEEVQLKSEFEKLS DADKISNYKKDGKNDKFVGLVADSVQMKGINQYIIFYKPKPTS FARFRS
ADDDGCLDADMDLIDNIDDELTYDCEHIGIECHGCHIEEADENKIDHETIGADHEDGQVHIDHOCEDHAKGEMV
```

AKSRKSLPAEMFLTFVNQADTLIVDGEAVSLTGHSNIFAFEGNTRYLTITYGAEKLPFGGSYALRVQGEFARGEMLA
GAAVYNGEVLHFHTENGRPYPTRGRFAAKVDFGSKSVDGIIDSGDDLHMGTOQFKAAIDGNGFKGTWTENGSGDV
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>SEQ ID NO: 7 [NadA]

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NITTFAEETKTNIVKIDEKLEAVADTVDKHAEAFNDIADSLDETNTKADEAVKTANEAKQTAEETKQNVDAKVKA
AETAAGKAEAAAAGTANTAADKAEAVAAKVTDIKADIATNKADIAKNSARIDS LDKNVANLRKETROGLAEQAALS
GLFQPYNVGRFNVTAAVGGYKSES AVAIGTGFRFTENFAAKAGVAVGTSSGSSAAYHVG VNYEW

>SEQ ID NO: 8 [NspA]

MKKALATLIALALPAAALAE GASGFYVQADAAHAKASSSLGSAKGFS PRISAGYRINDLRFAVDYTRYKNYKAPS
TDFKLYSIGASAIYDFDTQSPVKPYLGARLSLN RASVDLGGSDSFSQTSIGLGVLTGVS YAVTPNV DLDAGYRYN
YIGKVNTVKNVRSGELSAGVRVKF

>SEQ ID NO: 9 [HmbR]

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TGSGALGGGVNYQTLQGRDLLDDRQFGVMMKNGYSTRNREWTNTLGFGVSNDRVDAALLYSQRRGHETESAGNR
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DVNRRRNANL FYEWMPDSNWLSLKADEFDYQKTKVAAVNNKGSFPMDYSTWTRNYNQKDLDEIYNRSMDTRFKRF
TLRLDSHPLQLGGGRHRLSFKTFVSRRDFENLNRDDYFSGRVVRTTSSIQHPVKTTNYGFSLS DQIQWNDVFSS
RAGIRYDHTKMTPQELNAECHACDKTPPAANTYK GWSGFVGLAAQLNQAWRVGYDITSGYRVPNASEVYFTYNHG
SGNWLPNPNLKAERSTTHTLSLQGRSEKGM LDANLYQSNYRNFLSEEQKLTTSGTPGCTEENAYYGICSDPYKEK
LDWQMKNIDKARIRGIELTGRLNVDKVASFVPEGWKLF GSLGYAKSKLSGDNSLLSTQPLKVIAGIDYESPSEKW
GVFSRLTYLGAKKVKDAQYTVYENKGWGTPLQKKVKDYPWLNKSAYVFDMYGFYKPAKNLTLRAGVYNLFNRKYT
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>SEQ ID NO: 10 [NhhA]

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NKVNITSDTKGLNFAKETAGTNGD TT VH L NGIGSTLTD TLLNTGATTNV TNDNVTDDEKKRAASVKDVLNAGWNI
KGVKPGTTASDNVDFVRTYDTVEFLSADTKTTTVNVESKDN GK KTEVKIGAKTSVIKEKD GKLV TGKDKGENGSS
TDEGEGLVTAKEVIDAVNKAGWRMKT TTTANGQTGQADKFETVTS GTNVTEFASGKGTTATVSKDDQGNITVMYDVN
VGDALNVNQLQNSGWNLD SKAVAGSSGKVISGNVSPSKGKMDETVNI NAGNNIEITRNGKNIDIATSMTPQFSSV
SLGAGADAPTLSDGDALNVGSKKDNKPV RITNVA PGVKEGDVTNVAQLKGVAQNLNNRIDNV DGNARAGIAQAI
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>SEQ ID NO: 11 [App]

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KGHPYGGDYHMPRLHKFVTD AEPVEMTSYMDGRKYIDQNNYPDRVRIGAGRQYWR SDEDEPNNRESSYHIASAYS
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QLVRKDWFYDEIFAGDTHSVFYEP RQNGKYSFNDDNNGTGKINAKHEHNSLPNRLKTRTVQLFNVSLSETAREPV
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VNGVANDRLSKIGKGT LHVQAKGENQGSISVGDGTVILDQQADDKGKKQAFSEIGLVSGRGTVQLNADNQFNPDK
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TTKTNGRLNLVYQPAAEDRTLLL SGGTNLGNITQTNGK LFFSGRPTPHAYNHLNDHWSQKEGIPRGEIVWDNDW
INRTFKAENFQIKGGQAVVSRNVAKVKGDWHLSNHAQAVFGVAPHQSHTICTRSDWTGLTNCVEKTITDDKVIAS
LTKTDISGNVDLADHAHLNLTGLATLNGNLSANGDTRYTVSHNATQNGNLSLVGNAQATFNQATLNGNTSASGNA
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GNLNLDNATITLNSAYRHDAAGAQ TGSATDAPRRRSRRSRRSLLSVTPPTS VESRFNTLT VNGKLNQGTFRFMS
ELFGYRSDKLKLAESSEGTYTLAVNNTGN EPASLEQLTVVEGKDNKPLSENLF T LQNEHVDAGAWRYQLIRKDG
EFRLHNPVKEQELSDKL GKAEAKKQAEKDNAQSLDALIAAGRD AVEKTESVAEPARQAGGENVGIMQAE EKKRV
QADKDTALAKQREAE TRPATTAFFRARRARRDL PQLPQPQPQQRDLISRYANSGLSEFSATLNSVFAVQDELD
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ENVNIATPGLAFNRYRAGIKADYSFKPAQHISITPYLSLSYTDAASGKVRTRVNTAVLAQDFGKTRSAEWGVNAE
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>SEQ ID NO: 12 [Omp85]

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TPKVTKLARNRVDIDITIDEGKSAKITDIEFEGNQVYS DRKLMRQMSLTEGGIWTWL TRSNQFNEQKFAQDMEKV
TDFYQNNGYFDFRILDTDIQTNE DKTKQTIKITVHEGGRFRWGKVSIEGDTNEVPKAELEKLLTMKPGK WYERQQ
MTAVLGEIQNRMG SAGYAYSEISVQPLPNAETKTVDFVLHIEPGRKIIYVNEIHITGNNKTRDEVVRREL RQMESA

PYDTSKLQRSKERVELLGYFDNVQFDVPLAGTPDKVDLNMSLTERSTGSLDLSAGWVQDTGLVMSAGVSQDNLF
GTGKSAALRASRSKTTLNGSLSFDPYFTADGVSLGYDVYGKAFDPRKASTSIKQYKTTTAGAGIRMSVPVTEYD
RVNFGFLVAEHLTVNTYNKAPKHYADFIKKYGKTDGTDGSEFKGWLYKGTVGWGRNKTD
SALWPTRGYLTGVNAEIALPGSKLQYYSATHNQTWFFPLSKTFTLMLGGEVGIAGGYGRTKEIPFFENFYGGGLGSVRGYESGTLGPKVYDEY
GEKISYGGNKKANVSAELLFPMPGAKDARTVRLSLEADAGSVWDGKTYDDNSSSATGGRVQNIYGAGNTHKSTFT
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>SEQ ID NO: 13 [NMB2091]

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>SEQ ID NO: 14 [NHBA fusion]

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TNQAENNQTAGSQNPASSTNPSATNSGGDFGRNTNVGNSVVIDGPSQNTLTHCKGSDSCSGNNFLDEEVQLKSEFE
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ADTLIVDGEAVSLTGHSGNIFAPEGNRYRLTYGAEKLPGGSYALRVQGEPSKGEMLAGTAVYNGEVLHFHTENGR
PSPSRGRFAAKVDFGSKSVDGIIDSGDGLHMGTPQKFKAAIDGNGFKGTWTENGGGDVSGKFYGPAGEEVAGKYSY
RPTDAEKGGFGVFAGKKEQDGGSGGGGATYKVDEYHANARFAIDHFNTSTNVGGFYGLTGSVEFDQAKRDGKIDIT
IPVANLQSGSQHFTDHLKSADIFDAAQYPDIRFVSTKFNFNKGKKLVSDGNLTMHGKTAPVKLKA EKFN CYQSPM
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>SEQ ID NO: 15 [NadA fragment]

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TVDKHAEAFNDIADSLDETNTKADEAVKTANEAKQTAETKQNVDAKVKAAETAAGKAEAAAAGTANTAADKAEAV
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SDLRKETRQGLAEQAALSGLFQPYNVG

>SEQ ID NO: 16 [MC58, ΔG]

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F GSDDAGGKLTYYTIDFAAKQGNGKIEHLKSPELNVDLAAADIKPDGKRHAVISGSVLYNQAEKGSYS
LGI FGGKAQ EVAGSAEVKTVNGIRHIGLAAKQ

>SEQ ID NO: 17 [M1239, ΔG]

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LPGGKAEYHGKAFSSDDPNGRHLHYSIDFTKKQGYGRIEHLKTLEQNVELAAAE LKADEKSHAVILGDTRYG
SEEKGTYHLALFGDR AQEIAGSATVKIGEKVHEIGIAGKQ

>SEQ ID NO: 18 [MUTANT #1]

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QRSFLV SGLGGEHTAFNQLPDGKAEYHGKAFSSDDAGGKLTYYTIDFAAKQGHGKIEHLKTPEQNVELAA
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>SEQ ID NO: 19 [MUTANT #2]

MNRTAFCCLSLTAALILTACSSGGGGVAADIGAGLADALTAPLDHKDKSLQSLTLDQ**V**VRKNEKLKLAAQGA
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QRSFLV SGLGGEHTAFNQLPDGKAEYHGKAFSSDDAGGKLTYYTIDFAAKQGHGKIEHLKTPEQNVELAA
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>SEQ ID NO: 20 [MUTANT #3]

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>SEQ ID NO: 21 [MUTANT #4]

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>SEQ ID NO: 22 [MUTANT #5]

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>SEQ ID NO: 23 [MUTANT #6]

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>SEQ ID NO: 24 [MUTANT #7]

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>SEQ ID NO: 25 [MUTANT #8]

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>SEQ ID NO: 26 [MUTANT #9]

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>SEQ ID NO: 27 [MUTANT #10]

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SGLGGEHTAFNQLPDGKAEYHGKAF**S**CD**D**AGGKLTYTIDFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAV
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>SEQ ID NO: 28 [MUTANT #11]

MNRTAFCCLSLTAALILTACSSGGGGVAADIGAGLADALTAPLDHKDKSLQSLTLDQSVRKNEKLKLAAQGAECT
YNGGDSLNTGKLKNDKVSRRDFIRQIEVDGQLITLESGEFQIYKQDHSAV**T**ALQIEKINNPDKIDSLINQRSFLV
GDLGGEHTAFNQLPDGKAEYHGKAFSSDDAGGKLTYTIDFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAV
ILGDTRYGSEEKGTYHLALFGDRAQEIAGSATVKIGEKV**R**HIGIAGKQ

>SEQ ID NO: 29 [MUTANT #12]

MNRTAFCCLSLTAALILTACSSGGGGVAADIGAGLADALTAPLDHKDKSLQSLTLDQSVRKNEKLKLAAQGAECT
YNGGDSLNTGKLKNDKVSRRDFIRQIEVDGQLITLESGEFQIYKQDHSAVVALQIEKINNPDKIDSLINQRS**FRI**
GDIAGEHTAFNQLPDGKAEYHGKAFSSDDAGGKLTYTIDFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAV
ILGDTRYGSEEKGTYHLALFGDRAQEIAGSATVKIGEKVHEIGIAGKQ

>SEQ ID NO: 30 [MUTANT #13]

MNRTAFCCLSLTAALILTACSSGGGGVAADIGAGLADALTAPLDHKDKSLQSLTLDQSVRKNEKLKLAAQGAECT
YNGGDSLNTGKLKNDKVSRRDFIRQIEVDGQLITLESGEFQIYKQDHSAV**T**ALQIEKINNPDKIDSLINQRSFLV
SGLGGEHTAFNQLPDGKAEYHGKAFSSDDAGGKLTYTIDFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAV
ILGDTRYGSEEKGTYHLALFGDRAQEIAGSATVKIGEKVHEIGIAGKQ

>SEQ ID NO: 31 [MUTANT #14]

MNRTAFCCLSLTAALILTACSSGGGGVAADIGAGLADALTAPLDHKDKSLQSLTLDQSVRKNEKLK**C**AAQGAECT
YNGGDSLNTGKLKNDKVSRRDFIRQIEVDGQLITLESGEFQIYKQDHSAVVALQIEKINNPDKIDSLINQRSFLV
SGLGGEHTAFNQLPDGKAEYHGKAFSSDDAGGKLTYTIDFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAV

SGLGGEHTAFNQLPDGKAEYHGKAFSSDDAGGKLTYYTIDFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAV
ILGDTRYGSEEKGTYHLALFGDRAQEIAGSATVKIGEKVHEIGIAGKQ

>SEQ ID NO: 32 [MUTANT #15]

MNRTAFCCLSLTAALILTACSSGGGGVAADIGAGLADALTAPLDHKDKSLQSLTLDQSVRKNEKLKLAAQGAECT
YGNGDSLNTGKLKNDKVS RFDFIRQIEVDGQLITLESGEFQIYKQDHS AVVALQIEKINNPDKIDSLINQRSCLV
SGLGGEHTAFNQLPDGKAEYHGKAFSSDDAGGKLTYYTIDFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAV
ILGDTRYGSEEKGTYHLALFGDRAQEIAGSATVKIGEKVHEIGIAGKQ

>SEQ ID NO: 33 [MUTANT #19]

MNRTAFCCLSLTAALILTACSSGGGGVAADIGAGLADALTAPLDHKDKSLQSLTLDQVVRKNEKLKLAAQGAECT
YGNGDSLNTGKLKNDKVS RFDFIRQIEVDGQLITLESGEFQIYKQDHS AVVALQIEKINNPDKIDSLINQRSFLV
TGLGGEHTAFNQLPDGKAEYHGKAFSSDDAGGKLTYYTIDFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAV
ILGDTRYGSEEKGTYHLALFGDRAQEIAGSATVKIGEKVHEIGIAGKQ

>SEQ ID NO: 34 [MUTANT #20]

MNRTAFCCLSLTAALILTACSSGGGGVAADIGAGLADALTAPLDHKDKSLQSLTLDQVVRKNEKLKLAAQGAECT
YGNGDSLNTGKLKNDKVS RFDFIRQIEVDGQLITLESGEFQIYKQDHS AVVALQIEKINNPDKIDSLINQRSFRV
TGLGGEHTAFNQLPDGKAEYHGKAFSSDDAGGKLTYYTIDFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAV
ILGDTRYGSEEKGTYHLALFGDRAQEIAGSATVKIGEKVHEIGIAGKQ

>SEQ ID NO: 35 [MUTANT #21]

MNRTAFCCLSLTAALILTACSSGGGGVAADIGAGLADALTAPLDHKDKSLQSLTLDQVVRKNEKLKLAAQGAECT
YGNGDSLNTGKLKNDKVS RFDFIRQIEVDGQLITLESGEFQIYKQDHS AVVALQIEKINNPDKIDSLINQRSFLV
GGLGGEHTAFNQLPDGKAEYHGKAFSSDDAGGKLTYYTIDFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAV
ILGDTRYGSEEKGTYHLALFGDRAQEIAGSATVKIGEKVHEIGIAGKQ

>SEQ ID NO: 36 [MUTANT #22]

MNRTAFCCLSLTAALILTACSSGGGGVAADIGAGLADALTAPLDHKDKSLQSLTLDQVVRKNEKLKLAAQGAECT
YGNGDSLNTGKLKNDKVS RFDFIRQIEVDGQLITLESGEFQIYKQDHS AVVALQIEKINNPDKIDSLINQRSFRV
GGLGGEHTAFNQLPDGKAEYHGKAFSSDDAGGKLTYYTIDFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAV
ILGDTRYGSEEKGTYHLALFGDRAQEIAGSATVKIGEKVHEIGIAGKQ

>SEQ ID NO: 37

GPDS DRLQRR

>SEQ ID NO: 38

GSKDISS

>SEQ ID NO: 39

GSKDISSGGGG

>SEQ ID NO: 40 [M1239, mature]

CSSGGGGSGGGGVAADIGTGLADALTAPLDHKDKGLKSLTLED SIPQNGTLTLSAQGAECTFKAGDKD NSLNTGK
LKNDKISRFD FVQKIEVDGQTITLASGEFQIYKQNHSAVVALQIEKINNPDKTDSL INQRSFLVSGLGGEHTAFN
QLPGGKAEYHGKAFSSDDPNGR LHYSIDFTKKQGYGRIEHLKTLEQNVELAAAELKADEKSHAVILGDTRYGSEE
KGTYHLALFGDRAQEIAGSATVKIGEKVHEIGIAGKQ

>SEQ ID NO: 41 [v3(M1239), E243A, AG]

VAADIGTGLADALTAPLDHKDKGLKSLTLED SIPQNGTLTLSAQGAECTFKAGDKD NSLNTGKLKNDKISRFD FV
QKIEVDGQTITLASGEFQIYKQNHSAVVALQIEKINNPDKTDSL INQRSFLVSGLGGEHTAFNQLPGGKAEYHGK
AFSSDDPNGR LHYSIDFTKKQGYGRIEHLKTLEQNVELAAAELKADEKSHAVILGDTRYGSEEKGTYHLALFGDR
AQEIAGSATVKIGEKVHAIGIAGKQ

>SEQ ID NO: 42 [v3(M1239), S32V+E243A, AG]

VAADIGTGLADALTAPLDHKDKGLKSLTLEDVIPQNGTLTLSAQGAECTFKAGDKD NSLNTGKLKNDKISRFD FV
QKIEVDGQTITLASGEFQIYKQNHSAVVALQIEKINNPDKTDSL INQRSFLVSGLGGEHTAFNQLPGGKAEYHGK
AFSSDDPNGR LHYSIDFTKKQGYGRIEHLKTLEQNVELAAAELKADEKSHAVILGDTRYGSEEKGTYHLALFGDR
AQEIAGSATVKIGEKVHAIGIAGKQ

>**SEQ ID NO: 43 [v3(M1239), S32V+L126R+E243A, ΔG]**

VAADIGTGLADALTAPLDHKDKGLKSLTLEDVIPQNGTLTLTSAQGAEKTFKAGDKDNSLNTGKLKNDKISRFDV
QKIEVDGQTITLASGEFQIYKQNHSAVVALQIEKINNPDKTDSLINQRSFRVSGLGGEHTAFNQLPGGKAEYHGK
AFSSDDPNGLHYSIDFTKKQGYGRIEHLKTLEQNVELAAAEKKADEKSHAVILGDTRYGSEEKGTYHLALFGDR
AQEIAGSATVKIGEKVHAIGIAGKQ

>**SEQ ID NO: 44 [v3, S32V + L126R, ΔG]**

VAADIGTGLADALTAPLDHKDKGLKSLTLEDVIPQNGTLTLTSAQGAEKTFKAGDKDNSLNTGKLKNDKISRFDV
QKIEVDGQTITLASGEFQIYKQNHSAVVALQIEKINNPDKTDSLINQRSFRVSGLGGEHTAFNQLPGGKAEYHGK
AFSSDDPNGLHYSIDFTKKQGYGRIEHLKTLEQNVELAAAEKKADEKSHAVILGDTRYGSEEKGTYHLALFGDR
AQEIAGSATVKIGEKVHEIGIAGKQ

>**SEQ ID NO: 45 [v2 MUTANT #3 S32V + L123R, ΔG]**

VAADIGAGLADALTAPLDHKDKSLQSLTLDQVVRKNEKLKLAAQGAEKTYGNGDSLNTGKLKNDKVSRLFDFIRQI
EVDGQLITLESGEFQIYKQDHSADVVALQIEKINNPDKIDSLINQRSFRVSGLGGEHTAFNQLPDGKAEYHGKAFS
SDDAGGKLTYYTIDFAAQQGHGKIEHLKTPEQNVELAAAEKKADEKSHAVILGDTRYGSEEKGTYHLALFGDRAQE
IAGSATVKIGEKVHEIGIAGKQ

>**SEQ ID NO: 46 [MC58, v1, mature]**

CSSGGGGVAADIGAGLADALTAPLDHKDKGLQSLTLDQSVRKNEKLKLAAQGAEKTYGNGDSLNTGKLKNDKVS
RFDLIRQIEVDGQLITLESGEFQVYKQSHSALTAFQTEQIQDSEHSGKMAKQFRIGDIAGEHTSFDKLPEGGR
TYRGTAFGSDDAGGKLTYYTIDFAAQQGNKIEHLKSPELNVDLAAADIKPDGKRHAVISGSVLYNQAEGSYSLG
IFGGKAQEVAGSAEVKTVNGIRHIGLAQ

>**SEQ ID NO: 47 [v2-v3-v-1 mutant fusion]**

VAADIGAGLADALTAPLDHKDKSLQSLTLDQVVRKNEKLKLAAQGAEKTYGNGDSLNTGKLKNDKVSRLFDFIRQI
EVDGQLITLESGEFQIYKQDHSADVVALQIEKINNPDKIDSLINQRSFRVSGLGGEHTAFNQLPDGKAEYHGKAFS
SDDAGGKLTYYTIDFAAQQGHGKIEHLKTPEQNVELAAAEKKADEKSHAVILGDTRYGSEEKGTYHLALFGDRAQE
IAGSATVKIGEKVHEIGIAGKQSGGGGGVAADIGTGLADALTAPLDHKDKGLKSLTLEDVIPQNGTLTLTSAQGA
KTFKAGDKDNSLNTGKLKNDKISRFDVQKIEVDGQTITLASGEFQIYKQNHSAVVALQIEKINNPDKTDSLINQ
RSFRVSGLGGEHTAFNQLPGGKAEYHGKAFSSDDPNGLHYSIDFTKKQGYGRIEHLKTLEQNVELAAAEKKADE
KSHAVILGDTRYGSEEKGTYHLALFGDRAQEIAGSATVKIGEKVHEIGIAGKQSGGGGGVAADIGAGLADALTAP
LDHKDKGLQSLTLDQSVSKNEKLKLAAQGAEKTYGNGDSLNTGKLKNDKVSRLFDFIRQIEVDGQLITLESGEFQV
YKQSHSALTAFQTEQIQDSEHSGKMAKQFRIGDIAGEHTSFDKLPEGGRATYRGTAFGSDDAGGKLTYYTIDFA
AQQGNKIEHLKSPELNVDLAAADIKPDGKRHAVISGSVLYNQAEGSYSLGIFGGKAQEVAGSAEVKTVNGIRH
IGLAQ

>**SEQ ID NO: 48 [v2-v3-v-1 mutant fusion, with leader]**

MGPDSDRLQRRVAADIGAGLADALTAPLDHKDKSLQSLTLDQVVRKNEKLKLAAQGAEKTYGNGDSLNTGKLKN
DKVSRLFDFIRQIEVDGQLITLESGEFQIYKQDHSADVVALQIEKINNPDKIDSLINQRSFRVSGLGGEHTAFNQLP
DGKAEYHGKAFSSDDAGGKLTYYTIDFAAQQGHGKIEHLKTPEQNVELAAAEKKADEKSHAVILGDTRYGSEEKGT
YHLALFGDRAQEIAGSATVKIGEKVHEIGIAGKQSGGGGGVAADIGTGLADALTAPLDHKDKGLKSLTLEDVIPQ

NGTLTLTSAQGAEKTFKAGDKDNSLNTGKLKNDKISRFDVQKIEVDGQTITLASGEFQIYKQNHSAVVALQIEKI
NNPDKTDSLINQRSFRVSGLGGEHTAFNQLPGGKAEYHGKAFSSDDPNGLHYSIDFTKKQGYGRIEHLKTLEQ
VELAAAEKKADEKSHAVILGDTRYGSEEKGTYHLALFGDRAQEIAGSATVKIGEKVHEIGIAGKQSGGGGGVAAD
IGAGLADALTAPLDHKDKGLQSLTLDQSVSKNEKLKLAAQGAEKTYGNGDSLNTGKLKNDKVSRLFDFIRQIEVDG
QLITLESGEFQVYKQSHSALTAFQTEQIQDSEHSGKMAKQFRIGDIAGEHTSFDKLPEGGRATYRGTAFGSDD
AGGKLTYYTIDFAAQQGNKIEHLKSPELNVDLAAADIKPDGKRHAVISGSVLYNQAEGSYSLGIFGGKAQEVAG
SAEVKTVNGIRHIGLAQ

>**SEQ ID NO: 49 [MC58, ΔG, ‘R41S’ mutation]**

VAADIGAGLADALTAPLDHKDKGLQSLTLDQSVSKNEKLKLAAQGAEKTYGNGDSLNTGKLKNDKVSRLFDFIRQI
EVDGQLITLESGEFQVYKQSHSALTAFQTEQIQDSEHSGKMAKQFRIGDIAGEHTSFDKLPEGGRATYRGTA
GSDDAGGKLTYYTIDFAAQQGNKIEHLKSPELNVDLAAADIKPDGKRHAVISGSVLYNQAEGSYSLGIFGGKAQ
EVAGSAEVKTVNGIRHIGLAQ

>**SEQ ID NO: 50 [linker]**

GSGGGG

>**SEQ ID NO: 51 [wild-type v2 sequence e.g. for GMMA approach]**

VAADIGARLADALTAPLDHKDKSLQSLTLDQSVRKNEKLKLAAQGAEKTYGNGDSLNTGKLKNDKVSRLFDFIRQI
EVDGQLITLESGEFQIYKQDHSADVVALQIEKINNPDKIDSLINQRSFLVSGLGGEHTAFNQLPDGKAEYHGKAFS
SDDAGGKLTYYTIDFAAQQGHGKIEHLKTPEQNVELAAAEKKADEKSHAVILGDTRYGSEEKGTYHLALFGDRAQE
IAGSATVKIGEKVHEIGIAGKQ

>SEQ ID NO: 52 [wild-type v3 sequence e.g. for GMMA approach]

VAADIGAGLADALTAPLDHKDKGLQSLTLDQSVRKNEKLKLAAQGAEKTYGNGDSLNTGKLKNDKVSRFDFIRQI
EVDGKLITLESGEFQVYKQSHSALTALQTEQVQDSEDSGKMVAKRQFRIGDIAGEHTSFDKLPKGGSATYRGTAFF
GSDDAGGKLTYTIDFAAKQGHGKIEHLKSPELNVELATAELKADEKSHAVILGDTRYGGEEKGTYHLALFGDRAQ
EIAGSATVKIREKVHEIGIAGKQ

>SEQ ID NO: 53 [m1239, L126R mutation]

VAADIGTGLADALTAPLDHKDKGLKSLTLEDVIPQNGTLTLSAQGAEKTEFKAGDKDNSLNTGKLKNDKISRFDFFV
QKIEVDGQTITLASGEFQIYKQNHSAVVALQIEKINNPDKTDSLINQRSFRVSGLGGEHTAFNQLPGGKAEYHGK
AFSSDDPNGRHLHYSIDFTKKQGYGRIEHLKTLEQNVELAAAELKADEKSHAVILGDTRYGSEEKGTYHLALFGDR
AQEIAGSATVKIGEKVHEIGIAGKQ

>SEQ ID NO: 54 [v2, 8047 strain, wild-type]

MNRTAFCCLSLTTALILTACSSGGGGVAADIGARLADALTAPLDHKDKSLQSLTLDQSVRKNEKLKLAAQGAEK
TYGNGDSLNTGKLKNDKVSRFDFIRQIEVDGQLITLESGEFQIYKQDHSVVALQIEKINNPDKIDSLINQRSFLV
SGLGGEHTAFNQLPDGKAEYHGKAFSSDDAGGKLTYTIDFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAV
ILGDTRYGSEEKGTYHLALFGDRAQEIAGSATVKIGEKVHEIGIAGKQ

>SEQ ID NO: 55 [v2, 8047 strain, ΔG]

VAADIGARLADALTAPLDHKDKSLQSLTLDQSVRKNEKLKLAAQGAEKTYGNGDSLNTGKLKNDKVSRFDFIRQI
EVDGQLITLESGEFQIYKQDHSVVALQIEKINNPDKIDSLINQRSFLVSGLGGEHTAFNQLPDGKAEYHGKAFS
SDDAGGKLTYTIDFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAVILGDTRYGSEEKGTYHLALFGDRAQ
IAGSATVKIGEKVHEIGIAGKQ

>SEQ ID NO: 56 [v2, 'E313A' mutant, ΔG]

VAADIGAGLADALTAPLDHKDKSLQSLTLDQSVRKNEKLKLAAQGAEKTYGNGDSLNTGKLKNDKVSRFDFIRQI
EVDGQLITLESGEFQIYKQDHSVVALQIEKINNPDKIDSLINQRSFLVSGLGGEHTAFNQLPDGKAEYHGKAFS
SDDAGGKLTYTIDFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAVILGDTRYGSEEKGTYHLALFGDRAQ
IAGSATVKIGEKVHAIGIAGKQ

>SEQ ID NO: 57 [v2, mutant #3 + 'E313A', ΔG]

VAADIGAGLADALTAPLDHKDKSLQSLTLDQVVRKNEKLKLAAQGAEKTYGNGDSLNTGKLKNDKVSRFDFIRQI
EVDGQLITLESGEFQIYKQDHSVVALQIEKINNPDKIDSLINQRSFRVSGLGGEHTAFNQLPDGKAEYHGKAFS
SDDAGGKLTYTIDFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAVILGDTRYGSEEKGTYHLALFGDRAQ
IAGSATVKIGEKVHAIGIAGKQ

>SEQ ID NO: 58 [MUTANT #2 + #12]

VAADIGAGLADALTAPLDHKDKSLQSLTLDQVVRKNEKLKLAAQGAEKTYGNGDSLNTGKLKNDKVSRFDFIRQI
EVDGQLITLESGEFQIYKQDHSVVALQIEKINNPDKIDSLINQRSF**RIGDI**AGEHTAFNQLPDGKAEYHGKAFS
SDDAGGKLTYTIDFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAVILGDTRYGSEEKGTYHLALFGDRAQ
IAGSATVKIGEKVHEIGIAGKQ

>SEQ ID NO: 59 [v2, strain 8047 strain, mutant #4, mature]

CSSGGGGVAADIGARLADALTAPLDHKDKSLQSLTLDQSVRKNEKLKLAAQGAEKTYGNGDSLNTGKLKNDKVS
RFDFFIRQIEVDGQLITLESGEFQIYKQDHSVVALQIEKINNPDKIDSLINQRSF**RV**SGLGGEHTAFNQLPDGKAE
YHGKAFSSDDAGGKLTYTIDFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAVILGDTRYGSEEKGTYHLAL
FGDRAQEIAGSATVKIGEKVHEIGIAGKQ

>SEQ ID NO: 60 [v2, strain 8047 strain, mutant #3, mature]

CSSGGGGVAADIGARLADALTAPLDHKDKSLQSLTLDQVVRKNEKLKLAAQGAEKTYGNGDSLNTGKLKNDKVS
RFDFFIRQIEVDGQLITLESGEFQIYKQDHSVVALQIEKINNPDKIDSLINQRSF**RV**SGLGGEHTAFNQLPDGKAE
YHGKAFSSDDAGGKLTYTIDFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAVILGDTRYGSEEKGTYHLAL
FGDRAQEIAGSATVKIGEKVHEIGIAGKQ

>SEQ ID NO: 61 [v3, mutant #2 + #12, ΔG]

VAADIGTGLADALTAPLDHKDKGLKSLTLEDVIPQNGTLTLSAQGAEKTEFKAGDKDNSLNTGKLKNDKISRFDFFV
QKIEVDGQTITLASGEFQIYKQNHSAVVALQIEKINNPDKTDSLINQRSF**RIGDI**AGEHTAFNQLPGGKAEYHGK
AFSSDDPNGRHLHYSIDFTKKQGYGRIEHLKTLEQNVELAAAELKADEKSHAVILGDTRYGSEEKGTYHLALFGDR
AQEIAGSATVKIGEKVHEIGIAGKQ

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TABLE 1

#	Residue(s)*	Mutation(s)	Notes	SEQ ID NO	Chym**	Tm1 °C	Tm2 °C	Mon***
1	H239+E240	R, H	Interface between N- and C-terminal domains. The aim is to mimic v1. An additional DSC transition was observed at 100.3°C, and some aggregation was detected.	18	Yes	N/A	83.5	34.29
2	S32	V	N-terminal domain. Hydrophilic S32 side chain points into hydrophobic cavity. The aim is to increase hydrophobicity and stabilise the cavity.	19	Yes	57.0	84.2	80.38
3	S32+L123	V, R	Mutants #2 + #4	20	Yes	63.5	83.84	76.1
4	L123	R	N-terminal domain. In v1 the reverse change decreased stability [11].	21	Yes	54.1	84.1	89.97
5	S125+G126	G, D	N-terminal domain. The aim is to mimic v1	22	Yes	52.3	83.3	90.48
6	V100+S125+G126	T, G, D	N-terminal domain. The aim is to mimic v1	23	Yes	52	83.7	86.41
7	1113	s	Surface loop of the N-terminal	24	No	ND	ND	ND

#	Residue(s)*	Mutation(s)	Notes	SEQ ID NO	Chym **	Tm1 °C	Tm2 °C	Mon ***
			domain. Remove potential protease cleavage site from surface					
8	V33+L39	C, C	Core of the N-terminal domain. Introduce a S- S bridge. Some aggregation was detected.	25	No	55.9	85	28.71
9	L41+F69	C, C	Core of the N-terminal domain. Introduce a S- S bridge.	26	No	46.4	84.4	33.5 + 53.22
10	F122+S151	C, C	Core of the N-terminal domain. Introduce a S- S bridge.	27	No	-	-	-
11	V100+S125+G126 +H239+E240	T, G, D, R, H	Mutants #1 + #6	28	No	47.9	82.2	85.1
12	L123-G128	RIGDIA	N-terminal domain. The aim is to mimic v1 in the whole region of 123- 128	29	Yes	62.8	84.4	71.28
13	V100	T	Partial mutant #6	30	No	43	84.3	91.06
14	L41	C	Partial mutant #9. Some aggregation was detected.	31	No	-	85	24.82
15	F122	C	Partial mutant #10. Some aggregation was detected.	32	No	-	84.4	16.63
19	S32+S125	V, T	N-terminal domain.	33	No	50.6	83.5	81.3

#	Residue(s)*	Mutation(s)	Notes	SEQ ID NO	Chym**	Tm1 °C	Tm2 °C	Mon***
			Further increase hydrophobicity relative to #2					
20	S32+S125+L123	V, T, R	Combine #4 + #19	34	No	-	-	-
21	S32+S125	V, G	N-terminal domain. Further increase hydrophobicity relative to #2	35	No	52.8	84	75.3
22	S32+S125+L123	V, G, R	Combine #4 + #21	36	Yes	-	-	-
23	S32+L123-G128	V, RIGDIA	Combine #2 + #12	61	Yes	66.3	84.7	-
* Numbered according to SEQ ID NO: 5; add +26 to match SEQ ID NOs: 18 to 39. ** Resistance to chymotrypsin cleavage. *** % monomeric form								

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Gly Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala
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Ala Val Ile Ser Gly Ser Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser
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Tyr Ser Leu Gly Ile Phe Gly Gly Lys Ala Gln Glu Val Ala Gly Ser
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Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp
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Phe Ile Arg Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser
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          195          200          205

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

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 Leu Ile Thr Leu Glu Ser Gly Glu Phe Gln Ile Tyr Lys Gln Asp His
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 Glu Thr Asn Thr Lys Ala Asp Glu Ala Val Lys Thr Ala Asn Glu Ala
 195 200 205
 Lys Gln Thr Ala Glu Glu Thr Lys Gln Asn Val Asp Ala Lys Val Lys
 210 215 220
 Ala Ala Glu Thr Ala Ala Gly Lys Ala Glu Ala Ala Ala Gly Thr Ala
 225 230 235 240
 Asn Thr Ala Ala Asp Lys Ala Glu Ala Val Ala Ala Lys Val Thr Asp
 245 250 255
 Ile Lys Ala Asp Ile Ala Thr Asn Lys Ala Asp Ile Ala Lys Asn Ser
 260 265 270
 Ala Arg Ile Asp Ser Leu Asp Lys Asn Val Ala Asn Leu Arg Lys Glu
 275 280 285
 Thr Arg Gln Gly Leu Ala Glu Gln Ala Ala Leu Ser Gly Leu Phe Gln
 290 295 300
 Pro Tyr Asn Val Gly Arg Phe Asn Val Thr Ala Ala Val Gly Gly Tyr
 305 310 315 320
 Lys Ser Glu Ser Ala Val Ala Ile Gly Thr Gly Phe Arg Phe Thr Glu
 325 330 335
 Asn Phe Ala Ala Lys Ala Gly Val Ala Val Gly Thr Ser Ser Gly Ser
 340 345 350
 Ser Ala Ala Tyr His Val Gly Val Asn Tyr Glu Trp
 355 360

<210> 8

<211> 174

<212> PRT

<213> Neisseria meningitidis

<400> 8

Met Lys Lys Ala Leu Ala Thr Leu Ile Ala Leu Ala Leu Pro Ala Ala
 1 5 10 15
 Ala Leu Ala Glu Gly Ala Ser Gly Phe Tyr Val Gln Ala Asp Ala Ala
 20 25 30
 His Ala Lys Ala Ser Ser Ser Leu Gly Ser Ala Lys Gly Phe Ser Pro
 35 40 45
 Arg Ile Ser Ala Gly Tyr Arg Ile Asn Asp Leu Arg Phe Ala Val Asp
 50 55 60
 Tyr Thr Arg Tyr Lys Asn Tyr Lys Ala Pro Ser Thr Asp Phe Lys Leu
 65 70 75 80
 Tyr Ser Ile Gly Ala Ser Ala Ile Tyr Asp Phe Asp Thr Gln Ser Pro
 85 90 95
 Val Lys Pro Tyr Leu Gly Ala Arg Leu Ser Leu Asn Arg Ala Ser Val
 100 105 110
 Asp Leu Gly Gly Ser Asp Ser Phe Ser Gln Thr Ser Ile Gly Leu Gly

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      115      120      125
Val Leu Thr Gly Val Ser Tyr Ala Val Thr Pro Asn Val Asp Leu Asp
  130      135      140

Ala Gly Tyr Arg Tyr Asn Tyr Ile Gly Lys Val Asn Thr Val Lys Asn
  145      150      155      160

Val Arg Ser Gly Glu Leu Ser Ala Gly Val Arg Val Lys Phe
      165      170

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<210> 9

<211> 792

<212> PRT

<213> Neisseria meningitidis

<400> 9

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Met Lys Pro Leu Gln Met Leu Pro Ile Ala Ala Leu Val Gly Ser Ile
  1      5      10      15

Phe Gly Asn Pro Val Leu Ala Ala Asp Glu Ala Ala Thr Glu Thr Thr
      20      25      30

Pro Val Lys Ala Glu Ile Lys Ala Val Arg Val Lys Gly Gln Arg Asn
      35      40      45

Ala Pro Ala Ala Val Glu Arg Val Asn Leu Asn Arg Ile Lys Gln Glu
      50      55      60

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

Leu Ser Asp Ser Gly Arg His Gln Lys Gly Phe Ala Val Arg Gly Val
      85      90      95

Glu Gly Asn Arg Val Gly Val Ser Ile Asp Gly Val Asn Leu Pro Asp
      100      105      110

Ser Glu Glu Asn Ser Leu Tyr Ala Arg Tyr Gly Asn Phe Asn Ser Ser
      115      120      125

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

Gly Ala Asp Ser Phe Asn Thr Gly Ser Gly Ala Leu Gly Gly Gly Val
  145      150      155      160

Asn Tyr Gln Thr Leu Gln Gly Arg Asp Leu Leu Leu Asp Asp Arg Gln
      165      170      175

Phe Gly Val Met Met Lys Asn Gly Tyr Ser Thr Arg Asn Arg Glu Trp
      180      185      190

Thr Asn Thr Leu Gly Phe Gly Val Ser Asn Asp Arg Val Asp Ala Ala
      195      200      205

Leu Leu Tyr Ser Gln Arg Arg Gly His Glu Thr Glu Ser Ala Gly Asn
      210      215      220

Arg Gly Tyr Ala Val Glu Gly Glu Gly Ser Gly Ala Asn Ile Arg Gly
  225      230      235      240

Ser Ala Arg Gly Ile Pro Asp Ser Ser Lys His Lys Tyr Asn His His
      245      250      255

Ala Leu Gly Lys Ile Ala Tyr Gln Ile Asn Asp Asn His Arg Ile Gly
      260      265      270

Ala Ser Leu Asn Gly Gln Gln Gly His Asn Tyr Thr Val Glu Glu Ser
      275      280      285

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Tyr Asn Leu Thr Ala Ser Ser Trp Arg Glu Ala Asp Asp Val Asn Arg
 290 295 300
 Arg Arg Asn Ala Asn Leu Phe Tyr Glu Trp Met Pro Asp Ser Asn Trp
 305 310 315 320
 Leu Ser Ser Leu Lys Ala Asp Phe Asp Tyr Gln Lys Thr Lys Val Ala
 325 330 335
 Ala Val Asn Asn Lys Gly Ser Phe Pro Met Asp Tyr Ser Thr Trp Thr
 340 345 350
 Arg Asn Tyr Asn Gln Lys Asp Leu Asp Glu Ile Tyr Asn Arg Ser Met
 355 360 365
 Asp Thr Arg Phe Lys Arg Phe Thr Leu Arg Leu Asp Ser His Pro Leu
 370 375 380
 Gln Leu Gly Gly Gly Arg His Arg Leu Ser Phe Lys Thr Phe Val Ser
 385 390 395 400
 Arg Arg Asp Phe Glu Asn Leu Asn Arg Asp Asp Tyr Tyr Phe Ser Gly
 405 410 415
 Arg Val Val Arg Thr Thr Ser Ser Ile Gln His Pro Val Lys Thr Thr
 420 425 430
 Asn Tyr Gly Phe Ser Leu Ser Asp Gln Ile Gln Trp Asn Asp Val Phe
 435 440 445
 Ser Ser Arg Ala Gly Ile Arg Tyr Asp His Thr Lys Met Thr Pro Gln
 450 455 460
 Glu Leu Asn Ala Glu Cys His Ala Cys Asp Lys Thr Pro Pro Ala Ala
 465 470 475 480
 Asn Thr Tyr Lys Gly Trp Ser Gly Phe Val Gly Leu Ala Ala Gln Leu
 485 490 495
 Asn Gln Ala Trp Arg Val Gly Tyr Asp Ile Thr Ser Gly Tyr Arg Val
 500 505 510
 Pro Asn Ala Ser Glu Val Tyr Phe Thr Tyr Asn His Gly Ser Gly Asn
 515 520 525
 Trp Leu Pro Asn Pro Asn Leu Lys Ala Glu Arg Ser Thr Thr His Thr
 530 535 540
 Leu Ser Leu Gln Gly Arg Ser Glu Lys Gly Met Leu Asp Ala Asn Leu
 545 550 555 560
 Tyr Gln Ser Asn Tyr Arg Asn Phe Leu Ser Glu Glu Gln Lys Leu Thr
 565 570 575
 Thr Ser Gly Thr Pro Gly Cys Thr Glu Glu Asn Ala Tyr Tyr Gly Ile
 580 585 590
 Cys Ser Asp Pro Tyr Lys Glu Lys Leu Asp Trp Gln Met Lys Asn Ile
 595 600 605
 Asp Lys Ala Arg Ile Arg Gly Ile Glu Leu Thr Gly Arg Leu Asn Val
 610 615 620
 Asp Lys Val Ala Ser Phe Val Pro Glu Gly Trp Lys Leu Phe Gly Ser
 625 630 635 640
 Leu Gly Tyr Ala Lys Ser Lys Leu Ser Gly Asp Asn Ser Leu Leu Ser
 645 650 655
 Thr Gln Pro Leu Lys Val Ile Ala Gly Ile Asp Tyr Glu Ser Pro Ser
 660 665 670
 Glu Lys Trp Gly Val Phe Ser Arg Leu Thr Tyr Leu Gly Ala Lys Lys
 675 680 685
 Val Lys Asn Ala Gln Tyr Thr Val Tyr Glu Asn Lys Gly Trp Gly Thr

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Val Lys Asp Ala Ser Tyr Thr Val Tyr Glu Asn Lys Gly Asp Gly Thr
690                               695                               700

Pro Leu Gln Lys Lys Val Lys Asp Tyr Pro Trp Leu Asn Lys Ser Ala
705                               710                               715                               720

Tyr Val Phe Asp Met Tyr Gly Phe Tyr Lys Pro Ala Lys Asn Leu Thr
725                               730                               735

Leu Arg Ala Gly Val Tyr Asn Leu Phe Asn Arg Lys Tyr Thr Thr Trp
740                               745                               750

Asp Ser Leu Arg Gly Leu Tyr Ser Tyr Ser Thr Thr Asn Ala Val Asp
755                               760                               765

Arg Asp Gly Lys Gly Leu Asp Arg Tyr Arg Ala Pro Gly Arg Asn Tyr
770                               775                               780

Ala Val Ser Leu Glu Trp Lys Phe
785                               790

<210> 10
<211> 591
<212> PRT
<213> Neisseria meningitidis

<400> 10
Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
1                               5                               10                               15

Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
20                               25                               30

Thr Val Lys Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
35                               40                               45

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

Val Gln Arg Thr Val Ala Val Leu Ile Val Asn Ser Asp Lys Glu Gly
65                               70                               75                               80

Thr Gly Glu Lys Glu Lys Val Glu Glu Asn Ser Asp Trp Ala Val Tyr
85                               90                               95

Phe Asn Glu Lys Gly Val Leu Thr Ala Arg Glu Ile Thr Leu Lys Ala
100                              105                              110

Gly Asp Asn Leu Lys Ile Lys Gln Asn Gly Thr Asn Phe Thr Tyr Ser
115                              120                              125

Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser Val Gly Thr Glu Lys Leu
130                              135                              140

Ser Phe Ser Ala Asn Gly Asn Lys Val Asn Ile Thr Ser Asp Thr Lys
145                              150                              155                              160

Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly Thr Asn Gly Asp Thr Thr
165                              170                              175

Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Thr Leu Leu Asn
180                              185                              190

Thr Gly Ala Thr Thr Asn Val Thr Asn Asp Asn Val Thr Asp Asp Glu
195                              200                              205

Lys Lys Arg Ala Ala Ser Val Lys Asp Val Leu Asn Ala Gly Trp Asn
210                              215                              220

Ile Lys Gly Val Lys Pro Gly Thr Thr Ala Ser Asp Asn Val Asp Phe
225                              230                              235                              240

Val Arg Thr Tyr Asn Thr Val Glu Phe Leu Ser Ala Asn Thr Lys Thr

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Val Gly Thr Tyr Asp Thr Val Glu Phe Asn Ser Ala Asp Thr Lys Thr
245                               250                               255

Thr Thr Val Asn Val Glu Ser Lys Asp Asn Gly Lys Lys Thr Glu Val
260                               265                               270

Lys Ile Gly Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly Lys Leu
275                               280                               285

Val Thr Gly Lys Asp Lys Gly Glu Asn Gly Ser Ser Thr Asp Glu Gly
290                               295                               300

Glu Gly Leu Val Thr Ala Lys Glu Val Ile Asp Ala Val Asn Lys Ala
305                               310                               315                               320

Gly Trp Arg Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly Gln Ala
325                               330                               335

Asp Lys Phe Glu Thr Val Thr Ser Gly Thr Asn Val Thr Phe Ala Ser
340                               345                               350

Gly Lys Gly Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly Asn Ile
355                               360                               365

Thr Val Met Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val Asn Gln
370                               375                               380

Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala Gly Ser
385                               390                               395                               400

Ser Gly Lys Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly Lys Met
405                               410                               415

Asp Glu Thr Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile Thr Arg
420                               425                               430

Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser Met Thr Pro Gln Phe Ser
435                               440                               445

Ser Val Ser Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser Val Asp
450                               455                               460

Gly Asp Ala Leu Asn Val Gly Ser Lys Lys Asp Asn Lys Pro Val Arg
465                               470                               475                               480

Ile Thr Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val Thr Asn Val
485                               490                               495

Ala Gln Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg Ile Asp Asn
500                               505                               510

Val Asp Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile Ala Thr Ala
515                               520                               525

Gly Leu Val Gln Ala Tyr Leu Pro Gly Lys Ser Met Met Ala Ile Gly
530                               535                               540

Gly Gly Thr Tyr Arg Gly Glu Ala Gly Tyr Ala Ile Gly Tyr Ser Ser
545                               550                               555                               560

Ile Ser Asp Gly Gly Asn Trp Ile Ile Lys Gly Thr Ala Ser Gly Asn
565                               570                               575

Ser Arg Gly His Phe Gly Ala Ser Ala Ser Val Gly Tyr Gln Trp
580                               585                               590

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<210> 11

<211> 1457

<212> PRT

<213> Neisseria meningitidis

<400> 11

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Met Lys Thr Thr Asp Lys Arg Thr Thr Glu Thr His Arg Lys Ala Pro
1      5      10      15

Lys Thr Gly Arg Ile Arg Phe Ser Pro Ala Tyr Leu Ala Ile Cys Leu
      20      25      30

Ser Phe Gly Ile Leu Pro Gln Ala Trp Ala Gly His Thr Tyr Phe Gly
      35      40      45

Ile Asn Tyr Gln Tyr Tyr Arg Asp Phe Ala Glu Asn Lys Gly Lys Phe
      50      55      60

Ala Val Gly Ala Lys Asp Ile Glu Val Tyr Asn Lys Lys Gly Glu Leu
65      70      75      80

Val Gly Lys Ser Met Thr Lys Ala Pro Met Ile Asp Phe Ser Val Val
      85      90      95

Ser Arg Asn Gly Val Ala Ala Leu Val Gly Asp Gln Tyr Ile Val Ser
      100     105     110

Val Ala His Asn Gly Gly Tyr Asn Asn Val Asp Phe Gly Ala Glu Gly
      115     120     125

Arg Asn Pro Asp Gln His Arg Phe Thr Tyr Lys Ile Val Lys Arg Asn
      130     135     140

Asn Tyr Lys Ala Gly Thr Lys Gly His Pro Tyr Gly Gly Asp Tyr His
145     150     155     160

Met Pro Arg Leu His Lys Phe Val Thr Asp Ala Glu Pro Val Glu Met
      165     170     175

Thr Ser Tyr Met Asp Gly Arg Lys Tyr Ile Asp Gln Asn Asn Tyr Pro
      180     185     190

Asp Arg Val Arg Ile Gly Ala Gly Arg Gln Tyr Trp Arg Ser Asp Glu
      195     200     205

Asp Glu Pro Asn Asn Arg Glu Ser Ser Tyr His Ile Ala Ser Ala Tyr
210     215     220

Ser Trp Leu Val Gly Gly Asn Thr Phe Ala Gln Asn Gly Ser Gly Gly
225     230     235     240

Gly Thr Val Asn Leu Gly Ser Glu Lys Ile Lys His Ser Pro Tyr Gly
      245     250     255

Phe Leu Pro Thr Gly Gly Ser Phe Gly Asp Ser Gly Ser Pro Met Phe
      260     265     270

Ile Tyr Asp Ala Gln Lys Gln Lys Trp Leu Ile Asn Gly Val Leu Gln
      275     280     285

Thr Gly Asn Pro Tyr Ile Gly Lys Ser Asn Gly Phe Gln Leu Val Arg
290     295     300

Lys Asp Trp Phe Tyr Asp Glu Ile Phe Ala Gly Asp Thr His Ser Val
305     310     315     320

Phe Tyr Glu Pro Arg Gln Asn Gly Lys Tyr Ser Phe Asn Asp Asp Asn
      325     330     335

Asn Gly Thr Gly Lys Ile Asn Ala Lys His Glu His Asn Ser Leu Pro
      340     345     350

Asn Arg Leu Lys Thr Arg Thr Val Gln Leu Phe Asn Val Ser Leu Ser
      355     360     365

Glu Thr Ala Arg Glu Pro Val Tyr His Ala Ala Gly Gly Val Asn Ser
370     375     380

Tyr Arg Pro Arg Leu Asn Asn Gly Glu Asn Ile Ser Phe Ile Asp Glu
385     390     395     400

Gly Lys Gly Glu Leu Ile Leu Thr Ser Asn Ile Asn Gln Gly Ala Gly

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405					410					415					
Gly	Leu	Tyr	Phe	Gln	Gly	Asp	Phe	Thr	Val	Ser	Pro	Glu	Asn	Asn	Glu
			420					425					430		
Thr	Trp	Gln	Gly	Ala	Gly	Val	His	Ile	Ser	Glu	Asp	Ser	Thr	Val	Thr
		435					440					445			
Trp	Lys	Val	Asn	Gly	Val	Ala	Asn	Asp	Arg	Leu	Ser	Lys	Ile	Gly	Lys
	450					455					460				
Gly	Thr	Leu	His	Val	Gln	Ala	Lys	Gly	Glu	Asn	Gln	Gly	Ser	Ile	Ser
465					470					475					480
Val	Gly	Asp	Gly	Thr	Val	Ile	Leu	Asp	Gln	Gln	Ala	Asp	Asp	Lys	Gly
				485					490					495	
Lys	Lys	Gln	Ala	Phe	Ser	Glu	Ile	Gly	Leu	Val	Ser	Gly	Arg	Gly	Thr
			500					505					510		
Val	Gln	Leu	Asn	Ala	Asp	Asn	Gln	Phe	Asn	Pro	Asp	Lys	Leu	Tyr	Phe
		515					520					525			
Gly	Phe	Arg	Gly	Gly	Arg	Leu	Asp	Leu	Asn	Gly	His	Ser	Leu	Ser	Phe
	530					535					540				
His	Arg	Ile	Gln	Asn	Thr	Asp	Glu	Gly	Ala	Met	Ile	Val	Asn	His	Asn
545						550					555				560
Gln	Asp	Lys	Glu	Ser	Thr	Val	Thr	Ile	Thr	Gly	Asn	Lys	Asp	Ile	Ala
				565					570					575	
Thr	Thr	Gly	Asn	Asn	Asn	Ser	Leu	Asp	Ser	Lys	Lys	Glu	Ile	Ala	Tyr
				580				585						590	
Asn	Gly	Trp	Phe	Gly	Glu	Lys	Asp	Thr	Thr	Lys	Thr	Asn	Gly	Arg	Leu
		595					600					605			
Asn	Leu	Val	Tyr	Gln	Pro	Ala	Ala	Glu	Asp	Arg	Thr	Leu	Leu	Leu	Ser
		610				615					620				
Gly	Gly	Thr	Asn	Leu	Asn	Gly	Asn	Ile	Thr	Gln	Thr	Asn	Gly	Lys	Leu
625						630					635				640
Phe	Phe	Ser	Gly	Arg	Pro	Thr	Pro	His	Ala	Tyr	Asn	His	Leu	Asn	Asp
				645					650					655	
His	Trp	Ser	Gln	Lys	Glu	Gly	Ile	Pro	Arg	Gly	Glu	Ile	Val	Trp	Asp
			660					665					670		
Asn	Asp	Trp	Ile	Asn	Arg	Thr	Phe	Lys	Ala	Glu	Asn	Phe	Gln	Ile	Lys
		675					680					685			
Gly	Gly	Gln	Ala	Val	Val	Ser	Arg	Asn	Val	Ala	Lys	Val	Lys	Gly	Asp
		690				695					700				
Trp	His	Leu	Ser	Asn	His	Ala	Gln	Ala	Val	Phe	Gly	Val	Ala	Pro	His
705						710					715				720
Gln	Ser	His	Thr	Ile	Cys	Thr	Arg	Ser	Asp	Trp	Thr	Gly	Leu	Thr	Asn
				725					730					735	
Cys	Val	Glu	Lys	Thr	Ile	Thr	Asp	Asp	Lys	Val	Ile	Ala	Ser	Leu	Thr
			740					745					750		
Lys	Thr	Asp	Ile	Ser	Gly	Asn	Val	Asp	Leu	Ala	Asp	His	Ala	His	Leu
		755					760					765			
Asn	Leu	Thr	Gly	Leu	Ala	Thr	Leu	Asn	Gly	Asn	Leu	Ser	Ala	Asn	Gly
		770					775				780				
Asp	Thr	Arg	Tyr	Thr	Val	Ser	His	Asn	Ala	Thr	Gln	Asn	Gly	Asn	Leu
785						790					795				800
Ser	Leu	Val	Gly	Asn	Ala	Gln	Ala	Thr	Phe	Asn	Gln	Ala	Thr	Leu	Asn
				805					810					815	

Gly Asn Thr Ser Ala Ser Gly Asn Ala Ser Phe Asn Leu Ser Asp His
 820 825 830
 Ala Val Gln Asn Gly Ser Leu Thr Leu Ser Gly Asn Ala Lys Ala Asn
 835 840 845
 Val Ser His Ser Ala Leu Asn Gly Asn Val Ser Leu Ala Asp Lys Ala
 850 855 860
 Val Phe His Phe Glu Ser Ser Arg Phe Thr Gly Gln Ile Ser Gly Gly
 865 870 875 880
 Lys Asp Thr Ala Leu His Leu Lys Asp Ser Glu Trp Thr Leu Pro Ser
 885 890 895
 Gly Thr Glu Leu Gly Asn Leu Asn Leu Asp Asn Ala Thr Ile Thr Leu
 900 905 910
 Asn Ser Ala Tyr Arg His Asp Ala Ala Gly Ala Gln Thr Gly Ser Ala
 915 920 925
 Thr Asp Ala Pro Arg Arg Arg Ser Arg Arg Ser Arg Arg Ser Leu Leu
 930 935 940
 Ser Val Thr Pro Pro Thr Ser Val Glu Ser Arg Phe Asn Thr Leu Thr
 945 950 955 960
 Val Asn Gly Lys Leu Asn Gly Gln Gly Thr Phe Arg Phe Met Ser Glu
 965 970 975
 Leu Phe Gly Tyr Arg Ser Asp Lys Leu Lys Leu Ala Glu Ser Ser Glu
 980 985 990
 Gly Thr Tyr Thr Leu Ala Val Asn Asn Thr Gly Asn Glu Pro Ala Ser
 995 1000 1005
 Leu Glu Gln Leu Thr Val Val Glu Gly Lys Asp Asn Lys Pro Leu Ser
 1010 1015 1020
 Glu Asn Leu Asn Phe Thr Leu Gln Asn Glu His Val Asp Ala Gly Ala
 1025 1030 1035 1040
 Trp Arg Tyr Gln Leu Ile Arg Lys Asp Gly Glu Phe Arg Leu His Asn
 1045 1050 1055
 Pro Val Lys Glu Gln Glu Leu Ser Asp Lys Leu Gly Lys Ala Glu Ala
 1060 1065 1070
 Lys Lys Gln Ala Glu Lys Asp Asn Ala Gln Ser Leu Asp Ala Leu Ile
 1075 1080 1085
 Ala Ala Gly Arg Asp Ala Val Glu Lys Thr Glu Ser Val Ala Glu Pro
 1090 1095 1100
 Ala Arg Gln Ala Gly Gly Glu Asn Val Gly Ile Met Gln Ala Glu Glu
 1105 1110 1115 1120
 Glu Lys Lys Arg Val Gln Ala Asp Lys Asp Thr Ala Leu Ala Lys Gln
 1125 1130 1135
 Arg Glu Ala Glu Thr Arg Pro Ala Thr Thr Ala Phe Pro Arg Ala Arg
 1140 1145 1150
 Arg Ala Arg Arg Asp Leu Pro Gln Leu Gln Pro Gln Pro Gln Pro Gln
 1155 1160 1165
 Pro Gln Arg Asp Leu Ile Ser Arg Tyr Ala Asn Ser Gly Leu Ser Glu
 1170 1175 1180
 Phe Ser Ala Thr Leu Asn Ser Val Phe Ala Val Gln Asp Glu Leu Asp
 1185 1190 1195 1200
 Arg Val Phe Ala Glu Asp Arg Arg Asn Ala Val Trp Thr Ser Gly Ile
 1205 1210 1215
 Arg Asn Thr Lys His Tyr Arg Ser Gln Asn Phe Arg Ala Tyr Arg Gln

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Arg Asp Thr Tyr His Tyr Arg Ser Val Asp Thr Arg His Tyr Arg Ser
1220                               1225                               1230

Gln Thr Asp Leu Arg Gln Ile Gly Met Gln Lys Asn Leu Gly Ser Gly
1235                               1240                               1245

Arg Val Gly Ile Leu Phe Ser His Asn Arg Thr Glu Asn Thr Phe Asp
1250                               1255                               1260

Asp Gly Ile Gly Asn Ser Ala Arg Leu Ala His Gly Ala Val Phe Gly
1265                               1270                               1275                               1280

Gln Tyr Gly Ile Asp Arg Phe Tyr Ile Gly Ile Ser Ala Gly Ala Gly
1285                               1290                               1295

Phe Ser Ser Gly Ser Leu Ser Asp Gly Ile Gly Gly Lys Ile Arg Arg
1300                               1305                               1310

Arg Val Leu His Tyr Gly Ile Gln Ala Arg Tyr Arg Ala Gly Phe Gly
1315                               1320                               1325

Gly Phe Gly Ile Glu Pro His Ile Gly Ala Thr Arg Tyr Phe Val Gln
1330                               1335                               1340

Lys Ala Asp Tyr Arg Tyr Glu Asn Val Asn Ile Ala Thr Pro Gly Leu
1345                               1350                               1355                               1360

Ala Phe Asn Arg Tyr Arg Ala Gly Ile Lys Ala Asp Tyr Ser Phe Lys
1365                               1370                               1375

Pro Ala Gln His Ile Ser Ile Thr Pro Tyr Leu Ser Leu Ser Tyr Thr
1380                               1385                               1390

Asp Ala Ala Ser Gly Lys Val Arg Thr Arg Val Asn Thr Ala Val Leu
1395                               1400                               1405

Ala Gln Asp Phe Gly Lys Thr Arg Ser Ala Glu Trp Gly Val Asn Ala
1410                               1415                               1420

Glu Ile Lys Gly Phe Thr Leu Ser Leu His Ala Ala Ala Ala Lys Gly
1425                               1430                               1435                               1440

Pro Gln Leu Glu Ala Gln His Ser Ala Gly Ile Lys Leu Gly Tyr Arg
1445                               1450                               1455

Trp

<210> 12
<211> 797
<212> PRT
<213> Neisseria meningitidis

<400> 12
Met Lys Leu Lys Gln Ile Ala Ser Ala Leu Met Met Leu Gly Ile Ser
1      5      10      15

Pro Leu Ala Leu Ala Asp Phe Thr Ile Gln Asp Ile Arg Val Glu Gly
20     25     30

Leu Gln Arg Thr Glu Pro Ser Thr Val Phe Asn Tyr Leu Pro Val Lys
35     40     45

Val Gly Asp Thr Tyr Asn Asp Thr His Gly Ser Ala Ile Ile Lys Ser
50     55     60

Leu Tyr Ala Thr Gly Phe Phe Asp Asp Val Arg Val Glu Thr Ala Asp
65     70     75     80

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

Asn Ile Thr Gly Ala Lys Met Leu Gln Asn Asp Ala Ile Lys Lys Asn
100    105    110

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100					105					110					
Leu	Glu	Ser	Phe	Gly	Leu	Ala	Gln	Ser	Gln	Tyr	Phe	Asn	Gln	Ala	Thr
		115					120					125			
Leu	Asn	Gln	Ala	Val	Ala	Gly	Leu	Lys	Glu	Glu	Tyr	Leu	Gly	Arg	Gly
	130					135					140				
Lys	Leu	Asn	Ile	Gln	Ile	Thr	Pro	Lys	Val	Thr	Lys	Leu	Ala	Arg	Asn
145				150					155					160	
Arg	Val	Asp	Ile	Asp	Ile	Thr	Ile	Asp	Glu	Gly	Lys	Ser	Ala	Lys	Ile
			165						170					175	
Thr	Asp	Ile	Glu	Phe	Glu	Gly	Asn	Gln	Val	Tyr	Ser	Asp	Arg	Lys	Leu
		180					185						190		
Met	Arg	Gln	Met	Ser	Leu	Thr	Glu	Gly	Gly	Ile	Trp	Thr	Trp	Leu	Thr
	195						200					205			
Arg	Ser	Asn	Gln	Phe	Asn	Glu	Gln	Lys	Phe	Ala	Gln	Asp	Met	Glu	Lys
	210					215					220				
Val	Thr	Asp	Phe	Tyr	Gln	Asn	Asn	Gly	Tyr	Phe	Asp	Phe	Arg	Ile	Leu
225				230					235					240	
Asp	Thr	Asp	Ile	Gln	Thr	Asn	Glu	Asp	Lys	Thr	Lys	Gln	Thr	Ile	Lys
			245						250					255	
Ile	Thr	Val	His	Glu	Gly	Gly	Arg	Phe	Arg	Trp	Gly	Lys	Val	Ser	Ile
		260					265						270		
Glu	Gly	Asp	Thr	Asn	Glu	Val	Pro	Lys	Ala	Glu	Leu	Glu	Lys	Leu	Leu
	275						280					285			
Thr	Met	Lys	Pro	Gly	Lys	Trp	Tyr	Glu	Arg	Gln	Gln	Met	Thr	Ala	Val
	290					295					300				
Leu	Gly	Glu	Ile	Gln	Asn	Arg	Met	Gly	Ser	Ala	Gly	Tyr	Ala	Tyr	Ser
305				310					315					320	
Glu	Ile	Ser	Val	Gln	Pro	Leu	Pro	Asn	Ala	Glu	Thr	Lys	Thr	Val	Asp
			325						330					335	
Phe	Val	Leu	His	Ile	Glu	Pro	Gly	Arg	Lys	Ile	Tyr	Val	Asn	Glu	Ile
		340					345						350		
His	Ile	Thr	Gly	Asn	Asn	Lys	Thr	Arg	Asp	Glu	Val	Val	Arg	Arg	Glu
	355						360					365			
Leu	Arg	Gln	Met	Glu	Ser	Ala	Pro	Tyr	Asp	Thr	Ser	Lys	Leu	Gln	Arg
	370					375					380				
Ser	Lys	Glu	Arg	Val	Glu	Leu	Leu	Gly	Tyr	Phe	Asp	Asn	Val	Gln	Phe
385				390					395					400	
Asp	Ala	Val	Pro	Leu	Ala	Gly	Thr	Pro	Asp	Lys	Val	Asp	Leu	Asn	Met
			405						410					415	
Ser	Leu	Thr	Glu	Arg	Ser	Thr	Gly	Ser	Leu	Asp	Leu	Ser	Ala	Gly	Trp
		420					425						430		
Val	Gln	Asp	Thr	Gly	Leu	Val	Met	Ser	Ala	Gly	Val	Ser	Gln	Asp	Asn
	435						440						445		
Leu	Phe	Gly	Thr	Gly	Lys	Ser	Ala	Ala	Leu	Arg	Ala	Ser	Arg	Ser	Lys
	450					455					460				
Thr	Thr	Leu	Asn	Gly	Ser	Leu	Ser	Phe	Thr	Asp	Pro	Tyr	Phe	Thr	Ala
465				470					475						480
Asp	Gly	Val	Ser	Leu	Gly	Tyr	Asp	Val	Tyr	Gly	Lys	Ala	Phe	Asp	Pro
			485						490					495	
Arg	Lys	Ala	Ser	Thr	Ser	Ile	Lys	Gln	Tyr	Lys	Thr	Thr	Thr	Ala	Gly
			500				505						510		

Ala Gly Ile Arg Met Ser Val Pro Val Thr Glu Tyr Asp Arg Val Asn
515 520 525

Phe Gly Leu Val Ala Glu His Leu Thr Val Asn Thr Tyr Asn Lys Ala
530 535 540

Pro Lys His Tyr Ala Asp Phe Ile Lys Lys Tyr Gly Lys Thr Asp Gly
545 550 555 560

Thr Asp Gly Ser Phe Lys Gly Trp Leu Tyr Lys Gly Thr Val Gly Trp
565 570 575

Gly Arg Asn Lys Thr Asp Ser Ala Leu Trp Pro Thr Arg Gly Tyr Leu
580 585 590

Thr Gly Val Asn Ala Glu Ile Ala Leu Pro Gly Ser Lys Leu Gln Tyr
595 600 605

Tyr Ser Ala Thr His Asn Gln Thr Trp Phe Phe Pro Leu Ser Lys Thr
610 615 620

Phe Thr Leu Met Leu Gly Gly Glu Val Gly Ile Ala Gly Gly Tyr Gly
625 630 635 640

Arg Thr Lys Glu Ile Pro Phe Phe Glu Asn Phe Tyr Gly Gly Gly Leu
645 650 655

Gly Ser Val Arg Gly Tyr Glu Ser Gly Thr Leu Gly Pro Lys Val Tyr
660 665 670

Asp Glu Tyr Gly Glu Lys Ile Ser Tyr Gly Gly Asn Lys Lys Ala Asn
675 680 685

Val Ser Ala Glu Leu Leu Phe Pro Met Pro Gly Ala Lys Asp Ala Arg
690 695 700

Thr Val Arg Leu Ser Leu Phe Ala Asp Ala Gly Ser Val Trp Asp Gly
705 710 715 720

Lys Thr Tyr Asp Asp Asn Ser Ser Ser Ala Thr Gly Gly Arg Val Gln
725 730 735

Asn Ile Tyr Gly Ala Gly Asn Thr His Lys Ser Thr Phe Thr Asn Glu
740 745 750

Leu Arg Tyr Ser Ala Gly Gly Ala Val Thr Trp Leu Ser Pro Leu Gly
755 760 765

Pro Met Lys Phe Ser Tyr Ala Tyr Pro Leu Lys Lys Lys Pro Glu Asp
770 775 780

Glu Ile Gln Arg Phe Gln Phe Gln Leu Gly Thr Thr Phe
785 790 795

<210> 13

<211> 180

<212> PRT

<213> Neisseria meningitidis

<400> 13

Met Val Ser Ala Val Ile Gly Ser Ala Ala Val Gly Ala Lys Ser Ala
1 5 10 15

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

Thr Lys Gly Tyr Thr Pro Gln Ile Ser Val Val Gly Tyr Asp Arg His

50		55		60											
Leu 65	Leu 66	Leu 67	Leu 68	Gly 69	Gln 70	Val 71	Ala 72	Thr 73	Glu 74	Gly 75	Glu 76	Lys 77	Gln 78	Phe 79	Val 80
Gly 81	Gln 82	Ile 83	Ala 84	Arg 85	Ser 86	Glu 87	Gln 88	Ala 89	Ala 90	Glu 91	Gly 92	Val 93	Tyr 94	Asn 95	Tyr 96
Ile 97	Thr 98	Val 99	Ala 100	Ser 101	Leu 102	Pro 103	Arg 104	Thr 105	Ala 106	Gly 107	Asp 108	Ile 109	Ala 110	Gly 111	Asp 112
Thr 113	Trp 114	Asn 115	Thr 116	Ser 117	Lys 118	Val 119	Arg 120	Ala 121	Thr 122	Leu 123	Leu 124	Gly 125	Ile 126	Ser 127	Pro 128
Ala 129	Thr 130	Arg 131	Ala 132	Arg 133	Val 134	Lys 135	Ile 136	Val 137	Thr 138	Tyr 139	Gly 140	Asn 141	Val 142	Thr 143	Tyr 144
Val 145	Met 146	Gly 147	Ile 148	Leu 149	Thr 150	Pro 151	Glu 152	Glu 153	Gln 154	Ala 155	Gln 156	Ile 157	Thr 158	Gln 159	Lys 160
Val 161	Ser 162	Thr 163	Thr 164	Val 165	Gly 166	Val 167	Gln 168	Lys 169	Val 170	Ile 171	Thr 172	Leu 173	Tyr 174	Gln 175	Asn 176
Tyr 177	Val 178	Gln 179	Arg 180												

<210> 14

<211> 644

<212> PRT

<213> Neisseria meningitidis

<400> 14

Met 1	Ala 2	Ser 3	Pro 4	Asp 5	Val 6	Lys 7	Ser 8	Ala 9	Asp 10	Thr 11	Leu 12	Ser 13	Lys 14	Pro 15	Ala 16
Ala 17	Pro 18	Val 19	Val 20	Ser 21	Glu 22	Lys 23	Glu 24	Thr 25	Glu 26	Ala 27	Lys 28	Glu 29	Asp 30	Ala 31	Pro 32
Gln 33	Ala 34	Gly 35	Ser 36	Gln 37	Gly 38	Gln 39	Gly 40	Ala 41	Pro 42	Ser 43	Ala 44	Gln 45	Gly 46	Gly 47	Gln 48
Asp 49	Met 50	Ala 51	Ala 52	Val 53	Ser 54	Glu 55	Glu 56	Asn 57	Thr 58	Gly 59	Asn 60	Gly 61	Gly 62	Ala 63	Ala 64
Ala 65	Thr 66	Asp 67	Lys 68	Pro 69	Lys 70	Asn 71	Glu 72	Asp 73	Glu 74	Gly 75	Ala 76	Gln 77	Asn 78	Asp 79	Met 80
Pro 81	Gln 82	Asn 83	Ala 84	Ala 85	Asp 86	Thr 87	Asp 88	Ser 89	Leu 90	Thr 91	Pro 92	Asn 93	His 94	Thr 95	Pro 96
Ala 97	Ser 98	Asn 99	Met 100	Pro 101	Ala 102	Gly 103	Asn 104	Met 105	Glu 106	Asn 107	Gln 108	Ala 109	Pro 110	Asp 111	Ala 112
Gly 113	Glu 114	Ser 115	Glu 116	Gln 117	Pro 118	Ala 119	Asn 120	Gln 121	Pro 122	Asp 123	Met 124	Ala 125	Asn 126	Thr 127	Ala 128
Asp 129	Gly 130	Met 131	Gln 132	Gly 133	Asp 134	Asp 135	Pro 136	Ser 137	Ala 138	Gly 139	Gly 140	Glu 141	Asn 142	Ala 143	Gly 144
Asn 145	Thr 146	Ala 147	Ala 148	Gln 149	Gly 150	Thr 151	Asn 152	Gln 153	Ala 154	Glu 155	Asn 156	Asn 157	Gln 158	Thr 159	Ala 160
Gly 161	Ser 162	Gln 163	Asn 164	Pro 165	Ala 166	Ser 167	Ser 168	Thr 169	Asn 170	Pro 171	Ser 172	Ala 173	Thr 174	Asn 175	Ser 176
Gly 177	Gly 178	Asp 179	Phe 180	Gly 181	Arg 182	Thr 183	Asn 184	Val 185	Gly 186	Asn 187	Ser 188	Val 189	Val 190	Ile 191	Asp 192
Gly 193	Pro 194	Ser 195	Gln 196	Asn 197	Ile 198	Thr 199	Leu 200	Thr 201	His 202	Cys 203	Lys 204	Gly 205	Asp 206	Ser 207	Cys 208

Ser Gly Asn Asn Phe Leu Asp Glu Glu Val Gln Leu Lys Ser Glu Phe
 210 215 220
 Glu Lys Leu Ser Asp Ala Asp Lys Ile Ser Asn Tyr Lys Lys Asp Gly
 225 230 235 240
 Lys Asn Asp Gly Lys Asn Asp Lys Phe Val Gly Leu Val Ala Asp Ser
 245 250 255
 Val Gln Met Lys Gly Ile Asn Gln Tyr Ile Ile Phe Tyr Lys Pro Lys
 260 265 270
 Pro Thr Ser Phe Ala Arg Phe Arg Arg Ser Ala Arg Ser Arg Arg Ser
 275 280 285
 Leu Pro Ala Glu Met Pro Leu Ile Pro Val Asn Gln Ala Asp Thr Leu
 290 295 300
 Ile Val Asp Gly Glu Ala Val Ser Leu Thr Gly His Ser Gly Asn Ile
 305 310 315 320
 Phe Ala Pro Glu Gly Asn Tyr Arg Tyr Leu Thr Tyr Gly Ala Glu Lys
 325 330 335
 Leu Pro Gly Gly Ser Tyr Ala Leu Arg Val Gln Gly Glu Pro Ser Lys
 340 345 350
 Gly Glu Met Leu Ala Gly Thr Ala Val Tyr Asn Gly Glu Val Leu His
 355 360 365
 Phe His Thr Glu Asn Gly Arg Pro Ser Pro Ser Arg Gly Arg Phe Ala
 370 375 380
 Ala Lys Val Asp Phe Gly Ser Lys Ser Val Asp Gly Ile Ile Asp Ser
 385 390 395 400
 Gly Asp Gly Leu His Met Gly Thr Gln Lys Phe Lys Ala Ala Ile Asp
 405 410 415
 Gly Asn Gly Phe Lys Gly Thr Trp Thr Glu Asn Gly Gly Gly Asp Val
 420 425 430
 Ser Gly Lys Phe Tyr Gly Pro Ala Gly Glu Glu Val Ala Gly Lys Tyr
 435 440 445
 Ser Tyr Arg Pro Thr Asp Ala Glu Lys Gly Gly Phe Gly Val Phe Ala
 450 455 460
 Gly Lys Lys Glu Gln Asp Gly Ser Gly Gly Gly Gly Ala Thr Tyr Lys
 465 470 475 480
 Val Asp Glu Tyr His Ala Asn Ala Arg Phe Ala Ile Asp His Phe Asn
 485 490 495
 Thr Ser Thr Asn Val Gly Gly Phe Tyr Gly Leu Thr Gly Ser Val Glu
 500 505 510
 Phe Asp Gln Ala Lys Arg Asp Gly Lys Ile Asp Ile Thr Ile Pro Val
 515 520 525
 Ala Asn Leu Gln Ser Gly Ser Gln His Phe Thr Asp His Leu Lys Ser
 530 535 540
 Ala Asp Ile Phe Asp Ala Ala Gln Tyr Pro Asp Ile Arg Phe Val Ser
 545 550 555 560
 Thr Lys Phe Asn Phe Asn Gly Lys Lys Leu Val Ser Val Asp Gly Asn
 565 570 575
 Leu Thr Met His Gly Lys Thr Ala Pro Val Lys Leu Lys Ala Glu Lys
 580 585 590
 Phe Asn Cys Tyr Gln Ser Pro Met Ala Lys Thr Glu Val Cys Gly Gly
 595 600 605

Asp Phe Ser Thr Thr Ile Asp Arg Thr Lys Trp Gly Val Asp Tyr Leu
610 615 620

Val Asn Val Gly Met Thr Lys Ser Val Arg Ile Asp Ile Gln Ile Glu
625 630 635 640

Ala Ala Lys Gln

<210> 15

<211> 327

<212> PRT

<213> Neisseria meningitidis

<400> 15

Ala Thr Asn Asp Asp Asp Val Lys Lys Ala Ala Thr Val Ala Ile Ala
1 5 10 15

Ala Ala Tyr Asn Asn Gly Gln Glu Ile Asn Gly Phe Lys Ala Gly Glu
20 25 30

Thr Ile Tyr Asp Ile Asp Glu Asp Gly Thr Ile Thr Lys Lys Asp Ala
35 40 45

Thr Ala Ala Asp Val Glu Ala Asp Asp Phe Lys Gly Leu Gly Leu Lys
50 55 60

Lys Val Val Thr Asn Leu Thr Lys Thr Val Asn Glu Asn Lys Gln Asn
65 70 75 80

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

Thr Lys Leu Ala Asp Thr Asp Ala Ala Leu Ala Asp Thr Asp Ala Ala
100 105 110

Leu Asp Ala Thr Thr Asn Ala Leu Asn Lys Leu Gly Glu Asn Ile Thr
115 120 125

Thr Phe Ala Glu Glu Thr Lys Thr Asn Ile Val Lys Ile Asp Glu Lys
130 135 140

Leu Glu Ala Val Ala Asp Thr Val Asp Lys His Ala Glu Ala Phe Asn
145 150 155 160

Asp Ile Ala Asp Ser Leu Asp Glu Thr Asn Thr Lys Ala Asp Glu Ala
165 170 175

Val Lys Thr Ala Asn Glu Ala Lys Gln Thr Ala Glu Glu Thr Lys Gln
180 185 190

Asn Val Asp Ala Lys Val Lys Ala Ala Glu Thr Ala Ala Gly Lys Ala
195 200 205

Glu Ala Ala Ala Gly Thr Ala Asn Thr Ala Ala Asp Lys Ala Glu Ala
210 215 220

Val Ala Ala Lys Val Thr Asp Ile Lys Ala Asp Ile Ala Thr Asn Lys
225 230 235 240

Asp Asn Ile Ala Lys Lys Ala Asn Ser Ala Asp Val Tyr Thr Arg Glu
245 250 255

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

Glu Lys Leu Asp Thr Arg Leu Ala Ser Ala Glu Lys Ser Ile Ala Asp
275 280 285

His Asp Thr Arg Leu Asn Gly Leu Asp Lys Thr Val Ser Asp Leu Arg
290 295 300

Lys Glu Thr Arg Gln Gly Leu Ala Glu Gln Ala Ala Leu Ser Gly Leu
305 310 315 320

Phe Gln Pro Tyr Asn Val Gly
325

<210> 16

<211> 248

<212> PRT

<213> Neisseria meningitidis

<400> 16

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

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

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

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

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

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

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

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

His Ile Gly Leu Ala Ala Lys Gln
245

<210> 17

<211> 250

<212> PRT

<213> Neisseria meningitidis

<400> 17

Val Ala Ala Asp Ile Gly Thr Gly Leu Ala Asp Ala Leu Thr Ala Pro

1		5		10		15											
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					
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		
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		
			100					105					110				
Pro	Asp	Lys	Thr	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser		
		115					120					125					
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		
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		
			180					185					190				
Leu	Lys	Ala	Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg		
		195					200					205					
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		
Val	His	Glu	Ile	Gly	Ile	Ala	Gly	Lys	Gln								
			245						250								

<210> 18

<211> 273

<212> PRT

<213> Neisseria meningitidis

<400> 18

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	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			

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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 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 Arg His Ile Gly Ile Ala Gly Lys
      260      265      270

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Gln

<210> 19

<211> 273

<212> PRT

<213> Neisseria meningitidis

<400> 19

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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 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 Val 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

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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 Arg His Ile Gly Ile Ala Gly Lys
      260                      265                      270

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Gln

<210> 20

<211> 273

<212> PRT

<213> Neisseria meningitidis

<400> 20

```

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 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 Val 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 Arg 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

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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

<210> 21

<211> 273

<212> PRT

<213> Neisseria meningitidis

<400> 21

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 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 Arg 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

<210> 22

<211> 273

<212> PRT

<213> Neisseria meningitidis

<400> 22

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	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	Gly	Asp	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

<210> 23

<211> 273

<212> PRT

<213> Neisseria meningitidis

<400> 23

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 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 Thr 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 Gly Asp 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

<210> 24

<211> 273

<212> PRT

<213> Neisseria meningitidis

<400> 24

```

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 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 Asn

```

```

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

<210> 25

<211> 273

<212> PRT

<213> Neisseria meningitidis

<400> 25

```

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 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 Cys Arg Lys Asn Glu Lys
50                               55                               60

Cys 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

<210> 26

<211> 273

<212> PRT

<213> Neisseria meningitidis

<400> 26

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 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 Cys 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 Cys 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

<210> 27

<211> 273

<212> PRT

<213> Neisseria meningitidis

<400> 27

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 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 Cys 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
 Cys 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

<210> 28

<211> 273

<212> PRT

<213> Neisseria meningitidis

<400> 28

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 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 Thr 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 Gly Asp 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 Arg His Ile Gly Ile Ala Gly Lys
 260 265 270

Gln

<210> 29

<211> 273

<212> PRT

<213> Neisseria meningitidis

<400> 29

```

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 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 Arg Ile Gly Asp Ile Ala 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

<210> 30

<211> 273

<212> PRT

<213> Neisseria meningitidis

<400> 30

```

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

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```

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 Thr 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

<210> 31

<211> 273

<212> PRT

<213> Neisseria meningitidis

<400> 31

```

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 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 Cys 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

<210> 32

<211> 273

<212> PRT

<213> Neisseria meningitidis

<400> 32

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 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 Cys 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

<210> 33

<211> 273

<212> PRT

<213> Neisseria meningitidis

<400> 33

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 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 Val 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 Thr 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

```

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

<210> 34

<211> 273

<212> PRT

<213> Neisseria meningitidis

<400> 34

```

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 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 Val 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 Arg Val Thr 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

<210> 35

<211> 273

<212> PRT

<213> *Neisseria meningitidis*

<400> 35

```

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 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 Val 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 Gly 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

<210> 36

<211> 273

<212> PRT

<213> *Neisseria meningitidis*

<400> 36

```

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	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	Val	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	Arg	Val	Gly	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

<210> 37

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> N-terminal sequence

<400> 37

Gly	Pro	Asp	Ser	Asp	Arg	Leu	Gln	Gln	Arg	Arg
1				5					10	

<210> 38

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> N-terminal sequence

<400> 38

Gly	Ser	Lys	Asp	Ile	Ser	Ser
1				5		

<210> 39

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> N-terminal sequence

<400> 39

Gly	Ser	Lys	Asp	Ile	Ser	Ser	Gly	Gly	Gly	Gly
1				5					10	

<210> 40

<211> 262

<212> PRT

<213> Neisseria meningitidis

<400> 40

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

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

Asp	Lys	Gly	Leu	Lys	Ser	Leu	Thr	Leu	Glu	Asp	Ser	Ile	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				

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	

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
		115					120					125			

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

Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	His	Tyr	Ser
				165					170					175	

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
		195					200					205			

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
 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

<210> 41

<211> 250

<212> PRT

<213> Neisseria meningitidis

<400> 41

Val Ala Ala Asp Ile Gly Thr Gly Leu Ala Asp Ala Leu Thr Ala Pro
 1 5 10 15
 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
 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
 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
 100 105 110
 Pro Asp Lys Thr Asp Ser Leu Ile Asn Gln Arg Ser Phe Leu Val Ser
 115 120 125
 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
 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
 180 185 190
 Leu Lys Ala Asp Glu Lys Ser His Ala Val Ile Leu Gly Asp Thr Arg
 195 200 205
 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
 Val His Ala Ile Gly Ile Ala Gly Lys Gln
 245 250

<210> 42

<211> 250

<212> PRT

<213> Neisseria meningitidis

<400> 42

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

Leu Asp His Lys Asp Lys Gly Leu Lys Ser Leu Thr Leu Glu Asp Val
          20          25          30

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

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

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
          100          105          110

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

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

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
          180          185          190

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

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

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

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<210> 43

<211> 250

<212> PRT

<213> Neisseria meningitidis

<400> 43

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

Leu Asp His Lys Asp Lys Gly Leu Lys Ser Leu Thr Leu Glu Asp Val
          20          25          30

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

Thr Phe Lys Ala Gly Asp Lys Asp Asn Ser Leu Asn Thr Gly Lys Leu
          50          55          60

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Lys Asn Asp Lys Ile Ser Arg Phe Asp Phe Val Gln Lys Ile Glu Val
 65 70 75 80
 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
 100 105 110
 Pro Asp Lys Thr Asp Ser Leu Ile Asn Gln Arg Ser Phe Arg Val Ser
 115 120 125
 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
 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
 180 185 190
 Leu Lys Ala Asp Glu Lys Ser His Ala Val Ile Leu Gly Asp Thr Arg
 195 200 205
 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
 Val His Ala Ile Gly Ile Ala Gly Lys Gln
 245 250

<210> 44

<211> 250

<212> PRT

<213> Neisseria meningitidis

<400> 44

Val Ala Ala Asp Ile Gly Thr Gly Leu Ala Asp Ala Leu Thr Ala Pro
 1 5 10 15
 Leu Asp His Lys Asp Lys Gly Leu Lys Ser Leu Thr Leu Glu Asp Val
 20 25 30
 Ile Pro Gln Asn Gly Thr Leu Thr Leu Ser Ala Gln Gly Ala Glu Lys
 35 40 45
 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
 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
 100 105 110
 Pro Asp Lys Thr Asp Ser Leu Ile Asn Gln Arg Ser Phe Arg Val Ser
 115 120 125
 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

```

Ala Glu Tyr His Gly Lys Ala Thr Ser Ser Asp Asp Thr Asn Gly Arg
145                               150                      155                      160

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
                               180                      185                      190

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

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

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

```

<210> 45

<211> 247

<212> PRT

<213> Neisseria meningitidis

<400> 45

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

Leu Asp His Lys Asp Lys Ser Leu Gln Ser Leu Thr Leu Asp Gln Val
                               20                      25                      30

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

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 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
                               100                      105                      110

Ile Asp Ser Leu Ile Asn Gln Arg Ser Phe Arg Val Ser Gly Leu Gly
    115                      120                      125

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

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
                               180                      185                      190

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

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

```

Ile Gly Ile Ala Gly Lys Gln
245

<210> 46

<211> 255

<212> PRT

<213> Neisseria meningitidis

<400> 46

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

<210> 47

<211> 757

<212> PRT

<213> Artificial Sequence

<220>

<223> v2-v3-v1 mutant fusion

<400> 47

Val	Ala	Ala	Asp	Ile	Gly	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	1	5	10	15
Leu	Asp	His	Lys	Asp	Lys	Ser	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Val	20	25	30	
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	
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	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	100	105	110	
Ile	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Arg	Val	Ser	Gly	Leu	Gly	115	120	125	
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
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	180	185	190	
Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser	195	200	205	
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
Ile	Gly	Ile	Ala	Gly	Lys	Gln	Gly	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala	245	250	255	
Asp	Ile	Gly	Thr	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His	260	265	270	
Lys	Asp	Lys	Gly	Leu	Lys	Ser	Leu	Thr	Leu	Glu	Asp	Val	Ile	Pro	Gln	275	280	285	
Asn	Gly	Thr	Leu	Thr	Leu	Ser	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Phe	Lys	290	295	300	
Ala	Gly	Asp	Lys	Asp	Asn	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	305	310	315	320
Lys	Ile	Ser	Arg	Phe	Asp	Phe	Val	Gln	Lys	Ile	Glu	Val	Asp	Gly	Gln	325	330	335	
Thr	Ile	Thr	Leu	Ala	Ser	Gly	Glu	Phe	Gln	Ile	Tyr	Lys	Gln	Asn	His	340	345	350	
Ser	Ala	Val	Val	Ala	Leu	Gln	Ile	Glu	Lys	Ile	Asn	Asn	Pro	Asp	Lys	355	360	365	
Thr	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Arg	Val	Ser	Gly	Leu	Gly	370	375	380	
Gly	Glu	His	Thr	Ala	Phe	Asn	Gln	Leu	Pro	Gly	Gly	Lys	Ala	Glu	Tyr	385	390	395	400
His	Gly	Lys	Ala	Phe	Ser	Ser	Asp	Asp	Pro	Asn	Gly	Arg	Leu	His	Tyr	405	410	415	

405					410					415					
Ser	Ile	Asp	Phe	Thr	Lys	Lys	Gln	Gly	Tyr	Gly	Arg	Ile	Glu	His	Leu
			420					425					430		
Lys	Thr	Leu	Glu	Gln	Asn	Val	Glu	Leu	Ala	Ala	Ala	Glu	Leu	Lys	Ala
		435					440					445			
Asp	Glu	Lys	Ser	His	Ala	Val	Ile	Leu	Gly	Asp	Thr	Arg	Tyr	Gly	Ser
	450					455					460				
Glu	Glu	Lys	Gly	Thr	Tyr	His	Leu	Ala	Leu	Phe	Gly	Asp	Arg	Ala	Gln
465					470					475					480
Glu	Ile	Ala	Gly	Ser	Ala	Thr	Val	Lys	Ile	Gly	Glu	Lys	Val	His	Glu
				485					490					495	
Ile	Gly	Ile	Ala	Gly	Lys	Gln	Gly	Ser	Gly	Gly	Gly	Gly	Val	Ala	Ala
			500					505					510		
Asp	Ile	Gly	Ala	Gly	Leu	Ala	Asp	Ala	Leu	Thr	Ala	Pro	Leu	Asp	His
		515					520					525			
Lys	Asp	Lys	Gly	Leu	Gln	Ser	Leu	Thr	Leu	Asp	Gln	Ser	Val	Ser	Lys
	530					535					540				
Asn	Glu	Lys	Leu	Lys	Leu	Ala	Ala	Gln	Gly	Ala	Glu	Lys	Thr	Tyr	Gly
545				550					555						560
Asn	Gly	Asp	Ser	Leu	Asn	Thr	Gly	Lys	Leu	Lys	Asn	Asp	Lys	Val	Ser
			565						570					575	
Arg	Phe	Asp	Phe	Ile	Arg	Gln	Ile	Glu	Val	Asp	Gly	Gln	Leu	Ile	Thr
			580					585					590		
Leu	Glu	Ser	Gly	Glu	Phe	Gln	Val	Tyr	Lys	Gln	Ser	His	Ser	Ala	Leu
		595					600					605			
Thr	Ala	Phe	Gln	Thr	Glu	Gln	Ile	Gln	Asp	Ser	Glu	His	Ser	Gly	Lys
	610					615					620				
Met	Val	Ala	Lys	Arg	Gln	Phe	Arg	Ile	Gly	Asp	Ile	Ala	Gly	Glu	His
625				630					635					640	
Thr	Ser	Phe	Asp	Lys	Leu	Pro	Glu	Gly	Gly	Arg	Ala	Thr	Tyr	Arg	Gly
			645						650					655	
Thr	Ala	Phe	Gly	Ser	Asp	Asp	Ala	Gly	Gly	Lys	Leu	Thr	Tyr	Thr	Ile
			660					665					670		
Asp	Phe	Ala	Ala	Lys	Gln	Gly	Asn	Gly	Lys	Ile	Glu	His	Leu	Lys	Ser
		675					680					685			
Pro	Glu	Leu	Asn	Val	Asp	Leu	Ala	Ala	Ala	Asp	Ile	Lys	Pro	Asp	Gly
	690					695					700				
Lys	Arg	His	Ala	Val	Ile	Ser	Gly	Ser	Val	Leu	Tyr	Asn	Gln	Ala	Glu
705				710							715				720
Lys	Gly	Ser	Tyr	Ser	Leu	Gly	Ile	Phe	Gly	Gly	Lys	Ala	Gln	Glu	Val
			725						730					735	
Ala	Gly	Ser	Ala	Glu	Val	Lys	Thr	Val	Asn	Gly	Ile	Arg	His	Ile	Gly
			740					745					750		
Leu	Ala	Ala	Lys	Gln											
			755												

<210> 48

<211> 769

<212> PRT

<213> Artificial Sequence

<220>

<223> v2-v3-v1 mutant fusion

<400> 48

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Met Gly Pro Asp Ser Asp Arg Leu Gln Gln Arg Arg Val Ala Ala Asp
1           5           10           15

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Gly
          275          280          285

Leu Lys Ser Leu Thr Leu Glu Asp Val Ile Pro Gln Asn Gly Thr Leu
          290          295          300

Thr Leu Ser Ala Gln Gly Ala Glu Lys Thr Phe Lys Ala Gly Asp Lys
305          310          315          320

Asp Asn Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Ile Ser Arg
          325          330          335

Phe Asp Phe Val Gln Lys Ile Glu Val Asp Gly Gln Thr Ile Thr Leu
          340          345          350

Ala Ser Gly Glu Phe Gln Ile Tyr Lys Gln Asn His Ser Ala Val Val
          355          360          365

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Ala Leu Gln Ile Glu Lys Ile Asn Asn Pro Asp Lys Thr Asp Ser Leu
 370 375 380
 Ile Asn Gln Arg Ser Phe Arg Val Ser Gly Leu Gly Gly Glu His Thr
 385 390 395 400
 Ala Phe Asn Gln Leu Pro Gly Gly Lys Ala Glu Tyr His Gly Lys Ala
 405 410 415
 Phe Ser Ser Asp Asp Pro Asn Gly Arg Leu His Tyr Ser Ile Asp Phe
 420 425 430
 Thr Lys Lys Gln Gly Tyr Gly Arg Ile Glu His Leu Lys Thr Leu Glu
 435 440 445
 Gln Asn Val Glu Leu Ala Ala Ala Glu Leu Lys Ala Asp Glu Lys Ser
 450 455 460
 His Ala Val Ile Leu Gly Asp Thr Arg Tyr Gly Ser Glu Glu Lys Gly
 465 470 475 480
 Thr Tyr His Leu Ala Leu Phe Gly Asp Arg Ala Gln Glu Ile Ala Gly
 485 490 495
 Ser Ala Thr Val Lys Ile Gly Glu Lys Val His Glu Ile Gly Ile Ala
 500 505 510
 Gly Lys Gln Gly Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala
 515 520 525
 Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Gly
 530 535 540
 Leu Gln Ser Leu Thr Leu Asp Gln Ser Val Ser Lys Asn Glu Lys Leu
 545 550 555 560
 Lys Leu Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser
 565 570 575
 Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe
 580 585 590
 Ile Arg Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly
 595 600 605
 Glu Phe Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Phe Gln
 610 615 620
 Thr Glu Gln Ile Gln Asp Ser Glu His Ser Gly Lys Met Val Ala Lys
 625 630 635 640
 Arg Gln Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp
 645 650 655
 Lys Leu Pro Glu Gly Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe Gly
 660 665 670
 Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala
 675 680 685
 Lys Gln Gly Asn Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn
 690 695 700
 Val Asp Leu Ala Ala Ala Asp Ile Lys Pro Asp Gly Lys Arg His Ala
 705 710 715 720
 Val Ile Ser Gly Ser Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser Tyr
 725 730 735
 Ser Leu Gly Ile Phe Gly Gly Lys Ala Gln Glu Val Ala Gly Ser Ala
 740 745 750
 Glu Val Lys Thr Val Asn Gly Ile Arg His Ile Gly Leu Ala Ala Lys
 755 760 765

Gln

<210> 49

<211> 248

<212> PRT

<213> Neisseria meningitidis

<400> 49

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

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

Val	Ser	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				

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	

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			

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

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		

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				

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
							245

<210> 50

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker

<400> 50

Gly Ser Gly Gly Gly Gly

1

5

<210> 51

<211> 247

<212> PRT

<213> Neisseria meningitidis

<400> 51

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

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			

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

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
			100					105					110		

Ile	Asp	Ser	Leu	Ile	Asn	Gln	Arg	Ser	Phe	Leu	Val	Ser	Gly	Leu	Gly
		115					120					125			

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

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
			180					185					190		

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

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

Ile	Gly	Ile	Ala	Gly	Lys	Gln									
				245											

<210> 52

<211> 248

<212> PRT

<213> Neisseria meningitidis

<400> 52

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

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
 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 Lys
 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 Leu Gln Thr Glu Gln Val Gln Asp Ser Glu Asp
 100 105 110
 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 Lys Gly Gly Ser 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
 Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly His Gly Lys Ile Glu His
 165 170 175
 Leu Lys Ser Pro Glu Leu Asn Val Glu Leu Ala Thr Ala Glu Leu Lys
 180 185 190
 Ala Asp Glu Lys Ser His Ala Val Ile Leu Gly Asp Thr Arg Tyr Gly
 195 200 205
 Gly Glu Glu Lys Gly Thr Tyr His Leu Ala Leu Phe Gly Asp Arg Ala
 210 215 220
 Gln Glu Ile Ala Gly Ser Ala Thr Val Lys Ile Arg Glu Lys Val His
 225 230 235 240
 Glu Ile Gly Ile Ala Gly Lys Gln
 245

<210> 53

<211> 250

<212> PRT

<213> Neisseria meningitidis

<400> 53

Val Ala Ala Asp Ile Gly Thr Gly Leu Ala Asp Ala Leu Thr Ala Pro
 1 5 10 15
 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
 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
 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
 100 105 110
 Pro Asp Lys Thr Asp Ser Leu Ile Asn Gln Arg Ser Phe Arg Val Ser

115		120		125
Gly 130	Leu 130	Gly 130	Gly 130	Glu 130
				His 135
				Thr 135
				Ala 135
				Phe 135
				Asn 135
				Gln 140
				Leu 140
				Pro 140
				Gly 140
				Gly 140
				Lys 140
Ala 145	Glu 145	Tyr 145	His 145	Gly 150
				Lys 150
				Ala 150
				Phe 150
				Ser 155
				Ser 155
				Asp 155
				Asp 155
				Pro 155
				Asn 160
				Gly 160
				Arg 160
Leu 165	His 165	Tyr 165	Ser 165	Ile 165
				Asp 170
				Phe 170
				Thr 170
				Lys 170
				Lys 170
				Gln 170
				Gly 175
				Tyr 175
				Gly 175
				Arg 175
				Ile 175
Glu 180	His 180	Leu 180	Lys 180	Thr 180
				Leu 185
				Glu 185
				Gln 185
				Asn 185
				Val 185
				Glu 190
				Leu 190
				Ala 190
				Ala 190
				Ala 190
				Glu 190
Leu 195	Lys 195	Ala 195	Asp 195	Glu 195
				Lys 200
				Ser 200
				His 200
				Ala 205
				Val 205
				Ile 205
				Leu 205
				Gly 205
				Asp 205
				Thr 205
				Arg 205
Tyr 210	Gly 210	Ser 210	Glu 210	Glu 210
				Lys 215
				Gly 215
				Thr 215
				Tyr 215
				His 220
				Leu 220
				Ala 220
				Leu 220
				Phe 220
				Gly 220
				Asp 220
Arg 225	Ala 225	Gln 225	Glu 225	Ile 225
				Ala 230
				Gly 230
				Ser 230
				Ala 235
				Thr 235
				Val 235
				Lys 235
				Ile 235
				Gly 240
				Glu 240
				Lys 240
Val 245	His 245	Glu 245	Ile 245	Gly 245
				Ile 250
				Ala 250
				Gly 250
				Lys 250
				Gln 250

<210> 54

<211> 273

<212> PRT

<213> Neisseria meningitidis

<400> 54

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

<210> 55

<211> 247

<212> PRT

<213> Neisseria meningitidis

<400> 55

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

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

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

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
 100 105 110

Ile Asp Ser Leu Ile Asn Gln Arg Ser Phe Leu Val Ser Gly Leu Gly
 115 120 125

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

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
 180 185 190

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

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

Ile Gly Ile Ala Gly Lys Gln
 245

<210> 56

<211> 247

<212> PRT

<213> *Neisseria meningitidis*

<400> 56

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

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

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

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
100 105 110

Ile Asp Ser Leu Ile Asn Gln Arg Ser Phe Leu Val Ser Gly Leu Gly
115 120 125

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

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
180 185 190

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

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 Ala
225 230 235 240

Ile Gly Ile Ala Gly Lys Gln
245

<210> 57

<211> 247

<212> PRT

<213> *Neisseria meningitidis*

<400> 57

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

Leu Asp His Lys Asp Lys Ser Leu Gln Ser Leu Thr Leu Asp Gln Val
20 25 30

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

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 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
 100 105 110
 Ile Asp Ser Leu Ile Asn Gln Arg Ser Phe Arg Val Ser Gly Leu Gly
 115 120 125
 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
 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
 180 185 190
 Asp Glu Lys Ser His Ala Val Ile Leu Gly Asp Thr Arg Tyr Gly Ser
 195 200 205
 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 Ala
 225 230 235 240
 Ile Gly Ile Ala Gly Lys Gln
 245

<210> 58

<211> 247

<212> PRT

<213> Neisseria meningitidis

<400> 58

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

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<210> 59

<211> 254

<212> PRT

<213> Neisseria meningitidis

<400> 59

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

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

$\langle 210 \rangle$ 60

<211> 254

<212> PRT

<213> Neisseria meningitidis

<400> 60

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 61

$\langle 211 \rangle$ 250

<212> PRT

<213> Neisseria meningitidis

<400> 61

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

Leu Asp His Lys Asp Lys Gly Leu Lys Ser Leu Thr Leu Glu Asp Val
20 25 30

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

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

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
100 105 110

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

Asp Ile Ala 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

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
180 185 190

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

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

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

REFERENCES CITED IN THE DESCRIPTION

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regard.

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P A T E N T K R A V

1. Mutant v3- eller v2-fHbp som er:

(A) et polypeptid omfattende en mutant fHbp-v2-aminosyresekvens, hvor:

5 (i) aminosyresekvensen har mindst 80% sekvensidentitet til SEQ ID NO: 5 og/eller omfatter et fragment af SEQ ID NO: 5 som er mindst 7 aminosyrer langt og indbefatter en rest som svarer til rest 32 fra SEQ ID NO: 5; men

(ii) aminosyresekvensen er forskellig fra SEQ ID NO: 5 ved rest 32 ved substitutionen S32V,

10 hvor polypeptidet kan udløse antistoffer som kan genkende et vildtype-meningokokpolypeptid bestående af SEQ ID NO. 4, eller

(B) et polypeptid omfattende en mutant fHbp-v3-aminosyresekvens, hvor:

(i) aminosyresekvensen har mindst 80% sekvensidentitet til SEQ ID NO: 17 og/eller omfatter et fragment af SEQ ID NO: 17 som er mindst 7 aminosyrer langt og som 15 indbefatter en rest som svarer til rest 32 fra SEQ ID NO: 17; men

(ii) aminosyresekvensen er forskellig fra SEQ ID NO: 17 ved rest 32 ved substitutionen S32V,

20 hvor polypeptidet kan udløse antistoffer som kan genkende et vildtype-meningokokpolypeptid bestående af SEQ ID NO. 40.

2. Polypeptid ifølge krav 1, hvor:

(A) aminosyresekvensen er yderligere forskellig fra SEQ ID NO: 5 ved substitution ved én eller flere af L123, V124, S125, G126, L127 og/eller G128; hvor substitutionen/erne er valgt fra gruppen bestående af: L123R; V124I; S125G eller S125T; G126D; L127I; 25 G128A; eller

(B) aminosyresekvensen er yderligere forskellig fra SEQ ID NO: 17 ved substitution ved L126, hvor substitutionen er L126R.

3. Polypeptid ifølge et hvilket som helst af de foregående krav, også indbefattende 30 én eller flere yderligere mutation(er) som bryder polypeptidets evne til at binde til menne-skefaktor-H; for eksempel i v2 som indbefatter en substitution ved én eller flere af rest R73, D203, E210, G228, S121, F122, A192, E194, V199, I200, L201, T213, H215, F219, T231 og E240, eller i v3 som indbefatter en substitution ved én eller flere af rest Q35, 178, L87, A88, V127, V202, E213, T216, H218, T234, V241, E243 og G248.

35

4. Polypeptid omfattende:

i. aminosyresekvens SEQ ID NO: 45, eventuelt med 1, 2, 3, 4 eller 5 enkelt-aminosyresubstitutioner, -deletioner og/eller -indsættelser, hvor polypeptidet kan udløse antistoffer som binder til et meningokok-fHbp-polypeptid som består af aminosyresekvens 40 sen ifølge SEQ ID NO: 2 (for eksempel omfattende aminosyresekvens SEQ ID NO: 45 med

1, 2 eller 3 enkelt-aminosyresubstitutioner), men som ikke er muteret ved rest V32 eller R123; og/eller

- ii. aminosekvens SEQ ID NO: 44, eventuelt med 1, 2, 3, 4 eller 5 enkelt-aminosyresubstitutioner, -deletioner og/eller -indsættelser, hvor polypeptidet kan udløse antistoffer som binder til et meningokok-fHbp-polypeptid som består af aminosyresekvensen ifølge SEQ ID NO: 40 (for eksempel omfattende aminosyresekvens SEQ ID NO: 44 med 1, 2 eller 3 enkelt-aminosyresubstitutioner), men som ikke er muteret ved rest V32 eller R126.

10 **5.** Polypeptid ifølge krav 4 omfattende eller bestående af aminosyresekvensen ifølge SEQ ID NO: 45.

6. Polypeptid ifølge krav 4 omfattende eller bestående af aminosyresekvensen ifølge SEQ ID NO: 44.

15

7. Plasmid eller øvrig nukleinsyre omfattende en nukleotidsekvens som koder for polypeptidet ifølge et hvilket som helst af krav 1 til 6.

20 **8.** Værtscelle som er transformeret med plasmidet ifølge krav 7; for eksempel, hvor cellen er en meningokokbakterie, såsom en meningokokbakterie med nedregulering eller knockout af *mltA* og også eventuelt med nedregulering eller knockout af:

 (i) mindst ét gen involveret i at gøre lipid-A-delen af LPS toksisk, især af *lpxI1*; og/eller

25 (ii) mindst ét gen involveret i syntese eller eksport af kapselpolysakkaridet, især af *synX* og/eller *ctrA*.

9. Membranvesikler fremstillet fra værtscellen ifølge krav 8, hvor vesiklerne indbefatter et polypeptid ifølge et hvilket som helst af krav 1 til 6.

30 **10.** Immunogen sammensætning omfattende et polypeptid ifølge et hvilket som helst af krav 1 til 6 eller en vesikel ifølge krav 9.

35 **11.** Sammensætning ifølge krav 10, yderligere omfattende et andet polypeptid som, når det indgives til et pattedyr, udløser et antistofrespons som er bakteriedræbende for meningokok.

12. Sammensætning ifølge krav 10 eller krav 11, yderligere omfattende (i) et konjugeret kapselsakkarid fra *N. meningitidis* serogruppe A, C, W135 og/eller Y og/eller (ii) et konjugeret kapselsakkarid fra *S. pneumoniae*.

40

13. Immunogen sammensætning ifølge et hvilket som helst af krav 10 til 12 til anvendelse ved en fremgangsmåde til at hæve et antistofrespons i et pattedyr.

DRAWINGS

FIGURE 1

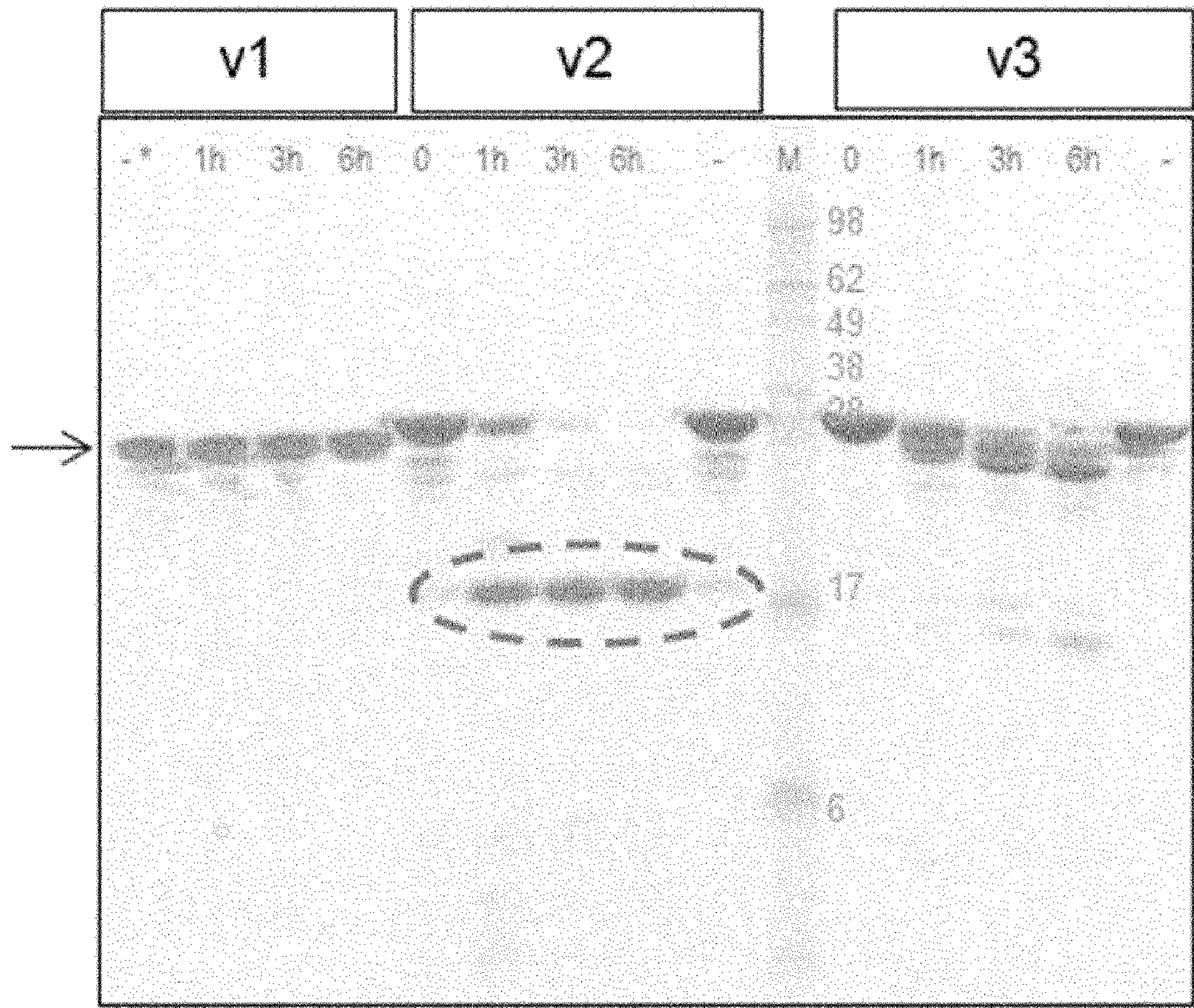


FIGURE 2

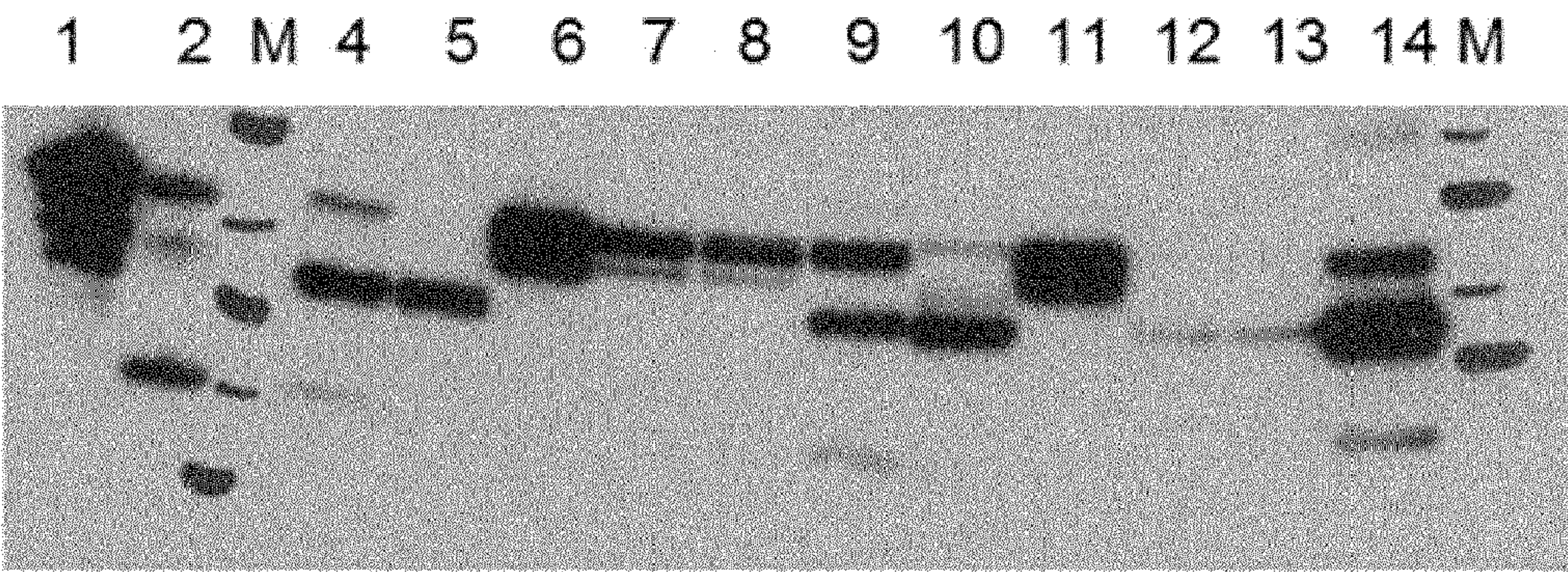


FIGURE 3

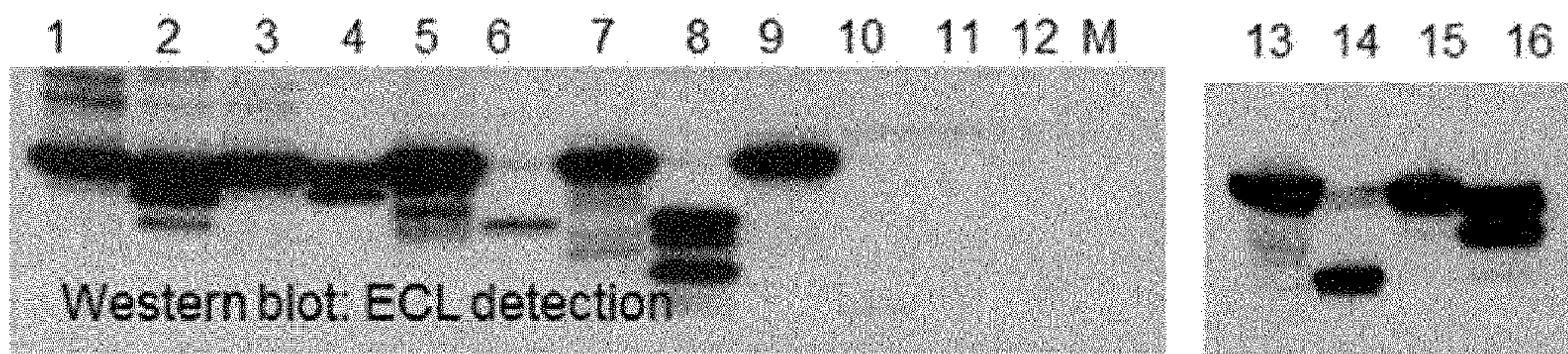


FIGURE 4

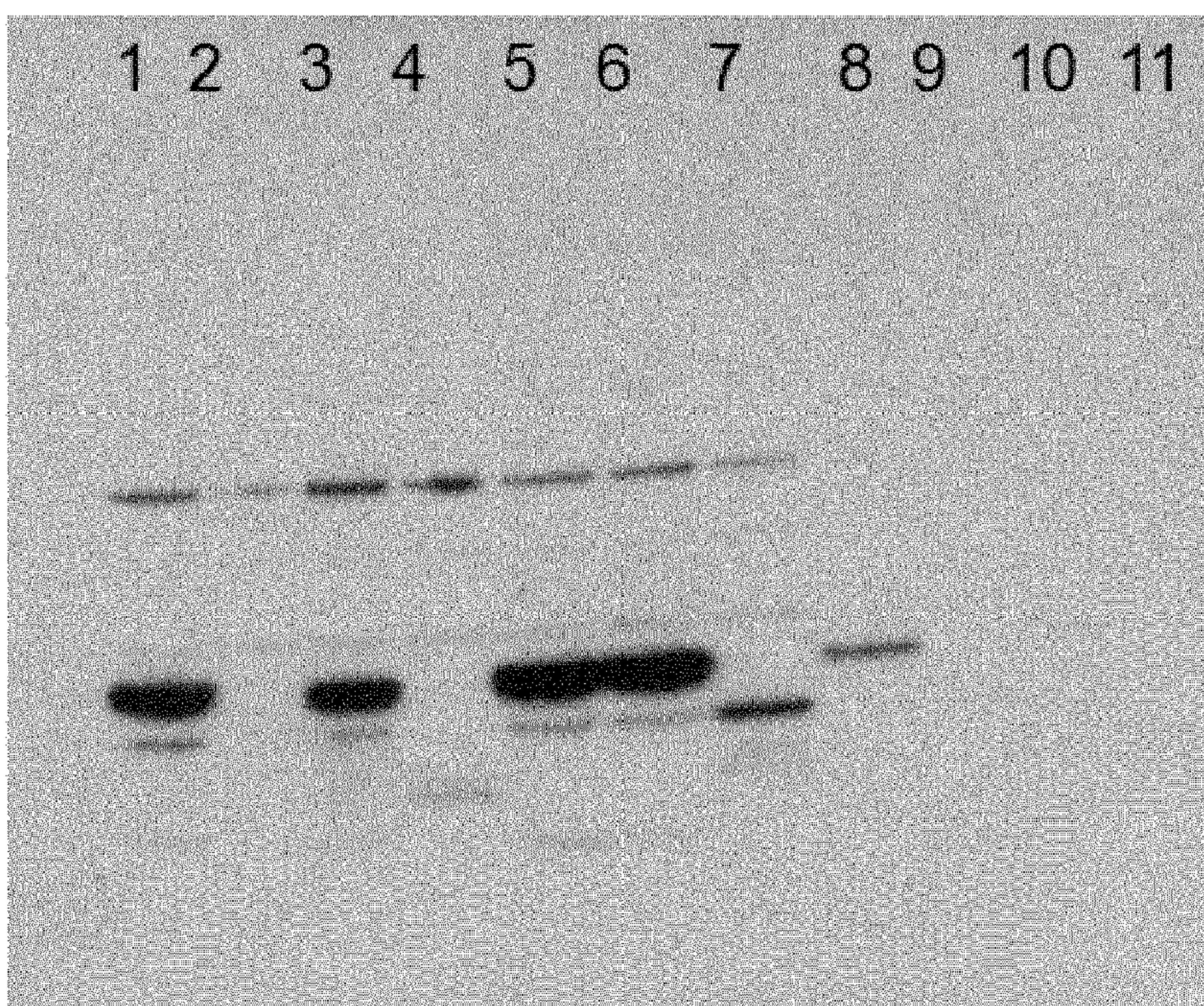


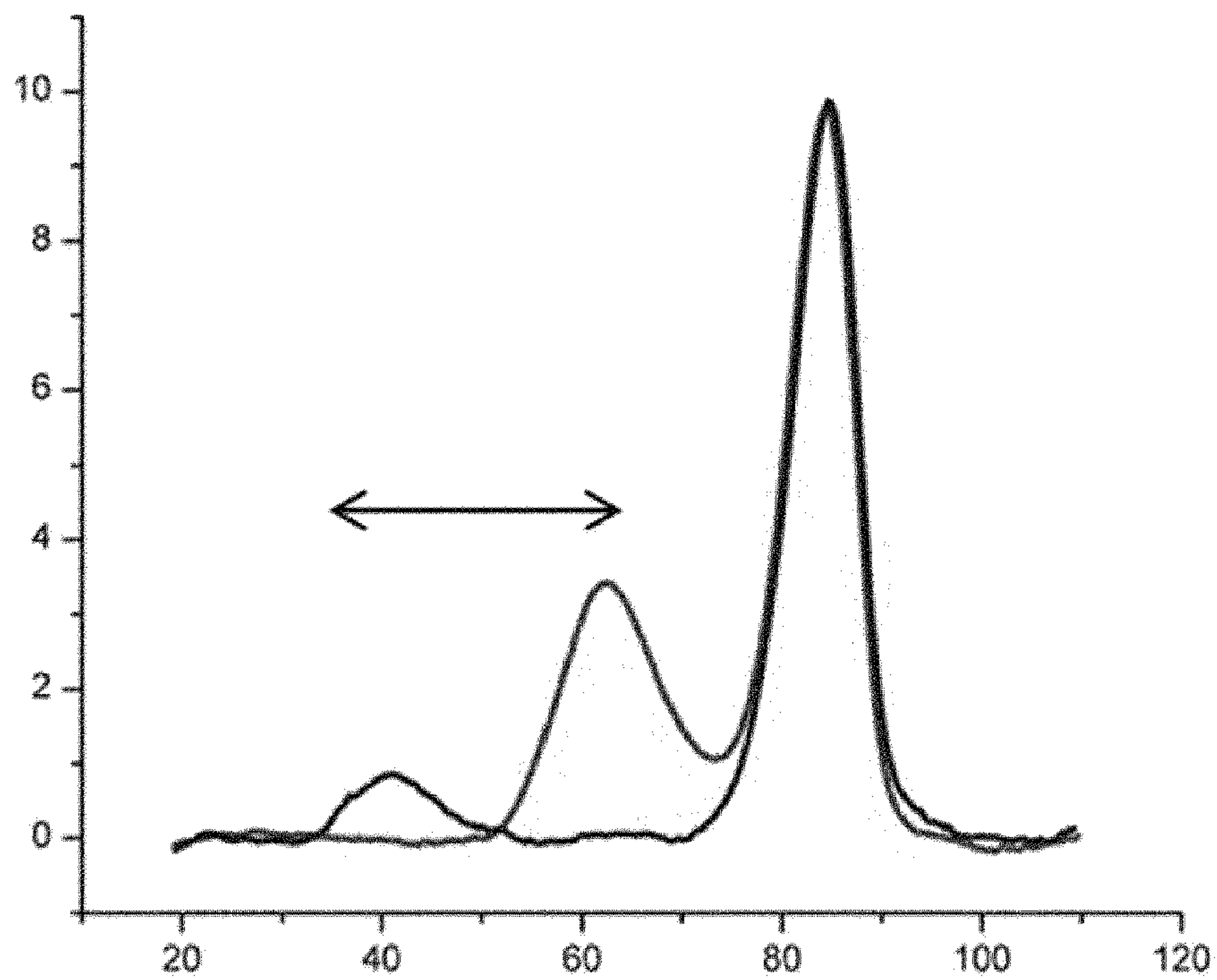
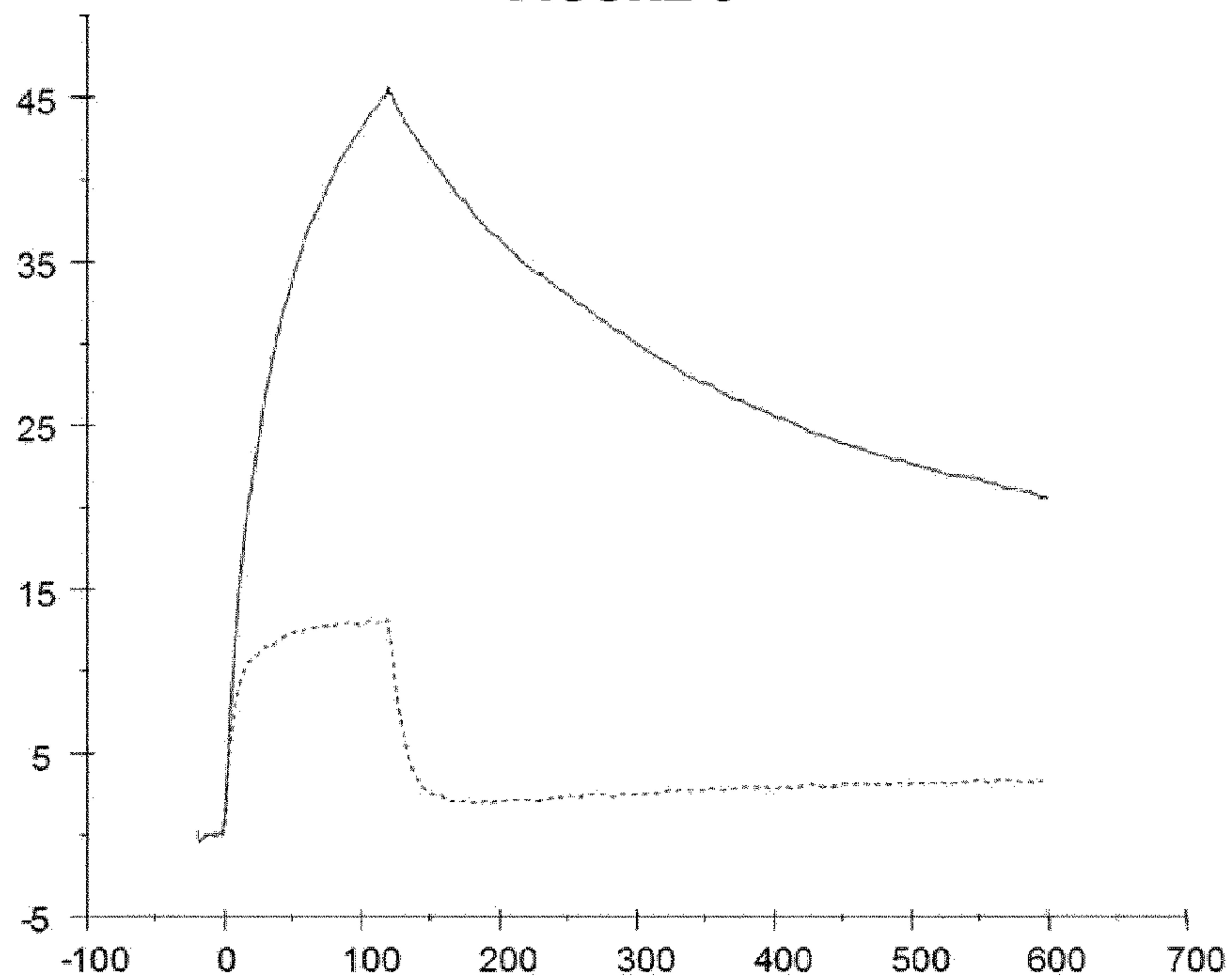
FIGURE 5**FIGURE 6**

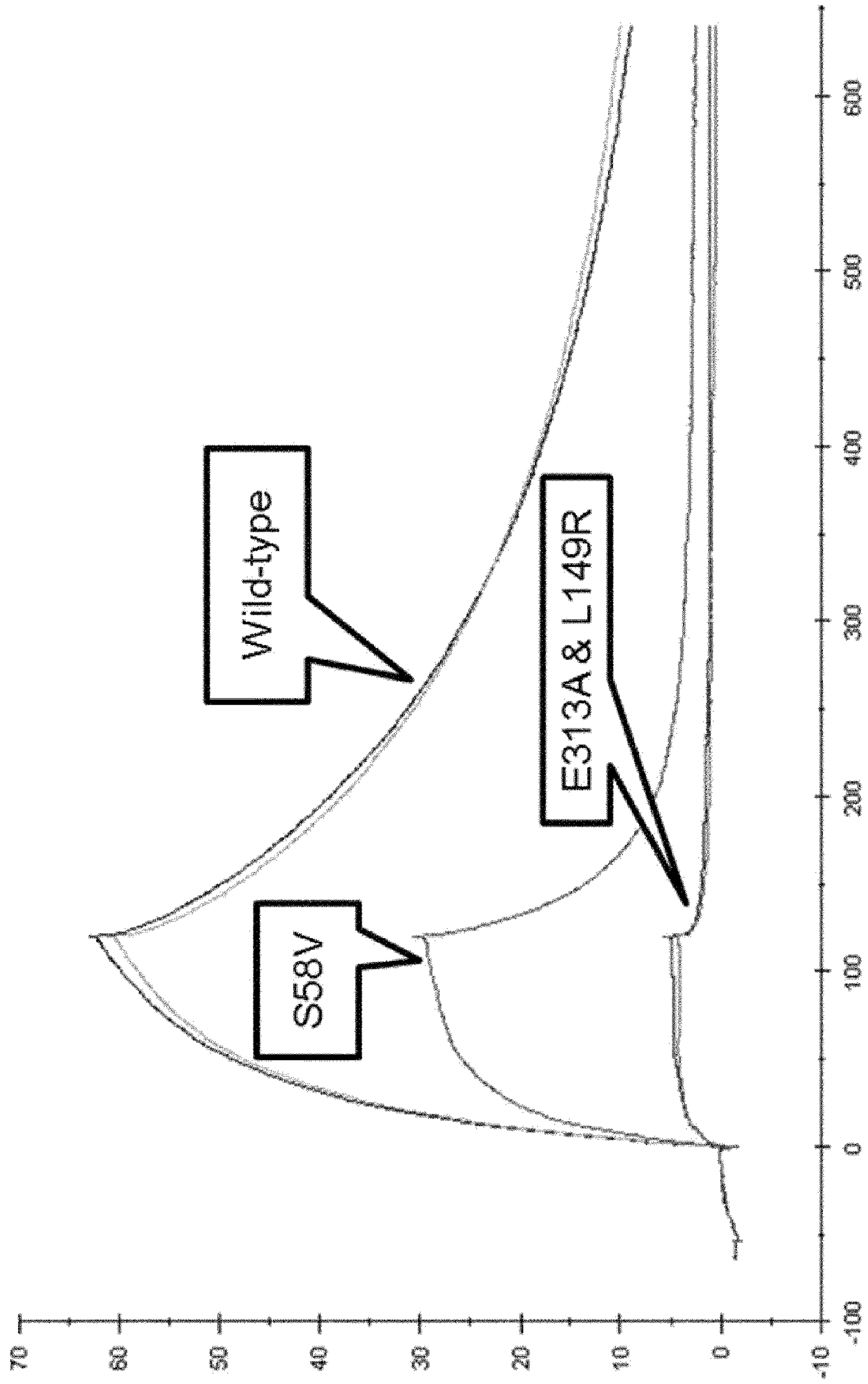
FIGURE 7

FIGURE 8