(19)

(12)



divisional application to the application mentioned under INID code 62.

#### (54) Compositions for immunising against Staphylococcus aureus

(57) An effective Staphylococcus aureus vaccine may require several antigenic components, and so various combinations of S.aureus antigens are identified for

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use in immunisation. These polypeptides may optionally be used in combination with S.aureus saccharides.

## Description

# **TECHNICAL FIELD**

<sup>5</sup> **[0001]** This invention relates to antigens derived from *S.aureus* and to their use in immunisation.

## **BACKGROUND ART**

- [0002] Staphylococcus aureus is a Gram-positive spherical bacterium. Annual US mortality exceeds that of any other <sup>10</sup> infectious disease, including HIV/AIDS, and *S.aureus* is the leading cause of bloodstream, lower respiratory tract, skin & soft tissue infections. There is currently no authorised vaccine. A vaccine based on a mixture of surface polysaccharides from bacterial types 5 and 8, StaphVAX<sup>™</sup>, failed to reduce infections when compared to the placebo group in a phase III clinical trial in 2005.
- [0003] Reference 1 reports that the "V710" vaccine from Merck and Intercell is undergoing a phase 2/3 trial on patients undergoing cardiothoracic surgery. The V710 vaccine is based on a single antigen, IsdB [2], a conserved iron-sequestering cell-surface protein.

**[0004]** *S.aureus* causes a range of illnesses from minor skin infections to life-threatening diseases such as pneumonia, meningitis, osteomyelitis, bacteremia, endocarditis, toxic shock syndrome, organ abscesses and septicemia. The bacterium has multiple virulence factors which are differentially expressed during different phases of its life cycle, and so a

- vaccine which can prevent one disease might not prevent another. For instance, the V710 vaccine may be effective against hematic spread of the *S.aureus*, but may be ineffective against pneumonia and may not elicit any opsonic activity. One aim of the invention is to provide vaccines which can protect against hematic spread and pneumonia, and which may also elicit an opsonic response.
- [0005] Thus there remains a need to identify further and improved antigens for use in *S.aureus* vaccines, and in particular for vaccines which are useful against multiple *S.aureus* pathologies.

## DISCLOSURE OF THE INVENTION

[0006] The inventors have identified various *S.aureus* polypeptides that are useful for immunisation, either alone or <sup>30</sup> in combination. These polypeptides may be combined with *S.aureus* saccharides or other *S.aureus* polypeptides. The antigens are useful in *S.aureus* vaccines but may also be used as components in vaccines for immunising against multiple pathogens.

**[0007]** The inventors have identified the following 36 polypeptides: clfA, clfB, coA, eap, ebhA, ebpS, efb, emp, esaC, esxA, esxB, FnBA, FnBB, HIa, hlgB, hlgC, isdA, isdB, isdC, isdG, isdH, isdI, lukD, lukE, lukF, lukS, nuc, sasA, sasB,

- sasC, sasD, sasF, sdrC, sdrD, spa, and sdrE2. This set of antigens is referred to herein as 'the first antigen group'. Thus the invention provides an immunogenic composition comprising a combination of antigens, said combination comprising two or more (i. e. 2, 3, 4, 5, 6 or more) antigens selected from the group consisting of: (1) a clfA antigen; (2) a clfB antigen; (3) a coA antigen; (4) a eap antigen; (5) a ebhA antigen; (6) a ebpS antigen; (7) a efb antigen; (8) a emp antigen; (9) a esaC antigen; (10) a esxA antigen; (11) a esxB antigen; (12) a FnBA antigen; (13) a FnBB antigen; (14) a Hla
- <sup>40</sup> antigen; (15) a hlgB antigen; (16) a hlgC antigen; (17) a isdA antigen; (18) a isdB antigen; (19) a isdC antigen; (20) a isdG antigen; (21) a isdH antigen; (22) a isdI antigen; (23) a lukD antigen; (24) a lukE antigen; (25) a lukF antigen; (26) a lukS antigen; (27) a nuc antigen; (28) a sasA antigen; (29) a sasB antigen; (30) a sasC antigen; (31) a sasD antigen; (32) a sasF antigen; (33) a sdrC antigen; (34) a sdrD antigen; (35) a spa antigen; (36) a sdrE2 antigen.
- **[0008]** Within the first antigen group, antigens are preferably selected from a subset of 16 of the 36 polypeptides, namely: clfA, clfB, emp, esaC, esxA, esxB, hla, isdA, isdB, isdC, sasD, sasF, sdrC, sdrD, spa, and sdrE2. Thus the invention provides an immunogenic composition comprising a combination of antigens, said combination comprising two or more (i.e. 2, 3, 4, 5, 6 or more) antigens selected from the group consisting of these sixteen antigens.
- [0009] The inventors have also identified the following 128 polypeptides: sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta021, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta031, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080,
- sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095,
  sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, NW\_6, NW\_9, NW\_10, NW\_7, NW\_8, NW\_2, NW\_1, and NW\_5. This set of antigens is referred to herein as 'the second antigen group'. Thus the invention provides an immunogenic composition comprising a combination of antigens, said combination comprising two or more

(i.e. 2, 3, 4, 5, 6 or more) antigens selected from the group consisting of: (1) a sta001 antigen; (2) a sta002 antigen; (3) a sta003 antigen; (4) a sta004 antigen; (5) a sta005 antigen; (6) a sta006 antigen; (7) a sta007 antigen; (8) a sta008 antigen; (9) a sta009 antigen; (10) a sta010 antigen; (11) a sta011 antigen; (12) a sta012 antigen; (13) a sta013 antigen; (14) a sta014 antigen; (15) a sta015 antigen; (16) a sta016 antigen; (17) a sta017 antigen; (18) a sta018 antigen; (19) a sta019 antigen; (20) a sta019 antigen; (21) a sta014 antigen; (22) a sta018 antigen; (23) a sta018 antigen; (24) a sta019 antigen; (24) a sta019 antigen; (25) a sta019 antigen; (26) a sta019 antigen; (27) a sta019 antigen; (28) a sta019 antigen; (28) a sta019 antigen; (28) a sta019 antigen; (29) a sta019 antigen; (20) a sta019 antigen; (21) a sta019 antigen; (22) a sta019 antigen; (23) a sta019 antigen; (24) a sta019 antigen; (26) a sta019 antigen; (27) a sta019 antigen; (28) a sta019 antigen; (29) a sta019 antigen; (29) a sta019 antigen; (20) a sta019 antigen; (21) a sta019 antigen; (22) a sta019 antigen; (23) a sta019 antigen; (24) a sta019 antigen; (26) a sta019 antigen; (27) a sta019 antigen; (28) a sta019 antigen; (29) a sta019 antigen; (29) a sta019 antigen; (21) a sta019 antigen; (22) a sta019 antigen; (21) a sta019 antigen; (22) a sta019 antigen; (22) a sta019 antigen; (22) a sta019 antigen; (23) a sta019 antigen; (24) a sta019 antigen; (24) a sta019 antigen; (26) a sta019 antigen; (27) a sta019 antigen; (28) a sta019 antigen;

- a sta019 antigen; (20) a sta020 antigen; (21) a sta021 antigen; (22) a sta022 antigen; (23) a sta023 antigen; (24) a sta024 antigen; (25) a sta025 antigen; (26) a sta026 antigen; (27) a sta027 antigen; (28) a sta028 antigen; (29) a sta029 antigen; (30) a sta030 antigen; (31) a sta031 antigen; (32) a sta032 antigen; (33) a sta033 antigen; (34) a sta034 antigen; (35) a sta035 antigen; (36) a sta036 antigen; (37) a sta037 antigen; (38) a sta038 antigen; (39) a sta039 antigen; (40) a sta040 antigen; (41) a sta041 antigen; (42) a sta042 antigen; (43) a sta043 antigen; (44) a sta044 antigen; (45) a
- 10 sta045 antigen; (46) a sta046 antigen; (47) a sta047 antigen; (48) a sta048 antigen; (49) a sta049 antigen; (50) a sta050 antigen; (51) a sta051 antigen; (52) a sta052 antigen; (53) a sta053 antigen; (54) a sta054 antigen; (55) a sta055 antigen; (56) a sta056 antigen; (57) a sta057 antigen; (58) a sta058 antigen; (59) a sta059 antigen; (60) a sta060 antigen; (61) a sta061 antigen; (62) a sta062 antigen; (63) a sta063 antigen; (64) a sta064 antigen; (65) a sta065 antigen; (66) a sta066 antigen; (67) a sta067 antigen; (68) a sta068 antigen; (69) a sta069 antigen; (70) a sta070 antigen; (71) a sta071
- <sup>15</sup> antigen; (72) a sta072 antigen; (73) a sta073 antigen; (74) a sta074 antigen; (75) a sta075 antigen; (76) a sta076 antigen; (77) a sta077 antigen; (78) a sta078 antigen; (79) a sta079 antigen; (80) a sta080 antigen; (81) a sta081 antigen; (82) a sta082 antigen; (83) a sta083 antigen; (84) a sta084 antigen; (85) a sta085 antigen; (86) a sta086 antigen; (87) a sta087 antigen; (88) a sta088 antigen; (89) a sta089 antigen; (90) a sta090 antigen; (91) a sta091 antigen; (92) a sta092 antigen; (93) a sta093 antigen; (94) a sta094 antigen; (95) a sta095 antigen; (96) a sta096 antigen; (97) a sta097 antigen;
- (98) a sta098 antigen; (99) a sta099 antigen; (100) a sta100 antigen; (101) a sta101 antigen; (102) a sta102 antigen; (103) a sta103 antigen; (104) a sta104 antigen; (105) a sta105 antigen; (106) a sta106 antigen; (107) a sta107 antigen; (108) a sta108 antigen; (109) a sta109 antigen; (110) a sta110 antigen; (111) a sta111 antigen; (112) a sta112 antigen; (113) a sta113 antigen; (114) a sta114 antigen; (115) a sta115 antigen; (116) a sta116 antigen; (117) a sta117 antigen; (118) a sta118 antigen; (119) a sta119 antigen; (120) a sta120 antigen; (121) a NW\_6 antigen; (122) a NW\_9 antigen;
- (123) a NW\_10 antigen; (124) a NW\_7 antigen; (125) a NW\_8 antigen; (126) a NW\_2 antigen; (127) a NW\_1 antigen; and (128) a NW\_5 antigen.

**[0010]** Within the second antigen group of 128 antigens, a preferred subset of 113 antigens omits (81) and (107) to (120) from this list.

- [0011] Within the second antigen group, a subset of 27 of the 128 polypeptides is referred to herein as 'the third antigen group', namely: sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta019, sta028, sta040, sta049, sta057, sta064, sta073, sta095, sta098, sta101, sta105, NW\_1, NW\_6, NW\_7, NW\_8, NW\_9 and NW\_10. The invention provides an immunogenic composition comprising a combination of antigens, said combination comprising two or more (i.e. 2, 3, 4, 5, 6 or more) antigens selected from the third antigen group.
- [0012] The 101 antigens that are in the second antigen group but not in the third antigen group are referred to herein as 'the fourth antigen group'. Within the fourth antigen group of 101 antigens, a preferred subset of 86 antigens omits (81) and (107) to (120) from the above list. The second antigen group thus consists of a combination of the third and fourth antigen groups.

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**[0013]** Within the second antigen group, a subset of 8 of the 128 polypeptides is referred to herein as 'the fifth antigen group', namely: sta004, sta006, sta007, sta011, sta028, sta060, sta098 and sta112. The invention provides an immunogenic composition comprising a combination of antigens, said combination comprising two or more (*i.e.* 2, 3, 4, 5, 6

or more) antigens selected from the fifth antigen group. [0014] Within the 36 antigens of the first antigen group there are 630 possible pairs of different antigens. All such pairs are disclosed herein and are part of the invention. Thus the invention provides an immunogenic composition comprising a pair of antigens, wherein said pair is one of said 630 pairs.

<sup>45</sup> **[0015]** Within the 128 antigens of the second antigen group there are 8128 possible pairs of different antigens. All such pairs are disclosed herein and are part of the invention. Thus the invention provides an immunogenic composition comprising a pair of antigens, wherein said pair is one of said 8128 pairs.

**[0016]** Within the preferred 113 antigens of the second antigen group there are 6328 possible pairs of different antigens. All such pairs are disclosed herein and are part of the invention. Thus the invention provides an immunogenic composition comprising a pair of antigens, wherein said pair is one of said 6328 pairs.

**[0017]** Within the preferred 27 antigens of the third antigen group there are 351 possible pairs of different antigens. All such pairs are disclosed herein and are part of the invention. Thus the invention provides an immunogenic composition comprising a pair of antigens, wherein said pair is one of said 351 pairs.

[0018] Within the 101 antigens of the fourth antigen group there are 5050 possible pairs of different antigens. All such pairs are disclosed herein and are part of the invention. Thus the invention provides an immunogenic composition comprising a pair of antigens, wherein said pair is one of said 5050 pairs.

**[0019]** Within the preferred 86 antigens of the fourth antigen group there are 3655 possible pairs of different antigens. All such pairs are disclosed herein and are part of the invention. Thus the invention provides an immunogenic composition

comprising a pair of antigens, wherein said pair is one of said 3655 pairs.

**[0020]** In one embodiment, a composition includes at least one antigen (*i.e.* 1, 2, 3, 4, 5, 6 or more) selected from the first antigen group and at least one antigen (*i.e.* 1, 2, 3, 4, 5, 6 or more) selected from the second antigen group. Antigens from the first antigen group may be selected from the preferred subset of 16 antigens, and antigens from the second antigen group may be selected from the third antigen group or the fifth antigen group.

- <sup>5</sup> antigen group may be selected from the third antigen group or the fifth antigen group.
  [0021] The invention also provides an immunogenic composition comprising a combination of antigens, said combination comprising two or more (*i.e.* 2, 3, 4, 5, 6 or more) antigens selected from the group consisting of: (1) a clfA antigen; (2) a clfB antigen; (3) a sdrE2 antigen; (4) a sdrC antigen; (5) a SasF antigen; (6) a emp antigen; (7) a sdrD antigen; (8) a spa antigen; (9) a esaC antigen; (10) a esxA antigen; (11) a esxB antigen; (12) a sta006 antigen; (13) a isdC antigen;
- (14) a hla antigen; (15) a sta011 antigen; (16) isdA antigen; (17) a isdB antigen; (18) a sasF antigen. This group of 18 antigens is sometimes referred to herein as the 'sixth antigen group'.
  [0022] The invention also provides an immunogenic composition comprising a combination of antigens, said combination comprising two or more (*i.e.* 2, 3, 4 or 5) antigens selected from the group consisting of: (1) a esxA antigen; (2) a esxB antigen; (3) a sta006 antigen; (4) a hla antigen; and/or (5) a sta011 antigen. The composition may also include
- <sup>15</sup> an adjuvant e.g. an aluminium hydroxide adjuvant. [0023] Advantageous combinations of the invention are those in which two or more antigens act synergistically. Thus the protection against *S.aureus* disease achieved by their combined administration exceeds that expected by mere addition of their individual protective efficacy.

[0024] Specific combinations of interest include, but are not limited to:

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(1) An immunogenic composition comprising a sdrD antigen, a sdrE2 antigen and a isdC antigen. The sdrD and sdrE2 antigens can usefully be combined as a hybrid polypeptide, as discussed below, e.g. an SdrDE hybrid with an sdrE2 antigen downstream of a sdrD antigen.

<sup>25</sup> (2) An immunogenic composition comprising a sasD antigen, a clfB antigen and a sdrC antigen.

(3) An immunogenic composition comprising a sasD antigen, a clfB antigen, a sdrC antigen and a clfA antigen.

- (4) An immunogenic composition comprising a sdrD antigen, a sdrE2 antigen, a isdC antigen and a sta011 antigen.
   The sdrD and sdrE2 antigens can usefully be combined as a hybrid polypeptide, as discussed below, *e.g.* a SdrDE hybrid with a sdrE2 antigen downstream of a sdrD antigen.
  - (5) An immunogenic composition comprising a sasD antigen, a clfB antigen, a sdrC antigen and a sta006 antigen.
- (6) An immunogenic composition comprising a sdrD antigen, a sdrE2 antigen, a isdC antigen and a hla antigen.
   The sdrD and sdrE2 antigens can usefully be combined as a hybrid polypeptide, as discussed below, *e.g.* a SdrDE hybrid with a sdrE2 antigen downstream of a sdrD antigen. The Hla antigen may be a detoxified mutant *e.g.* including a H35L mutation.
- 40 (7) An immunogenic composition comprising a sasD antigen, a clfB antigen, a sdrC antigen and a esxA antigen.

(8) An immunogenic composition comprising a esxA antigen, a esxB antigen, a sta006 antigen and a hla antigen. The esxA and esxB antigens can usefully be combined as a hybrid polypeptide, as discussed below, *e.g.* a EsxAB hybrid with a esxB antigen downstream of a esxA antigen. The Hla antigen may be a detoxified mutant *e.g.* including a H35L mutation.

(9) An immunogenic composition comprising a sdrD antigen, a sdrE2 antigen, a isdC antigen and a esxA antigen. The sdrD and sdrE2 antigens can usefully be combined as a hybrid polypeptide, as discussed below, *e.g.* a SdrDE hybrid with a sdrE2 antigen downstream of a sdrD antigen.

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(10) An immunogenic composition comprising a esxA antigen, a esxB antigen, a sta006 antigen and a sta011 antigen. The esxA and esxB antigens may be combined as a hybrid polypeptide, as discussed below, *e.g.* an EsxAB hybrid.

<sup>55</sup> (11) An immunogenic composition comprising a esxA antigen, a esxB antigen and a sta011 antigen. The esxA and esxB antigens can usefully be combined as a hybrid polypeptide, as discussed below, *e.g.* a EsxAB hybrid with a esxB antigen downstream of a esxA antigen.

(12) An immunogenic composition comprising a sasD antigen, a clfB antigen, a sdrC antigen and a spa antigen.

(13) An immunogenic composition comprising a esxA antigen, a esxB antigen, a isdA antigen, a sta006 antigen, a sta011 antigen and a spa antigen. The esxA and esxB antigens may be combined as a hybrid polypeptide, as discussed below, *e.g.* an EsxAB hybrid. The isdA antigen may be a fragment of a full-length isdA antigen *e.g.* SEQ ID NO: 157. The spa antigen may be a fragment of a full-length spa antigen, such as a Spa(D) domain mutated to disrupt or decrease binding to IgG Fc.

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(14) An immunogenic composition comprising a esxA antigen, a esxB antigen, a H1a antigen, a sta006 antigen and
 a sta011 antigen. The esxA and esxB antigens may be combined as a hybrid polypeptide, as discussed below, *e.g.* an EsxAB hybrid. The H1a antigen may be a detoxified mutant *e.g.* including a H35L mutation.

(15) An immunogenic composition comprising a sdrD antigen, a sdrE2 antigen, a isdC antigen and a sdrE2 antigen. The sdrD and sdrE2 antigens can usefully be combined as a hybrid polypeptide, as discussed below, *e.g.* a SdrDE hybrid with a sdrE2 antigen downstream of a sdrD antigen.

(16) An immunogenic composition comprising a esxA antigen, a esxB antigen and a hla antigen. The esxA and esxB antigens can usefully be combined as a hybrid polypeptide, as discussed below, *e.g.* a EsxAB hybrid with a esxB antigen downstream of a esxA antigen. The H1a antigen may be a detoxified mutant *e.g.* including a H35L mutation.

(17) An immunogenic composition comprising a hla antigen, a isdA antigen, a sta006 antigen and a sta011 antigen. The isdA antigen may be a fragment of a full-length isdA antigen *e.g.* SEQ ID NO: 157. The Hla antigen may be a detoxified mutant *e.g.* including a H35L mutation.

(18) An immunogenic composition comprising a esxA antigen, a esxB antigen, a sta006 antigen and a isdA antigen. The esxA and esxB antigens can usefully be combined as a hybrid polypeptide, as discussed below, *e.g.* a EsxAB hybrid with a esxB antigen downstream of a esxA antigen. The isdA antigen may be a fragment of a full-length isdA antigen *e.g.* SEQ ID NO: 157.

(19) An immunogenic composition comprising a sasD antigen, a clfB antigen, a sdrC antigen and a hla antigen. The Hla antigen may be a detoxified mutant *e.g.* including a H35L mutation.

(20) An immunogenic composition comprising a H1a antigen, a sta006 antigen and a sta011 antigen. The H1a antigen may be a detoxified mutant *e.g.* including a H35L mutation.

(21) An immunogenic composition comprising a esxA antigen and a esxB antigen. The esxA and esxB antigens can usefully be combined as a hybrid polypeptide, as discussed below, *e.g.* an EsxAB hybrid with an esxB antigen downstream of an esxA antigen.

(22) An immunogenic composition comprising a esxA antigen, a esxB antigen and a sta006 antigen. The esxA and esxB antigens can usefully be combined as a hybrid polypeptide, as discussed below, *e.g.* a EsxAB hybrid with a esxB antigen downstream of a esxA antigen.

- 45 (23) An immunogenic composition comprising a spa antigen, a sta006 antigen and a sta011 antigen. The spa antigen may be a fragment of a full-length spa antigen, such as a Spa(D) domain mutated to disrupt or decrease binding to IgG Fc.
- (24) An immunogenic composition comprising a esxA antigen, a esxB antigen, a isdA antigen, a sta006 antigen
   and a sta011 antigen. The esxA and esxB antigens may be combined as a hybrid polypeptide, as discussed below,
   e.g. an EsxAB hybrid. The isdA antigen may be a fragment of a full-length isdA antigen e.g. SEQ ID NO: 157.
  - (25) An immunogenic composition comprising a sta006 antigen and a sta011 antigen.
- <sup>55</sup> (26) An immunogenic composition comprising a esxA antigen, a esxB antigen, a sta006 antigen, a isdA antigen and a clfB antigen. The esxA and esxB antigens can usefully be combined as a hybrid polypeptide, as discussed below, *e.g.* a EsxAB hybrid with a esxB antigen downstream of a esxA antigen. The isdA antigen may be a fragment of a full-length isdA antigen e.g. SEQ ID NO: 157. The clfB antigen may be a fragment of a full-length clfB antigen

e.g. SEQ ID NO: 163.

- (27) An immunogenic composition comprising a sta006 antigen, a sta011 antigen and a sta019 antigen.
- (28) An immunogenic composition comprising a esxA antigen, a esxB antigen, a sta006 antigen, a hla antigen and a clfB antigen. The esxA and esxB antigens can usefully be combined as a hybrid polypeptide, as discussed below, e.g. a EsxAB hybrid with a esxB antigen downstream of a esxA antigen. The clfB antigen may be a fragment of a full-length clfB antigen *e.g.* SEQ ID NO: 163. The H1a antigen may be a detoxified mutant *e.g.* including a H35L mutation.
  - (29) An immunogenic composition comprising a sta006 antigen, a sta011 antigen, a sta019 antigen, and a hla antigen. The H1a antigen may be a detoxified mutant *e.g.* including a H35L mutation.
- (30) An immunogenic composition comprising a esxA antigen, a esxB antigen, a sta006 antigen, a sta011 antigen
   and a clfB antigen. The esxA and esxB antigens can usefully be combined as a hybrid polypeptide, as discussed below, *e.g.* a EsxAB hybrid with a esxB antigen downstream of a esxA antigen. The clfB antigen may be a fragment of a full-length clfB antigen *e.g.* SEQ ID NO: 163.
- (31) An immunogenic composition comprising a spa antigen, a esxA antigen, a esxB antigen, a sta006 antigen and
   a sta011 antigen. The spa antigen may be a fragment of a full-length spa antigen, such as a Spa(D) domain mutated to disrupt or decrease binding to IgG Fc. The esxA and esxB antigens may be combined as a hybrid polypeptide, as discussed below, *e.g.* an EsxAB hybrid.
- (32) An immunogenic composition comprising a sdrD antigen, a sdrE2 antigen, a isdC antigen and a esxB antigen.
   The sdrD and sdrE2 antigens can usefully be combined as a hybrid polypeptide, as discussed below, *e.g.* a SdrDE hybrid with a sdrE2 antigen downstream of a sdrD antigen.

(33) An immunogenic composition comprising a esxA antigen, a esxB antigen, a sta006 antigen, a sta011 antigen and a sta019 antigen. The esxA and esxB antigens can usefully be combined as a hybrid polypeptide, as discussed below, *e.g.* a EsxAB hybrid with a esxB antigen downstream of a esxA antigen.

(34) An immunogenic composition comprising a esxA antigen, a esxB antigen, a sta006 antigen, a isdA antigen and a sdrD antigen. The esxA and esxB antigens can usefully be combined as a hybrid polypeptide, as discussed below, *e.g.* a EsxAB hybrid with a esxB antigen downstream of a esxA antigen. The isdA antigen may be a fragment of a full-length isdA antigen *e.g.* SEQ ID NO: 157. The sdrD antigen may be a fragment of a full-length sdrD antigen *e.g.* SEQ ID NO: 156.

(35) An immunogenic composition comprising a esxA antigen, a esxB antigen, and a isdA antigen. The esxA and esxB antigens can usefully be combined as a hybrid polypeptide, as discussed below, *e.g.* a EsxAB hybrid with a esxB antigen downstream of a esxA antigen. The isdA antigen may be a fragment of a full-length isdA antigen *e.g.* SEQ ID NO: 157.

(36) An immunogenic composition comprising a sasD antigen, a clfB antigen, a sdrC antigen, a esxA antigen and a esxB antigen. The esxA and esxB antigens can usefully be combined as a hybrid polypeptide, as discussed below, e.g. an EsxAB hybrid with an esxB antigen downstream of an esxA antigen.

(37) An immunogenic composition comprising a H1a antigen, a spa antigen, a sta006 antigen and a sta011 antigen. The H1a antigen may be a detoxified mutant *e.g.* including a H35L mutation. The spa antigen may be a fragment of a full-length spa antigen, such as a Spa(D) domain mutated to disrupt or decrease binding to IgG Fc.

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**[0025]** In some embodiments, any of these 37 compositions may include additional staphylococcal antigens, and these further antigens can be polypeptides and/or saccharides. For example, they can usefully also include one or more *S.aureus* capsular saccharide conjugate(s) *e.g.* against a serotype 5 and/or a serotype 8 strain. The inclusion of one or both such conjugates is particularly useful for combinations (8), (10), (20), (23), (25), (31) and (37).

<sup>55</sup> **[0026]** In other embodiments, these 37 compositions include no additional staphylococcal polypeptide antigens. In other embodiments, these 37 compositions include no additional staphylococcal antigens. In other embodiments, these 37 compositions include no additional antigens.

[0027] The invention also provides a polypeptide comprising amino acid sequence (a) having 80% or more identity

(e.g. 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 151; and/or (b) comprising a fragment of at least 'n' consecutive amino acids from amino acids 1-97 of SEQ ID NO: 151 and at least 'n' consecutive amino acids from amino acids 104-207 of SEQ ID NO: 151, 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). The invention also provides a polypeptide

- <sup>5</sup> comprising amino acid sequence (a) having 80% or more identity (*e.g.* 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 152; and/or (b) comprising a fragment of at least 'n' consecutive amino acids from amino acids 1-104 of SEQ ID NO: 152 and at least 'n' consecutive amino acids from amino acids 1-104 of SEQ ID NO: 152 and at least 'n' consecutive amino acids from amino acids 1-104 of SEQ ID NO: 152 and at least 'n' consecutive amino acids from amino acids 1-104 of SEQ ID NO: 152 and at least 'n' consecutive amino acids from amino acids 1-104 of SEQ ID NO: 152 and at least 'n' consecutive amino acids from amino acids 1-104 of SEQ ID NO: 152 and at least 'n' consecutive amino acids from amino acids 1-104 of SEQ ID NO: 152 and at least 'n' consecutive amino acids from amino acids 1-104 of SEQ ID NO: 152 and at least 'n' consecutive amino acids from amino acids 1-104 of SEQ ID NO: 152 and at least 'n' consecutive amino acids from amino acids 1-104 of SEQ ID NO: 152 and at least 'n' consecutive amino acids from amino acids 1-104 of SEQ ID NO: 152 and at least 'n' consecutive amino acids from amino acids 1-104 of SEQ ID NO: 152 and at least 'n' consecutive amino acids from amino acids 1-104 of SEQ ID NO: 152 and at least 'n' consecutive amino acids from amino acids 1-104 of SEQ ID NO: 152 and at least 'n' consecutive amino acids from amino acids 1-104 of SEQ ID NO: 152 and at least 'n' consecutive amino acids from amino acids 1-104 of SEQ ID NO: 152 and at least 'n' consecutive amino acids from amino acids 1-104 of SEQ ID NO: 152 and at least 'n' consecutive amino acids from amino acids from amino acids 1-104 of SEQ ID NO: 152, 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). These polypeptides can elicit antibodies (*e.g.* when administered to a human) which
- recognise both the wild-type staphylococcal protein comprising SEQ ID NO: 10 and the wild-type staphylococcal protein comprising SEQ ID NO: 11. Thus the immune response will recognise both of antigens esxA and esxB. Preferred fragments of (b) provide an epitope from SEQ ID NO: 10 and an epitope from SEQ ID NO: 11. The invention also provides an immunogenic composition comprising a combination of such a protein and an adjuvant, such as an aluminium hydroxide adjuvant.
- <sup>15</sup> [0028] The invention also provides a polypeptide comprising amino acid sequence (a) having 80% or more identity (e.g. 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 241; and/or (b) comprising both a fragment of at least 'n' consecutive amino acids from amino acids 1-96 of SEQ ID NO: 241 and a fragment of at least 'n' consecutive amino acids from amino acids 103-205 of SEQ ID NO: 241, 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). These polypeptides
- 20 (e.g. SEQ ID NO: 250) can elicit antibodies (e.g. when administered to a human) which recognise both the wild-type staphylococcal protein comprising SEQ ID NO: 10 and the wild-type staphylococcal protein comprising SEQ ID NO: 11. Thus the immune response will recognise both of antigens esxA and esxB. Preferred fragments of (b) provide an epitope from SEQ ID NO: 10 and an epitope from SEQ ID NO: 11. The invention also provides an immunogenic composition comprising a combination of such a protein and an adjuvant, such as an aluminium hydroxide adjuvant.
- [0029] The invention also provides a polypeptide comprising a staphylococcal hemolysin sequence, wherein the sequence does not include a sequence having at least 90% identity to SEQ ID NO: 217 but can elicit antibodies which can kill staphylococci. The polypeptide may have a first sequence having 80% or more identity (*e.g.* 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 218 and a second sequence having 80% or more identity (*e.g.* 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ
- <sup>30</sup> ID NO: 219, wherein the first and second sequences are either directly joined or are joined by an intervening amino acid sequence having fewer than 40 amino acids (*e.g.* ≤35 amino acids, ≤30 amino acids, ≤25 amino acids, ≤20 amino acids, ≤15 amino acids, ≤10 amino acids, ≤5 amino acids). SEQ ID NOs: 189 and 216 are examples of such polypeptides, in which the first and second sequences are joined by a tetrapeptide PSGS sequence (SEQ ID NO: 225).
- [0030] The invention also provides an immunogenic composition comprising a Sta011 antigen and a Ca<sup>++</sup> ion. The antigen and Ca<sup>++</sup> ion may form a complex *e.g.* atoms in the antigen may coordinate the Ca<sup>++</sup> ion. The immunogenic composition may also include an adjuvant.

**[0031]** The invention also provides a oligomer of a Sta011 antigen, and also immunogenic compositions comprising such oligomers. The oligomer can be a dimer, trimer, tetramer, pentamer, hexamer, heptamer, octamer or higher. An oligomer may comprise a Ca<sup>++</sup> ion, and a composition comprising Sta011 oligomers may comprise 5-500mM Ca<sup>++</sup> ions.

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# Further polypeptide antigens

[0032] In additions to antigens from the various antigen groups of the invention, immunogenic compositions may include one or more of the following *S.aureus* antigens (or antigens comprising immunogenic fragment(s) thereof) to enhance the efficacy against *S.aureus* of an immune response elicited by the composition [e.g. see references 3-10]:

- AhpC
- AhpF
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- Autolysin amidase
- Autolysin glucosaminidase
- Collagen binding protein CAN
- EbhB

- GehD lipase
- Heparin binding protein HBP (17kDa)
- Laminin receptor
  - MAP
  - MntC (also known as SitC)
- MRPII

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- Npase
- 15 ORF0594
  - ORF0657n
  - ORF0826
  - PBP4
    - RAP (RNA III activating protein)
- 25 Sai-1
  - SasK
  - SBI
    - SdrG
    - SdrH
- 35 SSP-1
  - SSP-2
  - Vitronectin-binding protein
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#### Combinations with saccharides

**[0033]** The individual antigens identified in the antigen groups of the invention may be used in combination with conjugated saccharide antigens. Thus the invention provides an immunogenic composition comprising a combination of:

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- (1) one or more antigen(s) selected from the first, second, third or fourth antigen groups (as defined above); and
- (2) one or more conjugates of a S.aureus exopolysaccharide and a carrier protein.
- <sup>50</sup> **[0034]** A conjugate used in component (2) of this combination includes a saccharide moiety and a carrier moiety. The saccharide moiety is from the exopolysaccharide of *S. aureus*, which is a poly-N-acetylglucosamine (PNAG). The saccharide may be a polysaccharide having the size that arises during purification of the exopolysaccharide from bacteria, or it may be an oligosaccharide achieved by fragmentation of such a polysaccharide e.g. size can vary from over 400kDa to between 75 and 400kDa, or between 10 and 75kDa, or up to 30 repeat units. The saccharide moiety can have various
- <sup>55</sup> degrees of N-acetylation and, as described in reference 11, the PNAG may be less than 40% N-acetylated (e.g. less than 35, 30, 20, 15, 10 or 5% N-acetylated; deacetylated PNAG is also known as dPNAG). Deacetylated epitopes of PNAG can elicit antibodies that are capable of mediating opsonic killing. The PNAG may or may not be O-succinylated e.g. it may be O-succinylated on fewer less than 25, 20, 15, 10, 5, 2, 1 or 0.1 % of residues.

[0035] The invention also provides an immunogenic composition comprising a combination of:

- (1) one or more antigen(s) selected from the first, second, third or fourth antigen groups; and
- (2) one or more conjugates of a *S.aureus* capsular saccharide and a carrier protein.
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**[0036]** A conjugate used in component (2) of this combination includes a saccharide moiety and a carrier moiety. The saccharide moiety is from the capsular saccharide of a *S.aureus*. The saccharide may be a polysaccharide having the size that arises during purification of capsular polysaccharide from bacteria, or it may be an oligosaccharide achieved by fragmentation of such a polysaccharide. Capsular saccharides may be obtained from any suitable strain of *S.aureus* (or any bacterium having a similar or identical saccharide), such as from a type 5 and/or a type 8 *S.aureus* strain and/or a type 336 *S.aureus* strain. Most strains of infectious *S.aureus* contain either Type 5 or Type 8 capsular saccharides.

Both have FucNAcp in their repeat unit as well as ManNAcA which can be used to introduce a sulfhydryl group for linkage. The repeating unit of the Type 5 saccharide is →4)-β-D-Man NAcA-(1→4)-α-L-FucNAc(30Ac)-(1→3)-β-D-FucNAc-(1→, whereas the repeating unit of the Type 8 saccharide is →3)-β-D-ManNAcA(40Ac)-(1→3)-α-L-FucNAc
 (1→3)-α-D-FucNAc(1→. The type 336 saccharide is a β-linked hexosamine with no O-acetylation [12,13] and is cross-reactive with antibodies raised against the 336 strain (ATCC 55804). A combination of a type 5 and a type 8 saccharide

is typical, and a type 336 saccharide may be added to this pairing [14]. [0037] The invention also provides an immunogenic composition comprising a combination of:

- (1) one or more antigen(s) selected from the first, second, third or fourth antigen groups;
  - (2) one or more conjugates of a *S.aureus* exopolysaccharide and a carrier protein; and
  - (3) one or more conjugates of a *S.aureus* capsular saccharide and a carrier protein.
- [0038] The carrier moiety in these conjugates will usually be a protein, but usually not one of the antigens of (1). Typical carrier proteins are bacterial toxins, such as diphtheria or tetanus toxins, or toxoids or mutants or fragments thereof. The CRM197 diphtheria toxin mutant [15] is useful. Other suitable carrier proteins include the *N.meningitidis* outer membrane protein complex [16], synthetic peptides [17,18], heat shock proteins [19,20], pertussis proteins [21,22], cytokines [23], lymphokines [23], hormones [23], growth factors [23], artificial proteins comprising multiple human CD4<sup>+</sup> T cell epitopes from various pathogen-derived antigens [24] such as N19 [25], protein D from *H.influenzae* [26-28],
- <sup>30</sup> pneumolysin [29] or its non-toxic derivatives [30], pneumococcal surface protein PspA [31], iron-uptake proteins [32], toxin A or B from *C.difficile* [33], recombinant *P.aeruginosa* exoprotein A (rEPA) [34], *etc.* In some embodiments the carrier protein is a *S.aureus* protein, such as an antigen selected from the first, second, third or fourth antigen groups. [0039] Where a composition includes more than one conjugate, each conjugate may use the same carrier protein or a different carrier protein.
- <sup>35</sup> **[0040]** Conjugates may have excess carrier (w/w) or excess saccharide (w/w). In some embodiments, a conjugate may include substantially equal weights of each.

**[0041]** The carrier molecule may be covalently conjugated to the carrier directly or via a linker. Direct linkages to the protein may be achieved by, for instance, reductive amination between the saccharide and the carrier, as described in, for example, references 35 and 36. The saccharide may first need to be activated e.g. by oxidation. Linkages via a linker

- <sup>40</sup> group may be made using any known procedure, for example, the procedures described in references 37 and 38. A preferred type of linkage is an adipic acid linker, which may be formed by coupling a free -NH<sub>2</sub> group (*e.g.* introduced to a glucan by amination) with adipic acid (using, for example, diimide activation), and then coupling a protein to the resulting saccharide-adipic acid intermediate [39,40]. Another preferred type of linkage is a carbonyl linker, which may be formed by reaction of a free hydroxyl group of a saccharide CDI [41, 42] followed by reaction with a protein to form
- <sup>45</sup> a carbamate linkage. Other linkers include  $\beta$ -propionamido [43], nitrophenyl-ethylamine [44], haloacyl halides [45], glycosidic linkages [46], 6-aminocaproic acid [47], ADH [48], C<sub>4</sub> to C<sub>12</sub> moieties [49], *etc.* Carbodiimide condensation can also be used [50].

**[0042]** PNAG conjugates may be prepared in various ways *e.g.* by a process comprising: a) activating the PNAG by adding a linker comprising a maleimide group to form an activated PNAG; b) activating the carrier protein by adding a

- <sup>50</sup> linker comprising a sulphydryl group to form an activated carrier protein; and c) reacting the activated PNAG and the activated carrier protein to form a PNAG-carrier protein conjugate; or by a process comprising a) activating the PNAG by adding a linker comprising a sulphydryl group to form an activated PNAG; b) activating the carrier protein by adding a linker comprising a maleimide group to form an activated carrier protein; and c) reacting the activated PNAG and the activated carrier protein to form a PNAG-carrier protein conjugate; or by a process comprising a) activated PNAG and the activated carrier protein to form a PNAG-carrier protein conjugate; or by a process comprising a) activating the PNAG and the activated carrier protein to form a PNAG-carrier protein conjugate; or by a process comprising a) activating the PNAG and the activated carrier protein to form a PNAG-carrier protein conjugate; or by a process comprising a) activating the PNAG and the activated carrier protein to form a PNAG-carrier protein conjugate; or by a process comprising a) activating the PNAG and the activated carrier protein to form a PNAG-carrier protein conjugate; or by a process comprising a) activating the PNAG
- <sup>55</sup> by adding a linker comprising a sulphydryl group to form an activated PNAG; b) activating the carrier protein by adding a linker comprising a sulphydryl group to form an activated carrier protein; and c) reacting the activated PNAG and the activated carrier protein to form a PNAG-carrier protein conjugate.

[0043] The individual antigens identified in the antigen groups of the invention may be used as carrier proteins for

exopolysaccharides, to form a covalent conjugate. Thus the invention provides an immunogenic composition comprising a conjugate of (1) an antigen selected from the first, second, third and fourth antigen groups and (2) a *S. aureus* exopolysaccharide. The invention also provides an immunogenic composition comprising a conjugate of (1) an antigen selected from the first, second, third and fourth antigen groups and (2) a *S. aureus* exopolysaccharide. The invention also provides an immunogenic composition comprising a conjugate of (1) an antigen selected from the first, second, third and fourth antigen groups and (2) a *S. aureus* capsular saccharide. Further characteristics of such conjugates are described above. These conjugates may be combined with any of the antigens disclosed herein.

Combinations with non-staphylococcal antigens

[0044] The individual antigens identified in the antigen groups of the invention may be used in combination with nonstaphylococcal antigens, and in particular with antigens from bacteria associated with nosocomial infections. Thus the invention provides an immunogenic composition comprising a combination of:

- (1) one or more antigen(s) selected from the first, second, third and fourth antigen groups (as defined above); and
- (2) one or more antigen(s) selected from the group consisting of: Clostridium difficile; Pseudomonas aeruginosa;
- Candida albicans; and extraintestinal pathogenic Escherichia coli.

**[0045]** Further suitable antigens for use in combination with staphylococcal antigens of the invention are listed on pages 33-46 of reference 51.

#### 20 First antigen group

clfA

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- [0046] The 'clfA' antigen is annotated as 'clumping factor A'. In the NCTC 8325 strain clfA is SAOUHSC\_00812 and has amino acid sequence SEQ ID NO: 1 (GI:88194572). In the Newman strain it is nwmn\_0756 (GI:151220968).
  [0047] Useful clfA antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 1 and/or may 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: 1; and/or (b) comprising
- a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 1, 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). These clfA proteins include variants of SEQ ID NO: 1. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 1. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 1 while retaining at least one epitope of SEQ ID NO: 1. The final 368 C-terminal amino acids of SEQ ID NO: 1 can usefully be omitted. The first 39
- <sup>35</sup> N-terminal amino acids of SEQ ID NO: 1 can usefully be omitted. Other fragments omit one or more protein domains. [0048] SEQ ID NO: 224 is a useful fragment of SEQ ID NO: 1 ('Clf<sub>40-559</sub>'). This fragments omits the long repetitive region towards the C-terminal of SEQ ID NO: 1.

clfB

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[0049] The 'clfB' antigen is annotated as 'clumping factor B'. In the NCTC 8325 strain clfB is SAOUHSC\_02963 and has amino acid sequence SEQ ID NO: 2 (GI:88196585). In the Newman strain it is nwmn\_2529 (GI:151222741).
[0050] Useful clfB antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO:

- 2 and/or may 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: 2; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 2, 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). These clfB proteins include variants of SEQ ID NO: 2. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 2. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids
- (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 2 while retaining at least one epitope of SEQ ID NO: 2. The final 40 C-terminal amino acids of SEQ ID NO: 2 can usefully be omitted. The first 44 N-terminal amino acids of SEQ ID NO: 2 can usefully be omitted. Other fragments omit one or more protein domains. ClfB is naturally a long protein and so the use of fragments is helpful *e.g.* for purification, handling, fusion, expression, *etc.* SEQ ID NO: 163 is a useful fragment of SEQ ID NO: 2 ('ClfB<sub>45-552</sub>'). This fragment includes the most exposed domain
- of ClfB and is more easily used at an industrial scale. It also reduces the antigen's similarity with human proteins. Other useful fragments, based on a 3-domain model of ClfB, include: ClfB<sub>45-360</sub> (also known as CLfB-N12; SEQ ID NO: 196); ClfB<sub>212-542</sub> (also known as CLfB-N23; SEQ ID NO: 197); and ClfB<sub>360-542</sub> (also known as CLfB-N3; SEQ ID NO: 198).

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**[0051]** The 'coA' antigen is annotated as 'coagulase Coa'. In the NCTC 8325 strain coA is SAOUHSC\_00192 and has amino acid sequence SEQ ID NO: 3 (GI:88194002). In the Newman strain it is nwmn\_0166 (GI:151220378).

- <sup>5</sup> **[0052]** Useful coA antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 3 and/or may 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: 3; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 3, 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). These coA proteins include variants of SEQ ID NO:
- 3. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 3. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 3 while retaining at least one epitope of SEQ ID NO: 3. The first 14 N-terminal amino acids of SEQ ID NO: 3 can usefully be omitted. Other fragments omit one or more protein domains.
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eap

**[0053]** The 'eap' antigen is annotated as 'MHC class II analog protein'. In the NCTC 8325 strain eap is SAOUHSC\_ 02161 and has amino acid sequence SEQ ID NO: 4 (GI:88195840). In the Newman strain it is nwmn\_1872 (GI: 151222084).

**[0054]** Useful eap antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 4 and/or may 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: 4; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 4, 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). These eap proteins include variants of SEQ ID NO:
4. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 4. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 4 while retaining at least one epitope of SEQ ID NO: 4. The first 17 N-terminal amino acids of SEQ ID NO: 4 can usefully be omitted. Other fragments omit one or more protein domains.

ebhA

**[0055]** The 'ebhA' antigen is annotated as 'EbhA'. In the NCTC 8325 strain ebhA is SAOUHSC\_01447 and has amino acid sequence SEQ ID NO: 5 (GI:88195168).

**[0056]** Useful ebhA antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 5 and/or may 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: 5; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 5, 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). These ebhA proteins include variants of SEQ ID NO:
5. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 5. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 5 while retaining at least one epitope of SEQ ID NO: 5. The first 39 N-terminal amino acids of SEQ ID NO: 5 can usefully be omitted. Other fragments omit one or more protein domains.

ebpS

[0057] The 'ebpS' antigen is annotated as 'elastin binding protein EbpS'. In the NCTC 8325 strain ebpS is SAOUHSC\_
 01501 and has amino acid sequence SEQ ID NO: 6 (GI:88195217). In the Newman strain it is nwmn\_1389 (GI: 151221601).

**[0058]** Useful ebpS antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 6 and/or may 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

<sup>55</sup> 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). These ebpS proteins include variants of SEQ ID NO:
6. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 6. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids

(e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 6 while retaining at least one epitope of SEQ ID NO: 6. Other fragments omit one or more protein domains.

**[0059]** SEQ ID NO: 165 is a useful fragment of SEQ ID NO: 6 ('EbpS<sub>1-198</sub>'). This fragment includes the most exposed domain of EbpS and is more easily used at an industrial scale. It also reduces the antigen's similarity with human proteins.

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efb

**[0060]** The 'efb' antigen is annotated as 'fibrinogen-binding protein truncated'. In the NCTC 8325 strain efb is SAOUHSC\_01114 and has amino acid sequence SEQ ID NO: 7 (GI:88194860). In the Newman strain it is nwmn\_1069 (GI:151221281).

**[0061]** Useful efb antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 7 and/or may 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 or more). These efb proteins include variants of SEQ ID NO: 7. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 7. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 7 while retaining at least one epitope of SEQ ID NO: 7. The first 14 N-terminal amino acids of SEQ ID NO: 7 can usefully be omitted. Other fragments omit one or more protein domains.

emp

[0062] The 'emp' antigen is annotated as 'extracellular matrix and plasma binding protein'. In the NCTC 8325 strain emp is SAOUHSC\_00816 and has amino acid sequence SEQ ID NO: 8 (GI:88194575). In the Newman strain it is nwmn\_ 0758 (GI:151220970).

**[0063]** Useful emp antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 8 and/or may 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

- <sup>30</sup> 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). These emp proteins include variants of SEQ ID NO: 8. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 8. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 8 while retaining at least one
- <sup>35</sup> epitope of SEQ ID NO: 8. The first 26 N-terminal amino acids of SEQ ID NO: 8 can usefully be omitted. Other fragments omit one or more protein domains.
  [0064] SEQ ID NOs: 190, 191, 192 and 193 are useful fragments of SEQ ID NO: 8 ('Emp<sub>35-340</sub>', 'Emp<sub>27-334</sub>', 'EMP<sub>35-334</sub>' and 'Emp<sub>27-147</sub>', respectively).
- 40 esaC

**[0065]** The 'esaC' antigen is annotated as 'esaC'. In the NCTC 8325 strain esaC is SAOUHSC\_00264 and has amino acid sequence SEQ ID NO: 9 (GI:88194069).

- [0066] Useful esaC antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO:
  9 and/or may 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: 9; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 9, 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 or more). These esaC proteins include variants of SEQ ID NO: 9. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 9. Other preferred fragments lack one or more amino acids (e.g.
- 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 9 while retaining at least one epitope of SEQ ID NO: 9. Other fragments omit one or more protein domains.

esxA

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[0067] The 'esxA' antigen is annotated as 'protein'. In the NCTC 8325 strain esxA is SAOUHSC\_00257 and has amino acid sequence SEQ ID NO: 10 (GI:88194063).

[0068] Useful esxA antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO:

10 and/or may 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 or more). These esxA proteins include variants of SEQ ID NO: 10. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 10. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 10 while retaining at least one epitope of SEQ ID NO: 10. Other fragments omit one or more protein domains.

#### 10 esxB

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**[0069]** The 'esxB' antigen is annotated as 'esxB'. In the NCTC 8325 strain esxB is SAOUHSC\_00265 and has amino acid sequence SEQ ID NO: 11 (GI:88194070).

- [0070] Useful esxB antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO:
   <sup>15</sup> 11 and/or may 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 or more). These esxB proteins include variants of SEQ ID NO: 11. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 11. Other preferred fragments lack one or more amino acids
- (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 11 while retaining at least one epitope of SEQ ID NO: 11. Other fragments omit one or more protein domains.

FnBA

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**[0071]** The 'FnBA' antigen is annotated as 'fibronectin-binding protein A precursor FnBPA'. In the NCTC 8325 strain FnBA is SAOUHSC\_02803 and has amino acid sequence SEQ ID NO: 12 (GI:88196438). In the Newman strain it is nwm\_2399 (GI:151222611). Proteomic analysis has revealed that this protein is secreted or surface-exposed.

- [0072] Useful FnBA antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO:
   <sup>30</sup> 12 and/or may 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). These FnBA proteins include variants of SEQ ID NO: 12. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 12. Other preferred fragments lack one or
- <sup>35</sup> more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 12 while retaining at least one epitope of SEQ ID NO: 12. The final 37 C-terminal amino acids of SEQ ID NO: 12 can usefully be omitted. Other fragments omit one or more protein domains. FnBA is naturally a long protein and so the use of fragments is helpful *e.g.* for purification, handling, fusion, expression, *etc.*
- <sup>40</sup> **[0073]** SEQ ID NOs: 166 ('FnBA<sub>1-511</sub>') and 167 ('FnBA<sub>512-953</sub>') are useful fragments of SEQ ID NO: 12. These fragments are more easily used at an industrial scale.

FnBB

<sup>45</sup> [0074] The 'FnBB' antigen is annotated as 'fibronectin binding protein B FnBPB'. In the NCTC 8325 strain FnBB is SAOUHSC\_02802 and has amino acid sequence SEQ ID NO: 13 (GI:88196437). In the Newman strain it is nwmn\_ 2397 (GI:151222609).

**[0075]** Useful FnBB antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 13 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%,

- 50 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). These FnBB proteins include variants of SEQ ID NO: 13. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 13. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino
- <sup>55</sup> acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 13 while retaining at least one epitope of SEQ ID NO: 13. The final 37 C-terminal amino acids of SEQ ID NO: 13 can usefully be omitted. Other fragments omit one or more protein domains.

Hla

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**[0076]** The 'Hla' antigen is the 'alpha-hemolysin precursor' also known as 'alpha toxin' or simply 'hemolysin'. In the NCTC 8325 strain Hla is SAOUHSC\_01121 and has amino acid sequence SEQ ID NO: 14 (GI:88194865). In the Newman strain it is nwmn\_1073 (GI:151221285). Hla is an important virulence determinant produced by most strains of *S.aureus*, having pore-forming and haemolytic activity. Anti-Hla antibodies can neutralise the detrimental effects of the toxin in animal models, and Hla is particularly useful for protecting against pneumonia.

**[0077]** Useful HIa antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 14 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%,

- 10 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 14; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 14, 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). These HIa proteins include variants of SEQ ID NO: 14. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 14. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids
- (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 14 while retaining at least one epitope of SEQ ID NO: 14. The first 26 N-terminal amino acids of SEQ ID NO: 14 can usefully be omitted (e.g. to give SEQ ID NO: 231). Truncation at the C-terminus can also be used e.g. leaving only 50 amino acids (residues 27-76 of SEQ ID NO: 14) [52]. Other fragments omit one or more protein domains.
- [0078] Hla's toxicity can be avoided in compositions of the invention by chemical inactivation (*e.g.* using formaldehyde, glutaraldehyde or other cross-linking reagents). Instead, however, it is preferred to use mutant forms of Hla which remove its toxic activity while retaining its immunogenicity. Such detoxified mutants are already known in the art. One useful Hla antigen has a mutation at residue 61 of SEQ ID NO: 14, which is residue 35 of the mature antigen (*i.e.* after omitting the first 26 N-terminal amino acids = residue 35 of SEQ ID NO: 231). Thus residue 61 may not be histidine, and may instead be *e.g.* Ile, Val or preferably Leu. A His-Arg mutation at this position can also be used. For example, SEQ ID
- NO: 150 is the mature mutant HIa-H35L sequence (*i.e.* SEQ ID NO: 231 with a H35L mutation) and a useful HIa antigen comprises SEQ ID NO: 150. Another useful mutation replaces a long loop with a short sequence *e.g.* to replace the 39mer at residues 136-174 of SEQ ID NO: 14 with a tetramer such as PSGS (SEQ ID NO: 225), as in SEQ ID NO: 189 (which also includes the H35L mutation) and SEQ ID NO: 216 (which does not include the H35L mutation). Another useful mutation replaces residue Y101 *e.g.* with a leucine (SEQ ID NO: 242). Another useful mutation replaces residue
- <sup>30</sup> D152 *e.g.* with a leucine (SEQ ID NO: 243). Another useful mutant replaces residues H35 and Y101 *e.g.* with a leucine (SEQ ID NO: 244). Another useful mutant replaces residues H35 and D152 *e.g.* with a leucine (SEQ ID NO: 245).
   [0079] Further useful HIa antigens are disclosed in references 53 and 54.
   [0080] SEQ ID NOs: 160, 161 & 194 are three useful fragments of SEQ ID NO: 14 ('HIa<sub>27-76</sub>', 'HIa<sub>27-89</sub>' and 'HIa<sub>27-79</sub>',
  - respectively). SEQ ID NOs: 158, 159 and 195 are the corresponding fragments from SEQ ID NO: 150,  $102_{7-79}$ , 1
- <sup>35</sup> **[0081]** One useful HIa sequence is SEQ ID NO: 232, which was used in the examples. It has a N-terminal Met, then an Ala-Ser dipeptide from the expression vector, then SEQ ID NO: 150 (from NCTC8325 strain). It is encoded by SEQ ID NO: 233.

hlgB

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**[0082]** The 'hlgB' antigen is annotated as 'leukocidin f subunit precursor HlgB'. In the NCTC 8325 strain hlgB is SAOUHSC\_02710 and has amino acid sequence SEQ ID NO: 15 (GI:88196350).

- 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 15; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 15, 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). These hlgB proteins include variants of SEQ ID NO: 15. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 15. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids
- (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 15 while retaining at least one epitope of SEQ ID NO: 15. The first 26 N-terminal amino acids of SEQ ID NO: 15 can usefully be omitted. Other fragments omit one or more protein domains.

hlgC

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**[0084]** The 'hlgC' antigen is annotated as 'leukocidin s subunit precursor HlgC'. In the NCTC 8325 strain hlgC is SAOUHSC\_02709 and has amino acid sequence SEQ ID NO: 16 (GI:88196349).

[0085] Useful hlgC antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO:

16 and/or may 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: 16; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 16, 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). These hlgC proteins include variants of SEQ ID NO: 16. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 16. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 16 while retaining at least one epitope of SEQ ID NO: 16. The first 29 N-terminal amino acids of SEQ ID NO: 16 can usefully be omitted. Other fragments omit one or more protein domains.

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isdA

**[0086]** The 'isdA' antigen is annotated as 'IsdA protein'. In the NCTC 8325 strain isdA is SAOUHSC\_01081 and has amino acid sequence SEQ ID NO: 17 (GI:88194829). In the Newman strain it is nwmn\_1041 (GI: 151221253).

- <sup>15</sup> **[0087]** Useful isdA antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 17 and/or may 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: 17; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 17, 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). These isdA proteins include variants of SEQ ID NO:
- 17. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 17. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 17 while retaining at least one epitope of SEQ ID NO: 17. The final 38 C-terminal amino acids of SEQ ID NO: 17 can usefully be omitted. The first 46 N-terminal amino acids of SEQ ID NO: 17 can useful be omitted. Truncation to exclude the C-terminal 38mer of SEQ ID NO: 17 can useful be omitted.
- <sup>25</sup> ID NO: 17 (beginning with the LPKTG motif) is also useful. Other fragments omit one or more protein domains. [0088] SEQ ID NO: 157 is a useful fragment of SEQ ID NO: 17 (amino acids 40-184 of SEQ ID NO: 17; 'IsdA<sub>40-184</sub>') which includes the natural protein's heme binding site and includes the antigen's most exposed domain. It also reduces the antigen's similarity with human proteins. Other useful fragments are disclosed in references 55 and 56.
- [0089] IsdA does not adsorb well to aluminium hydroxide adjuvants, so IsdA present in a composition may me unad-30 sorbed or may be adsorbed to an alternative adjuvant *e.g.* to an aluminium phosphate.
  - [0090] Anti-IsdA antibodies protect mice against S.aureus abscess formation and lethal challenge [57].

isdB

<sup>35</sup> **[0091]** The 'isdB' antigen is annotated as 'neurofilament protein isdB'. In the NCTC 8325 strain isdB is SAOUHSC\_ 01079 and has amino acid sequence SEQ ID NO: 18 (GI:88194828). IsdB has been proposed for use as a vaccine antigen on its own [2], but this may not prevent pneumonia.

- 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 18; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 18, 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). These isdB proteins include variants of SEQ ID NO: 18. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 18. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids
- (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 18 while retaining at least one epitope of SEQ ID NO: 18. The final 36 C-terminal amino acids of SEQ ID NO: 18 can usefully be omitted. The first 40 N-terminal amino acids of SEQ ID NO: 18 can usefully be omitted. Other fragments omit one or more protein domains. Useful fragments of IsdB are disclosed in references 56 and 58 *e.g.* lacking 37 internal amino acids of SEQ ID 18.
   [0093] Anti-IsdB antibodies protect mice against *S.aureus* abscess formation and lethal challenge [57].
- <sup>50</sup> **[0094]** In some embodiments, compositions of the invention do not include an isdB antigen.

isdC

[0095] The 'isdC' antigen is annotated as 'protein'. In the NCTC 8325 strain isdC is SAOUHSC\_01082 and has amino acid sequence SEQ ID NO: 19 (GI:88194830).

[0096] Useful isdC antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 19 and/or may 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: 19; and/or (b) comprising

a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 19, 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 or more). These isdC proteins include variants of SEQ ID NO: 19. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 19. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1,

<sup>5</sup> 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 19 while retaining at least one epitope of SEQ ID NO: 19. The final 39 C-terminal amino acids of SEQ ID NO: 19 can usefully be omitted. The first 28 N-terminal amino acids of SEQ ID NO: 19 can usefully be omitted. Useful amino acids of SEQ ID NO: 19 can usefully be omitted. Useful fragments of IsdB are disclosed in reference 56.

[0097] Reference 59 discloses antigens which usefully include epitopes from both IsdB and IsdH.

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isdG

**[0098]** The 'isdG' antigen is annotated as 'heme-degrading monooxygenase IsdG'. In the NCTC 8325 strain isdG is SAOUHSC\_01089 and has amino acid sequence SEQ ID NO: 20 (GI:88194836).

- <sup>15</sup> **[0099]** Useful isdG antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 20 and/or may 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: 20; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 20, 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 or more). These isdG proteins include variants of SEQ ID NO: 20. Preferred
- fragments of (b) comprise an epitope from SEQ ID NO: 20. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 20 while retaining at least one epitope of SEQ ID NO: 20. Other fragments omit one or more protein domains.

**[0100]** The 'isdH' antigen is annotated as 'isdH'. In the NCTC 8325 strain isdH is SAOUHSC\_01843 and has amino acid sequence SEQ ID NO: 21 (GI:88195542). In the Newman strain it is nwmn\_1624 (GI:151221836). It has also been known as HarA.

- <sup>30</sup> **[0101]** Useful isdH antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 21 and/or may 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: 21; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 21, 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). These isdH proteins include variants of SEQ ID NO:
- 21. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 21. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 21 while retaining at least one epitope of SEQ ID NO: 21. The final 35 C-terminal amino acids of SEQ ID NO: 21 can usefully be omitted. The first 40 N-terminal amino acids of SEQ ID NO: 21 can usefully be omitted. Other fragments omit one or more protein domains.
- <sup>40</sup> **[0102]** Reference 59 discloses antigens which usefully include epitopes from both IsdB and IsdH.

isdl

- **[0103]** The 'isdl' antigen is annotated as 'heme-degrading monooxygenase Isdl'. In the NCTC 8325 strain isdl is SAOUHSC\_00130 and has amino acid sequence SEQ ID NO: 22 (GI:88193943).
- **[0104]** Useful isdl antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 22 and/or may 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: 22; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 22, 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 or more). These isdl proteins include variants of SEQ ID NO: 22. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 22. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 22 while retaining at least one epitope of SEQ ID NO: 22. Other fragments omit one or more protein domains.

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lukD

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<sup>25</sup> isdH

<sup>[0105]</sup> The 'lukD' antigen is annotated as 'leukotoxin LukD'. In the NCTC 8325 strain lukD is SAOUHSC\_01954 and

has amino acid sequence SEQ ID NO: 23 (GI:88195647). In the Newman strain it is nwmn\_1718 (GI:151221930). [0106] Useful lukD antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 23 and/or may 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: 23; and/or (b) comprising

- <sup>5</sup> a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 23, 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). These lukD proteins include variants of SEQ ID NO: 23. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 23. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 23 while retaining at least one
- 10 epitope of SEQ ID NO: 23. The final 43 C-terminal amino acids of SEQ ID NO: 23 can usefully be omitted. The first 26 N-terminal amino acids of SEQ ID NO: 23 can usefully be omitted. Other fragments omit one or more protein domains.

lukE

<sup>15</sup> **[0107]** The 'lukE' antigen is annotated as 'leukotoxin LukE'. In the NCTC 8325 strain lukE is SAOUHSC\_01955 and has amino acid sequence SEQ ID NO: 24 (GI:88195648).

**[0108]** Useful lukE antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 24 and/or may 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: 24; and/or (b) comprising

- a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 24, 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). These lukE proteins include variants of SEQ ID NO: 24. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 24. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 24 while retaining at least one
- <sup>25</sup> epitope of SEQ ID NO: 24. Other fragments omit one or more protein domains.

lukF

- [0109] The 'lukF' antigen is annotated as 'Leukocidin/Hemolysin toxin family LukF'. In the NCTC 8325 strain lukF is
  SAOUHSC\_02241 and has amino acid sequence SEQ ID NO: 25 (GI:88195914). Useful lukF antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 25 and/or may 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: 25; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 25, 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). These lukF proteins include variants of SEQ ID NO: 25. Preferred fragments of (b)
- So, 100, 150, 200, 250 of more). These fuck proteins include variants of SEQ ID NO. 25. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 25. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 25 while retaining at least one epitope of SEQ ID NO: 25. Other fragments omit one or more protein domains.

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lukS

**[0110]** The 'lukS' antigen is annotated as 'probable leukocidin S subunit LukS'. In the NCTC 8325 strain lukS is SAOUHSC\_02243 and has amino acid sequence SEQ ID NO: 26 (GI:88195915). In the Newman strain it is nwmn\_ 1928 (GI: 151222140).

**[0111]** Useful lukS antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 26 and/or may 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: 26; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 26, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18,

<sup>55</sup> omit one or more protein domains.

<sup>20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250</sup> or more). These lukS proteins include variants of SEQ ID NO:
26. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 26. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 26 while retaining at least one epitope of SEQ ID NO: 26. The first 22 N-terminal amino acids of SEQ ID NO: 26 can usefully be omitted. Other fragments

nuc

**[0112]** The 'nuc' antigen is annotated as 'thermonuclease precursor'. In the NCTC 8325 strain nuc is SAOUHSC\_ 01316 and has amino acid sequence SEQ ID NO: 27 (GI:88195046).

- <sup>5</sup> **[0113]** Useful nuc antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 27 and/or may 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: 27; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 27, 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 or more). These nuc proteins include variants of SEQ ID NO: 27. Preferred
- fragments of (b) comprise an epitope from SEQ ID NO: 27. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 27 while retaining at least one epitope of SEQ ID NO: 27. The final 39 C-terminal amino acids of SEQ ID NO: 27 can usefully be omitted. The first 19 N-terminal amino acids of SEQ ID NO: 27 can usefully be omitted. Other fragments omit one or more protein domains.

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sasA

**[0114]** The 'sasA' antigen is annotated as 'SasA'. In the NCTC 8325 strain sasA is SAOUHSC\_02990 and has amino acid sequence SEQ ID NO: 28 (GI:88196609).

- [0115] Useful sasA antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 28 and/or may 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: 28; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 28, 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). These sasA proteins include variants of SEQ ID NO:
- 25 28. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 28. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 28 while retaining at least one epitope of SEQ ID NO: 28. The final 43 C-terminal amino acids of SEQ ID NO: 28 can usefully be omitted. The first 90 N-terminal amino acids of SEQ ID NO: 28 can usefully be omitted. Other fragments omit one or more protein domains.

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sasB

**[0116]** The 'sasB' antigen is annotated as 'fmtB protein; SasB'. In the NCTC 8325 strain sasB is SAOUHSC\_02404 and has amino acid sequence SEQ ID NO: 29 (GI:88196065).

- <sup>35</sup> **[0117]** Useful sasB antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 29 and/or may 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: 29; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 29, 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). These sasB proteins include variants of SEQ ID NO:
- 29. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 29. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 29 while retaining at least one epitope of SEQ ID NO: 29. The final 39 C-terminal amino acids of SEQ ID NO: 29 can usefully be omitted. The first 38 N-terminal amino acids of SEQ ID NO: 29 can useful DNO: 29 can useful be omitted.

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sasC

**[0118]** The 'sasC' antigen is annotated as 'Mrp protein; SasC'. In the NCTC 8325 strain sasC is SAOUHSC\_01873 and has amino acid sequence SEQ ID NO: 30 (GI:88195570).

- 50 [0119] Useful sasC antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 30 and/or may 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: 30; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 30, 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). These sasC proteins include variants of SEQ ID NO:
- <sup>55</sup> 30. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 30. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 30 while retaining at least one epitope of SEQ ID NO: 30. The final 36 C-terminal amino acids of SEQ ID NO: 30 can usefully be omitted. The first 37

N-terminal amino acids of SEQ ID NO: 30 can usefully be omitted. Other fragments omit one or more protein domains.

sasD

<sup>5</sup> **[0120]** The 'sasD' antigen is annotated as 'SasD protein'. In the NCTC 8325 strain sasD is SAOUHSC\_00094 and has amino acid sequence SEQ ID NO: 31 (GI:88193909).

**[0121]** Useful sasD antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 31 and/or may 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: 31; and/or (b) comprising

- a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 31, 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 or more). These sasD proteins include variants of SEQ ID NO: 31. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 31. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 31 while retaining at least one epitope
- <sup>15</sup> of SEQ ID NO: 31. The first 28 N-terminal amino acids of SEQ ID NO: 31 can usefully be omitted. Other fragments omit one or more protein domains.

sasF

<sup>20</sup> **[0122]** The 'sasF' antigen is annotated as 'sasF protein'. In the NCTC 8325 strain sasF is SAOUHSC\_02982 and has amino acid sequence SEQ ID NO: 32 (GI:88196601).

**[0123]** Useful sasF antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 32 and/or may 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: 32; and/or (b) comprising

- a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 32, 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). These sasF proteins include variants of SEQ ID NO: 32. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 32. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 32 while retaining at least one
- <sup>30</sup> epitope of SEQ ID NO: 32. The final 39 C-terminal amino acids of SEQ ID NO: 32 can usefully be omitted. The first 37 N-terminal amino acids of SEQ ID NO: 32 can usefully be omitted. Other fragments omit one or more protein domains.

sdrC

<sup>35</sup> **[0124]** The 'sdrC' antigen is annotated as 'sdrC protein'. In the NCTC 8325 strain sdrC is SAOUHSC\_00544 and has amino acid sequence SEQ ID NO: 33 (GI:88194324).

**[0125]** Useful sdrC antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 33 and/or may 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: 33; and/or (b) comprising a factor of CEO ID NO: 22 where is in it is 7 or more) to 24 up to 12 up to 12

- <sup>40</sup> a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 33, 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). These sdrC proteins include variants of SEQ ID NO: 33. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 33. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 33 while retaining at least one
- <sup>45</sup> epitope of SEQ ID NO: 33. The final 38 C-terminal amino acids of SEQ ID NO: 33 can usefully be omitted. The first 50 N-terminal amino acids of SEQ ID NO: 33 can usefully be omitted. Other fragments omit one or more protein domains. SdrC is naturally a long protein and so the use of fragments is helpful *e.g.* for purification, handling, fusion, expression, *etc.*[0126] SEQ ID NO: 164 is a useful fragment of SEQ ID NO: 33 ('SdrC5<sub>1-518</sub>'). This fragment includes the most exposed domain of SdrC and is more easily used at an industrial scale. It also reduces the antigen's similarity with human proteins.

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sdrD

**[0127]** The 'sdrD' antigen is annotated as 'sdrD protein'. In the NCTC 8325 strain sdrD is SAOUHSC\_00545 and has amino acid sequence SEQ ID NO: 34 (GI:88194325).

<sup>55</sup> **[0128]** Useful sdrD antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 34 and/or may 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: 34; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 34, 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). These sdrD proteins include variants of SEQ ID NO: 34. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 34. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 34 while retaining at least one epitope of SEQ ID NO: 34. The final 38 C-terminal amino acids of SEQ ID NO: 34 can usefully be omitted. The first 52 N-terminal amino acids of SEQ ID NO: 34 can usefully be omitted. Other fragments omit one or more protein domains. SdrD is naturally a long protein and so the use of fragments is very helpful *e.g.* for purification, handling, fusion, expression,

etc.
[0129] SEQ ID NO: 156 is a useful fragment of SEQ ID NO: 34 ('SdrD<sub>53-592</sub>'). This fragment includes the most exposed domain of SdrD and is more easily used at an industrial scale. It also reduces the antigen's similarity with human proteins. Another useful fragment, with the same C-terminus residue, is SdrD<sub>394-592</sub> (also known as SdrD-N3; SEQ ID NO: 199). Another useful fragment is SEQ ID NO: 236 (amino acids 593-1123 of SEQ ID NO: 34), referred to herein as 'SdrD<sub>CnaB</sub>'.

sdrE2

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**[0130]** The 'sdrE2' antigen is annotated as 'Ser-Asp rich fibrinogen/bone sialoprotein-binding protein SdrE'. In the Newman strain sdrE2 is NWMN\_0525 and has amino acid sequence SEQ ID NO: 35 (GI: 151220737).

- 20 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 35; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 35, 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). These sdrE2 proteins include variants of SEQ ID NO: 35. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 35. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino
- <sup>25</sup> acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 35 while retaining at least one epitope of SEQ ID NO: 35. The final 38 C-terminal amino acids of SEQ ID NO: 35 can usefully be omitted. The first 52 N-terminal amino acids of SEQ ID NO: 35 can usefully be omitted. Other fragments omit one or more protein domains. SdrE2 is naturally a long protein and so the use of fragments is very helpful *e.g.* for purification, handling, fusion, expression, *etc.*
- <sup>30</sup> **[0132]** SEQ ID NO: 155 is a useful fragment of SEQ ID NO: 35 ('SdrE<sub>53-632</sub>'). This fragment includes the most exposed domain of SdrE2 and is more easily used at an industrial scale. It also reduces the antigen's similarity with human proteins.

spa

- <sup>35</sup> **[0133]** The 'spa' antigen is annotated as 'protein A' or 'SpA'. In the NCTC 8325 strain spa is SAOUHSC\_00069 and has amino acid sequence SEQ ID NO: 36 (GI:88193885). In the Newman strain it is nwmn\_0055 (GI:151220267). All *S.aureus* strains express the structural gene for spa, a well characterized virulence factor whose cell wall-anchored surface protein product has five highly homologous immunoglobulin binding domains designated E, D, A, B, and C [60]. These domains display ~80% identity at the amino acid level, are 56 to 61 residues in length, and are organized as
- tandem repeats [61]. SpA is synthesized as a precursor protein with an N-terminal signal peptide and a C-terminal sorting signal [62,63]. Cell wall-anchored spa is displayed in great abundance on the staphylococcal surface [64,65]. Each of its immunoglobulin binding domains is composed of antiparallel α-helices that assemble into a three helix bundle and can bind the Fc domain of immunoglobulin G (IgG) [66,67], the VH3 heavy chain (Fab) of IgM (*i.e.* the B cell receptor) [68], the von Willebrand factor at its A1 domain [69] and/or the TNF-α receptor I (TNFRI) [70], which is displayed on
- <sup>45</sup> surfaces of airway epithelia.
  [0134] Useful spa antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 36 and/or may 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: 36; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 36, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 10, 12, 14,
- 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These spa proteins include variants of SEQ ID NO: 36. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 36. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 36 while retaining at least one epitope of SEQ ID NO: 36. The final 35 C-terminal amino acids of SEQ ID NO: 36 can usefully be omitted. The first 36
- <sup>55</sup> N-terminal amino acids of SEQ ID NO: 36 can usefully be omitted. Other fragments omit one or more protein domains. Reference 71 suggests that individual IgG-binding domains might be useful immunogens, alone or in combination.
  [0135] SEQ ID NO: 162 is a useful fragment of SEQ ID NO: 36 ('Spa<sub>37-325</sub>'). This fragment contains all the five SpA Ig-binding domains (which are naturally arranged from N- to C-terminus in the order E, D, A, B, C) and includes the

most exposed domain of SpA. It also reduces the antigen's similarity with human proteins. Other useful fragments may omit 1, 2, 3 or 4 of the natural A, B, C, D and/or E domains to prevent the excessive B cell expansion and then apoptosis which might occur if spa functions as a B cell superantigen. As reported in reference 71, other useful fragments may include only 1, 2, 3 or 4 of the natural A, B, C, D and/or E domains *e.g.* comprise only the SpA(A) domain but not B to

- <sup>5</sup> E, or comprise only the SpA(D) domain but not A, B, C or E, *etc.* Thus a spa antigen useful with the invention may include 1, 2, 3, 4 or 5 lgG-binding domains, but ideally has 4 or fewer If an antigen includes only one type of spa domain *(e.g.* only the Spa(A) or SpA(D) domain), it may include more than one copy of this domain *e.g.* multiple SpA(D) domains in a single polypeptide chain.
- [0136] An individual domain within the antigen may be mutated at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acids
  relative to SEQ ID NO: 36 (*e.g.* see ref. 71, disclosing mutations at residues 3 and/or 24 of domain D, at residue 46 and/or 53 of domain A, *etc.*). Such mutants should not remove the antigen's ability to elicit an antibody that recognises SEQ ID NO: 36, but may remove the antigen's binding to IgG and/or other human proteins (such as human blood proteins).
  [0137] In certain aspects a spa antigen includes a substitution at (a) one or more amino acid substitution in an IgG Fc binding sub-domain of SpA domain A, B, C, D and/or E that disrupts or decreases binding to IgG Fc, and (b) one or
- <sup>15</sup> more amino acid substitution in a V<sub>H</sub>3 binding sub-domain of SpA domain A, B, C, D, and/or E that disrupts or decreases binding to V<sub>H</sub>3. In certain embodiments, a variant SpA comprises at least or at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more variant SpA domain D peptides.

#### Second antigen group

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sta001

**[0138]** The 'sta001' antigen is annotated as '5'-nucleotidase family protein'. In the NCTC 8325 strain sta001 is SAOUHSC\_00025 and has amino acid sequence SEQ ID NO: 37 (GI:88193846). In the Newman strain it is nwmn\_0022 (GI:151220234). It has also been referred to as AdsA and SasH and SA0024.

- **[0139]** Useful sta001 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 37 and/or may 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: 37; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 37, wherein 'n' is 7 or more (*e.g.* 8, 10,
- <sup>30</sup> 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta001 proteins include variants of SEQ ID NO: 37. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 37. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 37 while retaining at least one epitope of SEQ ID NO: 37. The final 34 C-terminal amino acids of SEQ ID NO: 37 can usefully be omitted.
- <sup>35</sup> The first 38 N-terminal amino acids of SEQ ID NO: 37 can usefully be omitted. Other fragments omit one or more protein domains.

#### sta002

- 40 [0140] The 'sta002' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta002 is SAOUHSC\_00356 and has amino acid sequence SEQ ID NO: 38 (GI:88194155). In the Newman strain it is nwm\_0364 (GI:151220576).
  [0141] Useful sta002 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 38 and/or may 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: 38; and/or (b)
- <sup>45</sup> comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 38, 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 or more). These sta002 proteins include variants of SEQ ID NO: 38. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 38. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 38 while retaining at least

one epitope of SEQ ID NO: 38. The first 18 N-terminal amino acids of SEQ ID NO: 38 can usefully be omitted. Other fragments omit one or more protein domains.
 [0142] SEQ ID NOs: 153 ('sta002<sub>19-187</sub>') and 154 ('sta002<sub>19-124</sub>') are two useful fragments of SEQ ID NO: 38 which reduce the antigen's similarity with human proteins.

<sup>55</sup> sta003

**[0143]** The 'sta003' antigen is annotated as 'surface protein'. In the NCTC 8325 strain sta003 is SAOUHSC\_00400 and has amino acid sequence SEQ ID NO: 39 (GI:88194195). In the Newman strain it is nwmn\_0401 (GI:151220613).

[0144] Useful sta003 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 39 and/or may 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: 39; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 39, wherein 'n' is 7 or more (e.g. 8, 10,

5 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta003 proteins include variants of SEQ ID NO: 39. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 39. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 39 while retaining at least one epitope of SEQ ID NO: 39. The first 32 N-terminal amino acids of SEQ ID NO: 39 can usefully be omitted. 10

Other fragments omit one or more protein domains.

#### sta004

[0145] The 'sta004' antigen is annotated as 'Siderophore binding protein FatB'. In the NCTC 8325 strain sta004 is 15 SAOUHSC\_00749 and has amino acid sequence SEQ ID NO: 40 (GI:88194514). In the Newman strain it is nwmn\_ 0705 (GI: 151220917).

[0146] Useful sta004 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 40 and/or may 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: 40; and/or (b)

- 20 comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 40, 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). These sta004 proteins include variants of SEQ ID NO: 40. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 40. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 40 while retaining
- 25 at least one epitope of SEQ ID NO: 40. The first 18 N-terminal amino acids of SEQ ID NO: 40 can usefully be omitted. Other fragments omit one or more protein domains.

sta005

30 [0147] The 'sta005' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta005 is SAOUHSC\_ 01127 and has amino acid sequence SEQ ID NO: 41 (GI:88194870). In the Newman strain it is nwmn\_1077 (GI: 151221289).

[0148] Useful sta005 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 41 and/or may comprise an amino acid sequence: (a) having 50% or more identity (e.g. 60%, 65%, 70%, 75%,

- 35 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 41; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 41, 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 or more). These sta005 proteins include variants of SEQ ID NO: 41. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 41. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more
- 40 amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 41 while retaining at least one epitope of SEQ ID NO: 41. The first 18 N-terminal amino acids of SEQ ID NO: 41 can usefully be omitted. Other fragments omit one or more protein domains.

sta006

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[0149] The 'sta006' antigen is annotated as 'ferrichrome-binding protein', and has also been referred to as 'FhuD2' in the literature [72]. In the NCTC 8325 strain sta006 is SAOUHSC\_02554 and has amino acid sequence SEQ ID NO: 42 (GI:88196199). In the Newman strain it is nwmn\_2185 (GI: 151222397).

- [0150] Useful sta006 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID 50 NO: 42 and/or may 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: 42; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 42, 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). These sta006 proteins include variants of SEQ ID NO: 42. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 42. Other preferred fragments lack
- 55 one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 42 while retaining at least one epitope of SEQ ID NO: 42. The first 17 N-terminal amino acids of SEQ ID NO: 42 can usefully be omitted (to provide SEQ ID NO: 246). Other fragments omit one or more protein domains. Mutant forms of sta006 are reported

in reference 73. A sta006 antigen may be lipidated *e.g.* with an acylated N-terminus cysteine. One useful sta006 sequence is SEQ ID NO: 248, which has a Met-Ala-Ser- sequence at the N-terminus.

sta007

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**[0151]** The 'sta007' antigen is annotated as 'secretory antigen precursor'. In the NCTC 8325 strain sta007 is SAOUHSC\_02571 and has amino acid sequence SEQ ID NO: 43 (GI:88196215). In the Newman strain it is nwmn\_2199 (GI:151222411). Proteomic analysis has revealed that this protein is secreted or surface-exposed.

[0152] Useful sta007 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 43 and/or may 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: 43; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 43, 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). These sta007 proteins include variants of SEQ ID NO: 43. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 43. Other preferred fragments lack

<sup>15</sup> one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 43 while retaining at least one epitope of SEQ ID NO: 43. The first 27 N-terminal amino acids of SEQ ID NO: 43 can usefully be omitted. Other fragments omit one or more protein domains.

20 sta008

**[0153]** The 'sta008' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta008 is SAOUHSC\_02650 and has amino acid sequence SEQ ID NO: 44 (GI:88196290). In the Newman strain it is nwmn\_2270 (GI:151222482). **[0154]** Useful sta008 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID

- NO: 44 and/or may 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: 44; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 44, 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 or more). These sta008 proteins include variants of SEQ ID NO: 44. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 44. Other preferred fragments lack
- <sup>30</sup> one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 44 while retaining at least one epitope of SEQ ID NO: 44. The first 17 N-terminal amino acids of SEQ ID NO: 44 can usefully be omitted. Other fragments omit one or more protein domains.
- 35 sta009

**[0155]** The 'sta009' antigen is annotated as 'immunoglobulin G-binding protein Sbi'. In the NCTC 8325 strain sta009 is SAOUHSC\_02706 and has amino acid sequence SEQ ID NO: 45 (GI:88196346). In the Newman strain it is nwmn\_2317 (GI: 151222529).

- <sup>40</sup> [0156] Useful sta009 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 45 and/or may 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: 45; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 45, 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). These sta009 proteins include variants
- of SEQ ID NO: 45. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 45. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 45 while retaining at least one epitope of SEQ ID NO: 45. The first 29 N-terminal amino acids of SEQ ID NO: 45 can usefully be omitted. Other fragments omit one or more protein domains.

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sta010

**[0157]** The 'sta010' antigen is annotated as 'immunodominant antigen A'. In the NCTC 8325 strain sta010 is SAOUHSC\_02887 and has amino acid sequence SEQ ID NO: 46 (GI:88196515). In the Newman strain it is nwmn\_2469 (GI:151222681). Proteomic analysis has revealed that this protein is secreted or surface-exposed.

**[0158]** Useful sta010 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 46 and/or may 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: 46; and/or (b)

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comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 46, 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 or more). These sta010 proteins include variants of SEQ ID NO: 46. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 46. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 46 while retaining at least one epitope of SEQ ID NO: 46. The first 29 N-terminal amino acids of SEQ ID NO: 46 can usefully be omitted. Other fragments omit one or more protein domains.

sta011

**[0159]** The 'sta011' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta011 is SAOUHSC\_00052 and has amino acid sequence SEQ ID NO: 47 (GI:88193872).

**[0160]** Useful sta011 antigens can elicit an antibody *(e.g.* when administered to a human) that recognises SEQ ID NO: 47 and/or may comprise an amino acid sequence: (a) having 50% or more identity *(e.g.* 60%, 65%, 70%, 75%,

- <sup>15</sup> 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 47; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 47, 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). These sta011 proteins include variants of SEQ ID NO: 47. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 47. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more
- amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 47 while retaining at least one epitope of SEQ ID NO: 47. The first 23 N-terminal amino acids of SEQ ID NO: 47 can usefully be omitted (to provide SEQ ID NO: 247). Other fragments omit one or more protein domains. A sta011 antigen may be lipidated *e.g.* with an acylated N-terminus cysteine. One useful sta011 sequence is SEQ ID NO: 249, which has a N-terminus methionine.
- [0161] Variant forms of SEQ ID NO: 47 which may be used as or for preparing sta011 antigens include, but are not limited to, SEQ ID NOs: 213, 214 and 215 with various lle/Val/Leu substitutions.
   [0162] Sta011 can exist as a monomer or an oligomer, with Ca<sup>++</sup> ions favouring oligomerisation. The invention can use monomers and/or oligomers of Sta011.
- <sup>30</sup> sta012

**[0163]** The 'sta012' antigen is annotated as 'protein with leader'. In the NCTC 8325 strain sta012 is SAOUHSC\_00106 and has amino acid sequence SEQ ID NO: 48 (GI:88193919).

- [0164] Useful sta012 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 48 and/or may 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: 48; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 48, 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). These sta012 proteins include variants of SEQ ID NO: 48. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 48. Other preferred fragments lack
- 40 one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 48 while retaining at least one epitope of SEQ ID NO: 48. The first 21 N-terminal amino acids of SEQ ID NO: 48 can usefully be omitted. Other fragments omit one or more protein domains.
- <sup>45</sup> sta013

**[0165]** The 'sta013' antigen is annotated as 'poly-gamma-glutamate capsule biosynthesis protein'. In the NCTC 8325 strain sta013 is SAOUHSC\_00107 and has amino acid sequence SEQ ID NO: 49 (GI:88193920).

- [0166] Useful sta013 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID
  NO: 49 and/or may 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: 49; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 49, 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). These sta013 proteins include variants of SEQ ID NO: 49. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 49. Other preferred fragments lack
- <sup>55</sup> one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 49 while retaining at least one epitope of SEQ ID NO: 49. Other fragments omit one or more protein domains.

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#### sta014

**[0167]** The 'sta014' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta014 is SAOUHSC\_00137 and has amino acid sequence SEQ ID NO: 50 (GI:88193950).

- <sup>5</sup> [0168] Useful sta014 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 50 and/or may 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: 50; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 50, 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). These sta014 proteins include variants
- of SEQ ID NO: 50. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 50. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 50 while retaining at least one epitope of SEQ ID NO: 50. The first 17 N-terminal amino acids of SEQ ID NO: 50 can usefully be omitted. Other fragments omit one or more protein domains.

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sta015

**[0169]** The 'sta015' antigen is annotated as 'extracellular solute-binding protein; RGD containing lipoprotein'. In the NCTC 8325 strain sta015 is SAOUHSC\_00170 and has amino acid sequence SEQ ID NO: 51 (GI:88193980).

20 [0170] Useful sta015 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 51 and/or may 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: 51; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 51, 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). These sta015 proteins include variants

of SEQ ID NO: 51. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 51. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 51 while retaining at least one epitope of SEQ ID NO: 51. The first 18 N-terminal amino acids of SEQ ID NO: 51 can usefully be omitted. Other fragments omit one or more protein domains.

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sta016

**[0171]** The 'sta016' antigen is annotated as 'gamma-glutamyltranspeptidase'. In the NCTC 8325 strain sta016 is SAOUHSC\_00171 and has amino acid sequence SEQ ID NO: 52 (GI:88193981).

- <sup>35</sup> [0172] Useful sta016 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 52 and/or may 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: 52; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 52, 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). These sta016 proteins include variants
- 40 of SEQ ID NO: 52. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 52. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 52 while retaining at least one epitope of SEQ ID NO: 52. Other fragments omit one or more protein domains.
- <sup>45</sup> sta017

**[0173]** The 'sta017' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta017 is SAOUHSC\_00186 and has amino acid sequence SEQ ID NO: 53 (GI:88193996).

- [0174] Useful sta017 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID
  NO: 53 and/or may 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: 53; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 53, 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). These sta017 proteins include variants of SEQ ID NO: 53. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 53. Other preferred fragments lack
- <sup>55</sup> one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 53 while retaining at least one epitope of SEQ ID NO: 53. The first 17 N-terminal amino acids of SEQ ID NO: 53 can usefully be omitted. Other fragments omit one or more protein domains.

# sta018

**[0175]** The 'sta018' antigen is annotated as 'extracellular solute-binding protein'. In the NCTC 8325 strain sta018 is SAOUHSC\_00201 and has amino acid sequence SEQ ID NO: 54 (GI:88194011).

- <sup>5</sup> [0176] Useful sta018 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 54 and/or may 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: 54; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 54, 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). These sta018 proteins include variants
- <sup>10</sup> of SEQ ID NO: 54. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 54. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 54 while retaining at least one epitope of SEQ ID NO: 54. Other fragments omit one or more protein domains.
- 15 sta019

**[0177]** The 'sta019' antigen is annotated as 'peptidoglycan hydrolase'. In the NCTC 8325 strain sta019 is SAOUHSC\_ 00248 and has amino acid sequence SEQ ID NO: 55 (GI:88194055). In the Newman strain it is nwmn\_0210 (GI: 151220422).

- 20 [0178] Useful sta019 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 55 and/or may 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: 55; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 55, 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). These sta019 proteins include variants
- of SEQ ID NO: 55. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 55. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 55 while retaining at least one epitope of SEQ ID NO: 55. The first 25 N-terminal amino acids of SEQ ID NO: 55 can usefully be omitted. Other fragments omit one or more protein domains. Useful fragments are SEQ ID NOs: 228 and 229.
- <sup>30</sup> **[0179]** Sta019 does not adsorb well to aluminium hydroxide adjuvants, so Sta019 present in a composition may me unadsorbed or may be adsorbed to an alternative adjuvant e.g. to an aluminium phosphate.

sta020

<sup>35</sup> **[0180]** The 'sta020' antigen is annotated as 'exported protein'. In the NCTC 8325 strain sta020 is SAOUHSC\_00253 and has amino acid sequence SEQ ID NO: 56 (GI:88194059).

**[0181]** Useful sta020 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 56 and/or may 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: 56; and/or (b)

- <sup>40</sup> comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 56, 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). These sta020 proteins include variants of SEQ ID NO: 56. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 56. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 56 while retaining
- <sup>45</sup> at least one epitope of SEQ ID NO: 56. The first 30 N-terminal amino acids of SEQ ID NO: 56 can usefully be omitted. Other fragments omit one or more protein domains.

sta021

- [0182] The 'sta021' antigen is annotated as 'secretory antigen SsaA-like protein'. In the NCTC 8325 strain sta021 is SAOUHSC\_00256 and has amino acid sequence SEQ ID NO: 57 (GI:88194062).
   [0183] Useful sta021 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 57 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 00%, 01%, 02%, 04%, 05%, 06%, 07%, 08%, 00%, 00 5% or more) to SEQ ID NO: 57; and/or (b)
- 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 57; and/or (b)
  comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 57, 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). These sta021 proteins include variants of SEQ ID NO: 57. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 57. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more

amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 57 while retaining at least one epitope of SEQ ID NO: 57. The first 24 N-terminal amino acids of SEQ ID NO: 57 can usefully be omitted. Other fragments omit one or more protein domains.

## 5 sta022

**[0184]** The 'sta022' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta022 is SAOUHSC\_00279 and has amino acid sequence SEQ ID NO: 58 (GI:88194083).

[0185] Useful sta022 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 58 and/or may 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: 58; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 58, 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 or more). These sta022 proteins include variants of SEQ ID NO: 58. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 58. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 58 while retaining at least one epitope of SEQ ID NO: 58. The first 17 N-terminal amino acids of SEQ ID NO: 58 can usefully be omitted. Other

20 sta023

fragments omit one or more protein domains.

**[0186]** The 'sta023' antigen is annotated as '5'-nucleotidase; lipoprotein e(P4) family'. In the NCTC 8325 strain sta023 is SAOUHSC\_00284 and has amino acid sequence SEQ ID NO: 59 (GI:88194087).

- [0187] Useful sta023 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID
  NO: 59 and/or may 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: 59; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 59, 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). These sta023 proteins include variants of SEQ ID NO: 59. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 59. Other preferred fragments lack
- <sup>30</sup> one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 59 while retaining at least one epitope of SEQ ID NO: 59. The first 31 N-terminal amino acids of SEQ ID NO: 59 can usefully be omitted. Other fragments omit one or more protein domains.
- 35 sta024

**[0188]** The 'sta024' antigen is annotated as 'lipase precursor'. In the NCTC 8325 strain sta024 is SAOUHSC\_00300 and has amino acid sequence SEQ ID NO: 60 (GI:88194101).

- [0189] Useful sta024 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID
  NO: 60 and/or may 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: 60; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 60, 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). These sta024 proteins include variants of SEQ ID NO: 60. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 60. Other preferred fragments lack
- <sup>45</sup> one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 60 while retaining at least one epitope of SEQ ID NO: 60. The first 37 N-terminal amino acids of SEQ ID NO: 60 can usefully be omitted. Other fragments omit one or more protein domains.
- 50 sta025

**[0190]** The 'sta025' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta025 is SAOUHSC\_00362 and has amino acid sequence SEQ ID NO: 61 (GI:88194160).

[0191] Useful sta025 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID
<sup>55</sup> NO: 61 and/or may 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: 61; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 61, 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 or more). These sta025 proteins include variants of SEQ

ID NO: 61. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 61. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 61 while retaining at least one epitope of SEQ ID NO: 61. The first 19 N-terminal amino acids of SEQ ID NO: 61 can usefully be omitted. Other fragments omit one or more protein domains.

sta026

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**[0192]** The 'sta026' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta026 is SAOUHSC\_00404 and has amino acid sequence SEQ ID NO: 62 (GI:88194198).

**[0193]** Useful sta026 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 62 and/or may 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: 62; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 62, 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). These sta026 proteins include variants of SEQ ID NO: 62. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 62. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 62 while retaining at least one epitope of SEQ ID NO: 62. The first 22 N-terminal amino acids of SEQ ID NO: 62 can usefully be omitted.

20 Other fragments omit one or more protein domains.

sta027

[0194] The 'sta027' antigen is annotated as 'probable lipase'. In the NCTC 8325 strain sta027 is SAOUHSC\_00661 and has amino acid sequence SEQ ID NO: 63 (GI:88194426).

**[0195]** Useful sta027 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 63 and/or may 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: 63; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 63, 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). These sta027 proteins include variants of SEQ ID NO: 63. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 63. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 63 while retaining at least one epitope of SEQ ID NO: 63. The first 23 N-terminal amino acids of SEQ ID NO: 63 can usefully be omitted.
- <sup>35</sup> Other fragments omit one or more protein domains.

sta028

[0196] The 'sta028' antigen is annotated as 'secretory antigen SsaA-like protein'. In the NCTC 8325 strain sta028 is
 SAOUHSC\_00671 and has amino acid sequence SEQ ID NO: 64 (GI:88194436). In the Newman strain it is nwmn\_0634 (GI:151220846).

**[0197]** Useful sta028 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 64 and/or may 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: 64; and/or (b)

- <sup>45</sup> comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 64, 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). These sta028 proteins include variants of SEQ ID NO: 64. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 64. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 64 while retaining
- <sup>50</sup> at least one epitope of SEQ ID NO: 64. The first 25 N-terminal amino acids of SEQ ID NO: 64 can usefully be omitted. Other fragments omit one or more protein domains.

sta029

<sup>55</sup> **[0198]** The 'sta029' antigen is annotated as 'ferrichrome binding protein'. In the NCTC 8325 strain sta029 is SAOUHSC\_ 00754 and has amino acid sequence SEQ ID NO: 65 (GI:88194518).

**[0199]** Useful sta029 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 65 and/or may 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: 65; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 65, 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). These sta029 proteins include variants of SEQ ID NO: 65. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 65. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 65 while retaining at least one epitope of SEQ ID NO: 65. The final 25 C-terminal amino acids of SEQ ID NO: 65 can usefully be omitted. The first 19 N-terminal amino acids of SEQ ID NO: 65 can usefully be omitted. Other fragments omit one or more protein domains.

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sta030

**[0200]** The 'sta030' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta030 is SAOUHSC\_00808 and has amino acid sequence SEQ ID NO: 66 (GI:88194568).

- **IDENTIFY and SET USE 10 IDENTIFY and S**
- SEQ ID NO: 66. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 66. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 66 while retaining at least one epitope of SEQ ID NO: 66. The first 17 N-terminal amino acids of SEQ ID NO: 66 can usefully be omitted. Other fragments omit one or more protein domains.

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sta031

**[0202]** The 'sta031' antigen is annotated as '5-nucleotidase family protein'. In the NCTC 8325 strain sta031 is SAOUHSC\_00860 and has amino acid sequence SEQ ID NO: 67 (GI:88194617).

- <sup>30</sup> [0203] Useful sta031 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 67 and/or may 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: 67; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 67, 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). These sta031 proteins include variants
- <sup>35</sup> of SEQ ID NO: 67. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 67. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 67 while retaining at least one epitope of SEQ ID NO: 67. Other fragments omit one or more protein domains.

<sup>40</sup> sta032

**[0204]** The 'sta032' antigen is annotated as 'serine protease HtrA'. In the NCTC 8325 strain sta032 is SAOUHSC\_00958 and has amino acid sequence SEQ ID NO: 68 (GI:88194715).

[0205] Useful sta032 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID
NO: 68 and/or may 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: 68; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 68, 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). These sta032 proteins include variants of SEQ ID NO: 68. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 68. Other preferred fragments lack
one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 68 while retaining

at least one epitope of SEQ ID NO: 68. Other fragments omit one or more protein domains.

sta033

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**[0206]** The 'sta033' antigen is annotated as 'cysteine protease precursor'. In the NCTC 8325 strain sta033 is SAOUHSC\_00987 and has amino acid sequence SEQ ID NO: 69 (GI:88194744).

[0207] Useful sta033 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID

NO: 69 and/or may 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: 69; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 69, 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). These sta033 proteins include variants of SEQ ID NO: 69. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 69. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 69 while retaining at least one epitope of SEQ ID NO: 69. The first 29 N-terminal amino acids of SEQ ID NO: 69 can usefully be omitted. Other fragments omit one or more protein domains.

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sta034

**[0208]** The 'sta034' antigen is annotated as 'glutamyl endopeptidase precursor'. In the NCTC 8325 strain sta034 is SAOUHSC\_00988 and has amino acid sequence SEQ ID NO: 70 (GI:88194745).

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- of SEQ ID NO: 70. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 70. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 70 while retaining at least one epitope of SEQ ID NO: 70. The first 29 N-terminal amino acids of SEQ ID NO: 70 can usefully be omitted. Other fragments omit one or more protein domains.

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sta035

**[0210]** The 'sta035' antigen is annotated as 'fmt protein'. In the NCTC 8325 strain sta035 is SAOUHSC\_00998 and has amino acid sequence SEQ ID NO: 71 (GI:88194754).

- 30 [0211] Useful sta035 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 71 and/or may 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: 71; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 71, 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). These sta035 proteins include variants
- <sup>35</sup> of SEQ ID NO: 71. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 71. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 71 while retaining at least one epitope of SEQ ID NO: 71. The first 25 N-terminal amino acids of SEQ ID NO: 71 can usefully be omitted. Other fragments omit one or more protein domains.

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sta036

**[0212]** The 'sta036' antigen is annotated as 'iron-regulated protein with leader'. In the NCTC 8325 strain sta036 is SAOUHSC\_01084 and has amino acid sequence SEQ ID NO: 72 (GI:88194831).

- <sup>45</sup> [0213] Useful sta036 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 72 and/or may 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: 72; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 72, 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). These sta036 proteins include variants
- of SEQ ID NO: 72. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 72. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 72 while retaining at least one epitope of SEQ ID NO: 72. The final 27 C-terminal amino acids of SEQ ID NO: 72 can usefully be omitted. The first 32 N-terminal amino acids of SEQ ID NO: 72 can usefully be omitted. Other fragments omit one or more protein domains.

#### sta037

**[0214]** The 'sta037' antigen is annotated as 'iron ABC transporter; iron -binding protein IsdE'. In the NCTC 8325 strain sta037 is SAOUHSC\_01085 and has amino acid sequence SEQ ID NO: 73 (GI:88194832).

- <sup>5</sup> [0215] Useful sta037 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 73 and/or may 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: 73; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 73, 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). These sta037 proteins include variants
- of SEQ ID NO: 73. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 73. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 73 while retaining at least one epitope of SEQ ID NO: 73. The first 9 N-terminal amino acids of SEQ ID NO: 73 can usefully be omitted. Other fragments omit one or more protein domains.
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sta038

**[0216]** The 'sta038' antigen is annotated as 'NPQTN specific sortase B'. In the NCTC 8325 strain sta038 is SAOUHSC\_ 01088 and has amino acid sequence SEQ ID NO: 74 (GI:88194835).

- **[0217]** Useful sta038 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 74 and/or may 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: 74; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 74, 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 or more). These sta038 proteins include variants of
- SEQ ID NO: 74. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 74. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 74 while retaining at least one epitope of SEQ ID NO: 74. The first 21 N-terminal amino acids of SEQ ID NO: 74 can usefully be omitted. Other fragments omit one or more protein domains.

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sta039

**[0218]** The 'sta039' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta039 is SAOUHSC\_01124 and has amino acid sequence SEQ ID NO: 75 (GI:88194868).

- IO219] Useful sta039 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 75 and/or may 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: 75; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 75, 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 or more). These sta039 proteins include variants of
- 40 SEQ ID NO: 75. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 75. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 75 while retaining at least one epitope of SEQ ID NO: 75. The first 22 N-terminal amino acids of SEQ ID NO: 75 can usefully be omitted. Other fragments omit one or more protein domains.
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sta040

**[0220]** The 'sta040' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta040 is SAOUHSC\_ 01125 and has amino acid sequence SEQ ID NO: 76 (GI:88194869). In the Newman strain it is nwmn\_1076 (GI: 151221288).

**[0221]** Useful sta040 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 76 and/or may 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: 76; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 76, wherein 'n' is 7 or more (*e.g.* 8, 10,

<sup>55</sup> 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta040 proteins include variants of SEQ ID NO: 76. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 76. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 76 while retaining

at least one epitope of SEQ ID NO: 76. The first 21 N-terminal amino acids of SEQ ID NO: 76 can usefully be omitted. Other fragments omit one or more protein domains.

sta041

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**[0222]** The 'sta041' antigen is annotated as 'fibronectin-binding protein A-related'. In the NCTC 8325 strain sta041 is SAOUHSC\_01175 and has amino acid sequence SEQ ID NO: 77 (GI:88194914).

[0223] Useful sta041 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 77 and/or may 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: 77; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 77, 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). These sta041 proteins include variants of SEQ ID NO: 77. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 77. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 77 while retaining

at least one epitope of SEQ ID NO: 77. Other fragments omit one or more protein domains.

sta042

<sup>20</sup> **[0224]** The 'sta042' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta042 is SAOUHSC\_01180 and has amino acid sequence SEQ ID NO: 78 (GI:88194919).

**[0225]** Useful sta042 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 78 and/or may 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: 78; and/or (b)

- <sup>25</sup> comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 78, 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). These sta042 proteins include variants of SEQ ID NO: 78. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 78. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 78 while retaining
- <sup>30</sup> at least one epitope of SEQ ID NO: 78. The first 18 N-terminal amino acids of SEQ ID NO: 78 can usefully be omitted. Other fragments omit one or more protein domains.

sta043

<sup>35</sup> **[0226]** The 'sta043' antigen is annotated as 'cell wall hydrolase'. In the NCTC 8325 strain sta043 is SAOUHSC\_01219 and has amino acid sequence SEQ ID NO: 79 (GI:88194955).

**[0227]** Useful sta043 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 79 and/or may 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: 79; and/or (b)

- <sup>40</sup> comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 79, 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). These sta043 proteins include variants of SEQ ID NO: 79. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 79. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 79 while retaining
- <sup>45</sup> at least one epitope of SEQ ID NO: 79. The first 38 N-terminal amino acids of SEQ ID NO: 79 can usefully be omitted. Other fragments omit one or more protein domains.

sta044

50 **[0228]** The 'sta044' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta044 is SAOUHSC\_01508 and has amino acid sequence SEQ ID NO: 80 (GI:88195223).

**[0229]** Useful sta044 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 80 and/or may 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: 80; and/or (b)

<sup>55</sup> comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 80, 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). These sta044 proteins include variants of SEQ ID NO: 80. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 80. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more

amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 80 while retaining at least one epitope of SEQ ID NO: 80. The first 17 N-terminal amino acids of SEQ ID NO: 80 can usefully be omitted. Other fragments omit one or more protein domains.

## <sup>5</sup> sta045

**[0230]** The 'sta045' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta045 is SAOUHSC\_01627 and has amino acid sequence SEQ ID NO: 81 (GI:88195337).

- [0231] Useful sta045 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID
  NO: 81 and/or may 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: 81; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 81, 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 or more). These sta045 proteins include variants of SEQ ID NO: 81. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 81. Other preferred fragments lack one or
- <sup>15</sup> more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 81 while retaining at least one epitope of SEQ ID NO: 81. The first 16 N-terminal amino acids of SEQ ID NO: 81 can usefully be omitted. Other fragments omit one or more protein domains.

20 sta046

**[0232]** The 'sta046' antigen is annotated as 'Excalibur protein'. In the NCTC 8325 strain sta046 is SAOUHSC\_01918 and has amino acid sequence SEQ ID NO: 82 (GI:88195613).

- [0233] Useful sta046 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID
  NO: 82 and/or may 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: 82; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 82, 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 or more). These sta046 proteins include variants of SEQ ID NO: 82. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 82. Other preferred fragments lack one or
- <sup>30</sup> more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 82 while retaining at least one epitope of SEQ ID NO: 82. The first 53 N-terminal amino acids of SEQ ID NO: 82 can usefully be omitted. Other fragments omit one or more protein domains.
- 35 sta047

**[0234]** The 'sta047' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta047 is SAOUHSC\_01920 and has amino acid sequence SEQ ID NO: 83 (GI:88195615).

- [0235] Useful sta047 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID
   NO: 83 and/or may 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: 83; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 83, 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 or more). These sta047 proteins include variants of SEQ ID NO: 83. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 83. Other preferred fragments lack one or
- <sup>45</sup> more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 83 while retaining at least one epitope of SEQ ID NO: 83. The first 18 N-terminal amino acids of SEQ ID NO: 83 can usefully be omitted. Other fragments omit one or more protein domains.
- 50 sta048

**[0236]** The 'sta048' antigen is annotated as 'intracellular serine protease'. In the NCTC 8325 strain sta048 is SAOUHSC\_01949 and has amino acid sequence SEQ ID NO: 84 (GI:88195642).

[0237] Useful sta048 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID
<sup>55</sup> NO: 84 and/or may 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: 84; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 84, 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). These sta048 proteins include variants

of SEQ ID NO: 84. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 84. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 84 while retaining at least one epitope of SEQ ID NO: 84. The first 27 N-terminal amino acids of SEQ ID NO: 84 can usefully be omitted. Other fragments omit one or more protein domains.

sta049

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[0238] The 'sta049' antigen is annotated as 'protein export protein PrsA'. In the NCTC 8325 strain sta049 is SAOUHSC\_
 01972 and has amino acid sequence SEQ ID NO: 85 (GI:88195663). In the Newman strain it is nwmn\_1733 (GI: 151221945).

**[0239]** Useful sta049 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 85 and/or may 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: 85; and/or (b)

<sup>15</sup> comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 85, 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). These sta049 proteins include variants of SEQ ID NO: 85. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 85. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 85 while retaining

at least one epitope of SEQ ID NO: 85. The first 25 N-terminal amino acids of SEQ ID NO: 85 can usefully be omitted. Other fragments omit one or more protein domains.

sta050

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- [0240] The 'sta050' antigen is annotated as 'staphopain thiol proteinase'. In the NCTC 8325 strain sta050 is SAOUHSC\_02127 and has amino acid sequence SEQ ID NO: 86 (GI:88195808).
   [0241] Useful sta050 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 96 and/or more administered to a human) that recognises SEQ ID NO: 96 and/or more administered to a human.
  - NO: 86 and/or may 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: 86; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 86, 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). These sta050 proteins include variants of SEQ ID NO: 86. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 86. Other preferred fragments lack
- one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 86 while retaining
   <sup>35</sup> at least one epitope of SEQ ID NO: 86. The first 25 N-terminal amino acids of SEQ ID NO: 86 can usefully be omitted. Other fragments omit one or more protein domains.

sta051

- 40 [0242] The 'sta051' antigen is annotated as 'protein with leader'. In the NCTC 8325 strain sta051 is SAOUHSC\_02147 and has amino acid sequence SEQ ID NO: 87 (GI:88195827).
  [0243] Useful sta051 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID
- NO: 87 and/or may 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: 87; and/or (b) 5 comprising a fragment of at least 'a' consecutive amino acids of SEO ID NO: 87 wherein 'a' is 7 or more (e.g. 8, 10)
- <sup>45</sup> comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 87, 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). These sta051 proteins include variants of SEQ ID NO: 87. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 87. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 87 while retaining
- <sup>50</sup> at least one epitope of SEQ ID NO: 87. The first 24 N-terminal amino acids of SEQ ID NO: 87 can usefully be omitted. Other fragments omit one or more protein domains.

sta052

<sup>55</sup> [0244] The 'sta052' antigen is annotated as 'ferric hydroxamate receptor 1'. In the NCTC 8325 strain sta052 is SAOUHSC\_02246 and has amino acid sequence SEQ ID NO: 88 (GI:88195918).
 [0245] Useful sta052 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID

NO: 88 and/or may 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: 88; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 88, 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). These sta052 proteins include variants of SEQ ID NO: 88. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 88. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 88 while retaining at least one epitope of SEQ ID NO: 88. The first 17 N-terminal amino acids of SEQ ID NO: 88 can usefully be omitted. Other fragments omit one or more protein domains.

#### 10 sta053

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**[0246]** The 'sta053' antigen is annotated as 'srdH family protein'. In the NCTC 8325 strain sta053 is SAOUHSC\_02257 and has amino acid sequence SEQ ID NO: 89 (GI:88195928).

- [0247] Useful sta053 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 89 and/or may 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: 89; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 89, 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). These sta053 proteins include variants of SEQ ID NO: 89. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 89. Other preferred fragments lack
- one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 89 while retaining at least one epitope of SEQ ID NO: 89. The first 26 N-terminal amino acids of SEQ ID NO: 89 can usefully be omitted. Other fragments omit one or more protein domains.

## <sup>25</sup> sta054

**[0248]** The 'sta054' antigen is annotated as 'Probable transglycosylase isaA precursor'. In the NCTC 8325 strain sta054 is SAOUHSC\_02333 and has amino acid sequence SEQ ID NO: 90 (GI:88195999). Useful sta054 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 90 and/or may comprise an amino

- <sup>30</sup> 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: 90; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 90, 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 or more). These sta054 proteins include variants of SEQ ID NO: 90. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 90. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9,
- <sup>35</sup> 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 90 while retaining at least one epitope of SEQ ID NO: 90. The first 27 N-terminal amino acids of SEQ ID NO: 90 can usefully be omitted. Other fragments omit one or more protein domains.

#### sta055

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**[0249]** The 'sta055' antigen is annotated as 'surface hydrolase'. In the NCTC 8325 strain sta055 is SAOUHSC\_02448 and has amino acid sequence SEQ ID NO: 91 (GI:88196100).

[0250] Useful sta055 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 91 and/or may 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: 91; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 91, 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). These sta055 proteins include variants of SEQ ID NO: 91. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 91. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more

<sup>50</sup> amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 91 while retaining at least one epitope of SEQ ID NO: 91. The first 31 N-terminal amino acids of SEQ ID NO: 91 can usefully be omitted. Other fragments omit one or more protein domains.

sta056

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**[0251]** The 'sta056' antigen is annotated as 'hyaluronate lyase'. In the NCTC 8325 strain sta056 is SAOUHSC\_02463 and has amino acid sequence SEQ ID NO: 92 (GI:88196115).

[0252] Useful sta056 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID

NO: 92 and/or may 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: 92; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 92, 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). These sta056 proteins include variants of SEQ ID NO: 92. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 92. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 92 while retaining at least one epitope of SEQ ID NO: 92. The first 24 N-terminal amino acids of SEQ ID NO: 92 can usefully be omitted. Other fragments omit one or more protein domains.

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sta057

**[0253]** The 'sta057' antigen is annotated as 'secretory antigen precursor SsaA'. In the NCTC 8325 strain sta057 is SAOUHSC\_02576 and has amino acid sequence SEQ ID NO: 93 (GI:88196220). In the Newman strain it is nwmn\_2203 (GI:151222415).

**[0254]** Useful sta057 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 93 and/or may 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: 93; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 93, 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 or more). These sta057 proteins include variants of SEQ ID NO: 93. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 93. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 93 while retaining at least one epitope of SEQ ID NO: 93. The first 27 N-terminal amino acids of SEQ ID NO: 93 can usefully be omitted. Other
- <sup>25</sup> fragments omit one or more protein domains.

sta058

[0255] The 'sta058' antigen is annotated as 'Zn-binding lipoprotein adcA-like'. In the NCTC 8325 strain sta058 is SAOUHSC\_02690 and has amino acid sequence SEQ ID NO: 94 (GI:88196330).

**[0256]** Useful sta058 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 94 and/or may 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: 94; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 94, 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). These sta058 proteins include variants of SEQ ID NO: 94. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 94. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 94 while retaining at least one epitope of SEQ ID NO: 94. The first 20 N-terminal amino acids of SEQ ID NO: 94 can usefully be omitted.
Other fragments omit one or more protein domains.

sta059

- [0257] The 'sta059' antigen is annotated as 'gamma-hemolysin h-gamma-ii subunit'. In the NCTC 8325 strain sta059 is SAOUHSC\_02708 and has amino acid sequence SEQ ID NO: 95 (GI:88196348).
- **[0258]** Useful sta059 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 95 and/or may 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: 95; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 95, 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). These sta059 proteins include variants of SEQ ID NO: 95. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 95. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 95 while retaining at least one epitope of SEQ ID NO: 95. The first 20 N-terminal amino acids of SEQ ID NO: 95 can usefully be omitted.
- <sup>55</sup> Other fragments omit one or more protein domains.
#### sta060

**[0259]** The 'sta060' antigen is annotated as 'peptide ABC transporter; peptide-binding protein'. In the NCTC 8325 strain sta060 is SAOUHSC\_02767 and has amino acid sequence SEQ ID NO: 96 (GI:88196403).

- <sup>5</sup> [0260] Useful sta060 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 96 and/or may 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: 96; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 96, 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). These sta060 proteins include variants
- of SEQ ID NO: 96. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 96. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 96 while retaining at least one epitope of SEQ ID NO: 96. The first 20 N-terminal amino acids of SEQ ID NO: 96 can usefully be omitted. Other fragments omit one or more protein domains.
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sta061

**[0261]** The 'sta061' antigen is annotated as 'protein with leader'. In the NCTC 8325 strain sta061 is SAOUHSC\_02783 and has amino acid sequence SEQ ID NO: 97 (GI:88196419).

20 [0262] Useful sta061 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 97 and/or may 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: 97; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 97, 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). These sta061 proteins include variants

of SEQ ID NO: 97. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 97. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 97 while retaining at least one epitope of SEQ ID NO: 97. The first 21 N-terminal amino acids of SEQ ID NO: 97 can usefully be omitted. Other fragments omit one or more protein domains.

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sta062

**[0263]** The 'sta062' antigen is annotated as 'protein with leader'. In the NCTC 8325 strain sta062 is SAOUHSC\_02788 and has amino acid sequence SEQ ID NO: 98 (GI:88196424).

- <sup>35</sup> **[0264]** Useful sta062 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 98 and/or may 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: 98; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 98, 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). These sta062 proteins include variants
- 40 of SEQ ID NO: 98. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 98. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 98 while retaining at least one epitope of SEQ ID NO: 98. The first 22 N-terminal amino acids of SEQ ID NO: 98 can usefully be omitted. Other fragments omit one or more protein domains.

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sta063

**[0265]** The 'sta063' antigen is annotated as 'aureolysin'. In the NCTC 8325 strain sta063 is SAOUHSC\_02971 and has amino acid sequence SEQ ID NO: 99 (GI:88196592).

- <sup>50</sup> **[0266]** Useful sta063 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 99 and/or may 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: 99; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 99, 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). These sta063 proteins include variants
- <sup>55</sup> of SEQ ID NO: 99. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 99. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 99 while retaining at least one epitope of SEQ ID NO: 99. The first 16 N-terminal amino acids of SEQ ID NO: 99 can usefully be omitted.

Other fragments omit one or more protein domains.

be omitted. Other fragments omit one or more protein domains.

sta064

- <sup>5</sup> [0267] The 'sta064' antigen is annotated as 'lipase'. In the NCTC 8325 strain sta064 is SAOUHSC\_03006 and has amino acid sequence SEQ ID NO: 100 (GI:88196625). In the Newman strain it is nwmn\_2569 (GI:151222781).
  [0268] Useful sta064 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 100 and/or may 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: 100; and/or (b)
- comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 100, 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). These sta064 proteins include variants of SEQ ID NO: 100. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 100. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 100 while
   retaining at least one epitope of SEQ ID NO: 100. The first 34 N-terminal amino acids of SEQ ID NO: 100 can usefully
- retaining at least one epitope of SEQ ID NO: 100. The first 34 N-terminal amino acids of SEQ ID NO: be omitted. Other fragments omit one or more protein domains.

sta065

- [0269] The 'sta065' antigen is annotated as '1-phosphatidylinositol phosphodiesterase precursor'. In the NCTC 8325 strain sta065 is SAOUHSC\_00051 and has amino acid sequence SEQ ID NO: 101 (GI:88193871).
   [0270] Useful sta065 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 101 and/or may 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: 101; and/or (b)
  comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 101, 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). These sta065 proteins include variants of SEQ ID NO: 101. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 101. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 101 while
  retaining at least one epitope of SEQ ID NO: 101. The first 26 N-terminal amino acids of SEQ ID NO: 101 can usefully

sta066

<sup>35</sup> **[0271]** The 'sta066' antigen is annotated as 'protein'. In the NCTC 8325 strain sta066 is SAOUHSC\_00172 and has amino acid sequence SEQ ID NO: 102 (GI:88193982).

**[0272]** Useful sta066 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 102 and/or may 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: 102; and/or (b)

- <sup>40</sup> comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 102, 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). These sta066 proteins include variants of SEQ ID NO: 102. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 102. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 102 while
- <sup>45</sup> retaining at least one epitope of SEQ ID NO: 102. The first 21 N-terminal amino acids of SEQ ID NO: 102 can usefully be omitted. Other fragments omit one or more protein domains.

sta067

- <sup>50</sup> [0273] The 'sta067' antigen is annotated as 'bacterial extracellular solute-binding protein'. In the NCTC 8325 strain sta067 is SAOUHSC\_00176 and has amino acid sequence SEQ ID NO: 103 (GI:88193986).
  [0274] Useful sta067 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 103 and/or may 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: 103; and/or (b)
- <sup>55</sup> comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 103, 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). These sta067 proteins include variants of SEQ ID NO: 103. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 103. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or

more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 103 while retaining at least one epitope of SEQ ID NO: 103. The first 20 N-terminal amino acids of SEQ ID NO: 103 can usefully be omitted. Other fragments omit one or more protein domains.

# <sup>5</sup> sta068

**[0275]** The 'sta068' antigen is annotated as 'iron permease FTR1'. In the NCTC 8325 strain sta068 is SAOUHSC\_ 00327 and has amino acid sequence SEQ ID NO: 104 (GI:88194127).

- [0276] Useful sta068 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID
  NO: 104 and/or may 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: 104; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 104, 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). These sta068 proteins include variants of SEQ ID NO: 104. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 104. Other preferred fragments
- <sup>15</sup> lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 104 while retaining at least one epitope of SEQ ID NO: 104. The final 20 C-terminal amino acids of SEQ ID NO: 104 can usefully be omitted. The first 14 N-terminal amino acids of SEQ ID NO: 104 can usefully be omitted. Other fragments omit one or more protein domains.

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sta069

sta070

**[0277]** The 'sta069' antigen is annotated as 'autolysin precursor'. In the NCTC 8325 strain sta069 is SAOUHSC\_ 00427 and has amino acid sequence SEQ ID NO: 105 (GI:88194219).

- [0278] Useful sta069 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 105 and/or may 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: 105; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 105, 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). These sta069 proteins include variants
- <sup>30</sup> of SEQ ID NO: 105. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 105. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 105 while retaining at least one epitope of SEQ ID NO: 105. The first 25 N-terminal amino acids of SEQ ID NO: 105 can usefully be omitted. Other fragments omit one or more protein domains.

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**[0279]** The 'sta070' antigen is annotated as 'immunogenic secreted precursor-like protein (truncated)'. In the NCTC 8325 strain sta070 is SAOUHSC\_00773 and has amino acid sequence SEQ ID NO: 106 (GI:88194535).

- <sup>40</sup> [0280] Useful sta070 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 106 and/or may 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: 106; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 106, 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). These sta070 proteins include variants
- <sup>45</sup> of SEQ ID NO: 106. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 106. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 106 while retaining at least one epitope of SEQ ID NO: 106. The first 24 N-terminal amino acids of SEQ ID NO: 106 can usefully be omitted. Other fragments omit one or more protein domains.

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sta071

**[0281]** The 'sta071' antigen is annotated as 'hemolysin'. In the NCTC 8325 strain sta071 is SAOUHSC\_00854 and has amino acid sequence SEQ ID NO: 107 (GI:88194612).

<sup>55</sup> **[0282]** Useful sta071 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 107 and/or may 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: 107; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 107, 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). These sta071 proteins include variants of SEQ ID NO: 107. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 107. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 107 while retaining at least one epitope of SEQ ID NO: 107. The first 24 N-terminal amino acids of SEQ ID NO: 107 can usefully be omitted. Other fragments omit one or more protein domains.

sta072

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10 [0283] The 'sta072' antigen is annotated as 'extramembranal protein'. In the NCTC 8325 strain sta072 is SAOUHSC\_ 00872 and has amino acid sequence SEQ ID NO: 108 (GI:88194629).

**[0284]** Useful sta072 antigens can elicit an antibody *(e.g.* when administered to a human) that recognises SEQ ID NO: 108 and/or may 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: 108; and/or (b)

comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 108, 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). These sta072 proteins include variants of SEQ ID NO: 108. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 108. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 108 while
retaining at least one epitope of SEQ ID NO: 108. The first 24 N-terminal amino acids of SEQ ID NO: 108 can usefully

be omitted. Other fragments omit one or more protein domains.

sta073

- <sup>25</sup> [0285] The 'sta073' antigen is annotated as 'bifunctional autolysin precursor'. In the NCTC 8325 strain sta073 is SAOUHSC\_00994 and has amino acid sequence SEQ ID NO: 109 (GI:88194750). In the Newman strain it is nwmn\_0922 (GI: 151221134). Proteomic analysis has revealed that this protein is secreted or surface-exposed. [0286] Useful sta073 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID
- NO: 109 and/or may 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: 109; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 109, 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). These sta073 proteins include variants of SEQ ID NO: 109. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 109. Other preferred fragments
- lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or
   <sup>35</sup> more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 109 while retaining at least one epitope of SEQ ID NO: 109. The first 24 N-terminal amino acids of SEQ ID NO: 109 can usefully be omitted. Other fragments omit one or more protein domains.

[0287] A Sta073 antigen can usefully be included in a composition in combination with a Sta112 [74].

[0288] Sta073 does not adsorb well to aluminium hydroxide adjuvants, so Sta073 present in a composition may be unadsorbed or may be adsorbed to an alternative adjuvant *e.g.* to an aluminium phosphate.

sta074

- [0289] The 'sta074' antigen is annotated as 'factor essential for methicillin resistance'. In the NCTC 8325 strain sta074 is SAOUHSC\_01220 and has amino acid sequence SEQ ID NO: 110 (GI:88194956).
- [0290] Useful sta074 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 110 and/or may 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: 110; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 110, wherein 'n' is 7 or more (e.g. 8, 10, 12, 14, 16, 18, 20, 25, 40, 50, 60, 70, 80, 90, 00, 100, 150, and 50, 200, 250 or more).
- 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta074 proteins include variants of SEQ ID NO: 110. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 110. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 110 while retaining at least one epitope of SEQ ID NO: 110. Other fragments omit one or more protein domains.

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sta075

<sup>[0291]</sup> The 'sta075' antigen is annotated as 'insulysin; peptidase family M16'. In the NCTC 8325 strain sta075 is

SAOUHSC\_01256 and has amino acid sequence SEQ ID NO: 111 (GI:88194989).

[0292] Useful sta075 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 111 and/or may 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: 111; and/or (b) 5 comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 111, 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). These sta075 proteins include variants of SEQ ID NO: 111. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 111. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 111 while 10 retaining at least one epitope of SEQ ID NO: 111. Other fragments omit one or more protein domains.

#### sta076

[0293] The 'sta076' antigen is annotated as 'hydrolase'. In the NCTC 8325 strain sta076 is SAOUHSC\_01263 and 15 has amino acid sequence SEQ ID NO: 112 (GI:88194996).

- [0294] Useful sta076 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 112 and/or may 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: 112; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 112, wherein 'n' is 7 or more (e.g. 8, 10,
- 20 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta076 proteins include variants of SEQ ID NO: 112. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 112. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 112 while retaining at least one epitope of SEQ ID NO: 112. The first 24 N-terminal amino acids of SEQ ID NO: 112 can usefully 25
- be omitted. Other fragments omit one or more protein domains.

#### sta077

[0295] The 'sta077' antigen is annotated as 'protein'. In the NCTC 8325 strain sta077 is SAOUHSC\_01317 and has 30 amino acid sequence SEQ ID NO: 113 (GI:88195047). Proteomic analysis has revealed that this protein is secreted or surface-exposed.

[0296] Useful sta077 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 113 and/or may 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: 113; and/or (b)

- comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 113, wherein 'n' is 7 or more (e.g. 8, 10, 35 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta077 proteins include variants of SEQ ID NO: 113. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 113. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 113 while
- 40 retaining at least one epitope of SEQ ID NO: 113. The first 20 N-terminal amino acids of SEQ ID NO: 113 can usefully be omitted. Other fragments omit one or more protein domains.

sta078

45 [0297] The 'sta078' antigen is annotated as 'FtsK/SpoIIIE family protein'. In the NCTC 8325 strain sta078 is SAOUHSC\_ 01857 and has amino acid sequence SEQ ID NO: 114 (GI:88195555).

[0298] Useful sta078 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 114 and/or may 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: 114; and/or (b)

- 50 comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 114, 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). These sta078 proteins include variants of SEQ ID NO: 114. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 114. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 114 while
- 55 retaining at least one epitope of SEQ ID NO: 114. Other fragments omit one or more protein domains.

#### sta079

**[0299]** The 'sta079' antigen is annotated as 'serine protease SpIF'. In the NCTC 8325 strain sta079 is SAOUHSC\_ 01935 and has amino acid sequence SEQ ID NO: 115 (GI:88195630).

- <sup>5</sup> [0300] Useful sta079 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 115 and/or may 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: 115; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 115, 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 or more). These sta079 proteins include variants of
- <sup>10</sup> SEQ ID NO: 115. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 115. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 115 while retaining at least one epitope of SEQ ID NO: 115. The first 36 N-terminal amino acids of SEQ ID NO: 115 can usefully be omitted. Other fragments omit one or more protein domains.
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sta080

**[0301]** The 'sta080' antigen is annotated as 'serine protease SpIE'. In the NCTC 8325 strain sta080 is SAOUHSC\_ 01936 and has amino acid sequence SEQ ID NO: 116 (GI:88195631).

[0302] Useful sta080 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 116 and/or may 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: 116; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 116, 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 or more). These sta080 proteins include variants of

SEQ ID NO: 116. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 116. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 116 while retaining at least one epitope of SEQ ID NO: 116. The first 36 N-terminal amino acids of SEQ ID NO: 116 can usefully be omitted. Other fragments omit one or more protein domains.

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sta081

**[0303]** The 'sta081' antigen is annotated as 'serine protease SpID (EC:3.4.21.19)'. In the NCTC 8325 strain sta081 is SAOUHSC\_01938 and has amino acid sequence SEQ ID NO: 170 (GI:88195633).

- ICONT [10304] Useful sta081 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 170 and/or may 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: 170; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 170, 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 or more). These sta081 proteins include variants of
- 40 SEQ ID NO: 170. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 170. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 170 while retaining at least one epitope of SEQ ID NO: 170. The first 36 N-terminal amino acids of SEQ ID NO: 170 can usefully be omitted. Other fragments omit one or more protein domains.

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sta082

**[0305]** The 'sta082' antigen is annotated as 'serine protease SpIC'. In the NCTC 8325 strain sta082 is SAOUHSC\_ 01939 and has amino acid sequence SEQ ID NO: 117 (GI:88195634).

- 50 [0306] Useful sta082 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 117 and/or may 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: 117; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 117, 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 or more). These sta082 proteins include variants of
- SEQ ID NO: 117. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 117. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 117 while retaining at least one epitope of SEQ ID NO: 117. The first 36 N-terminal amino acids of SEQ ID NO: 117 can usefully be omitted.

Other fragments omit one or more protein domains.

sta083

- <sup>5</sup> [0307] The 'sta083' antigen is annotated as 'serine protease SplB'. In the NCTC 8325 strain sta083 is SAOUHSC\_01941 and has amino acid sequence SEQ ID NO: 118 (GI:88195635).
  [0308] Useful sta083 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 118 and/or may 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: 118; and/or (b)
- <sup>10</sup> comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 118, 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 or more). These sta083 proteins include variants of SEQ ID NO: 118. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 118. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 118 while retaining
- <sup>15</sup> at least one epitope of SEQ ID NO: 118. The first 36 N-terminal amino acids of SEQ ID NO: 118 can usefully be omitted. Other fragments omit one or more protein domains.

sta084

- [0309] The 'sta084' antigen is annotated as 'serine protease SpIA'. In the NCTC 8325 strain sta084 is SAOUHSC\_01942 and has amino acid sequence SEQ ID NO: 119 (GI:88195636).
  [0310] Useful sta084 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 119 and/or may 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: 119; and/or (b)
  <sup>25</sup> comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 119, 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 or more). These sta084 proteins include variants of SEQ ID NO: 119. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 119. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 119 while retaining
- <sup>30</sup> at least one epitope of SEQ ID NO: 119. The first 35 N-terminal amino acids of SEQ ID NO: 119 can usefully be omitted. Other fragments omit one or more protein domains.

sta085

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<sup>35</sup> **[0311]** The 'sta085' antigen is annotated as 'staphylokinase precursor'. In the NCTC 8325 strain sta085 is SAOUHSC\_ 02171 and has amino acid sequence SEQ ID NO: 120 (GI:88195848).

**[0312]** Useful sta085 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 120 and/or may 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: 120; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 120, 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 or more). These sta085 proteins include variants of SEQ ID NO: 120. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 120. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 120 while retaining at least
- <sup>45</sup> one epitope of SEQ ID NO: 120. The first 27 N-terminal amino acids of SEQ ID NO: 120 can usefully be omitted. Other fragments omit one or more protein domains.

sta086

50 [0313] The 'sta086' antigen is annotated as 'OxaA-like protein'. In the NCTC 8325 strain sta086 is SAOUHSC\_02327 and has amino acid sequence SEQ ID NO: 121 (GI:88195993).
(0214) Useful sta086 estimate can align an artified (or a when administered to a human) that recognizes SEQ ID

**[0314]** Useful sta086 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 121 and/or may 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: 121; and/or (b)

<sup>55</sup> comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 121, 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). These sta086 proteins include variants of SEQ ID NO: 121. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 121. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or

more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 121 while retaining at least one epitope of SEQ ID NO: 121. The first 19 N-terminal amino acids of SEQ ID NO: 121 can usefully be omitted. Other fragments omit one or more protein domains.

# 5 sta087

**[0315]** The 'sta087' antigen is annotated as 'teicoplanin resistance protein TcaA'. In the NCTC 8325 strain sta087 is SAOUHSC\_02635 and has amino acid sequence SEQ ID NO: 122 (GI:88196276).

- [0316] Useful sta087 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID
  NO: 122 and/or may 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: 122; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 122, 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). These sta087 proteins include variants of SEQ ID NO: 122. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 122. Other preferred fragments
- <sup>15</sup> lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 122 while retaining at least one epitope of SEQ ID NO: 122. Other fragments omit one or more protein domains.

#### sta088

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**[0317]** The 'sta088' antigen is annotated as 'esterase'. In the NCTC 8325 strain sta088 is SAOUHSC\_02844 and has amino acid sequence SEQ ID NO: 123 (GI:88196477).

**[0318]** Useful sta088 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 123 and/or may 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: 123; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 123, 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). These sta088 proteins include variants of SEQ ID NO: 123. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 123. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 123 while retaining at least one epitope of SEQ ID NO: 123. The first 18 N-terminal amino acids of SEQ ID NO: 123 can usefully

be omitted. Other fragments omit one or more protein domains.

sta089

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**[0319]** The 'sta089' antigen is annotated as 'LysM domain protein'. In the NCTC 8325 strain sta089 is SAOUHSC\_ 02855 and has amino acid sequence SEQ ID NO: 124 (GI:88196486).

[0320] Useful sta089 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 124 and/or may 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: 124; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 124, 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 or more). These sta089 proteins include variants of SEQ ID NO: 124. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 124. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino

acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 124 while retaining at least one epitope of SEQ ID NO: 124. The first 20 N-terminal amino acids of SEQ ID NO: 124 can usefully be omitted. Other fragments omit one or more protein domains.

#### sta090

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**[0321]** The 'sta090' antigen is annotated as 'LysM domain protein'. In the NCTC 8325 strain sta090 is SAOUHSC\_ 02883 and has amino acid sequence SEQ ID NO: 125 (GI:88196512).

**[0322]** Useful sta090 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 125 and/or may 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: 125; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 125, 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). These sta090 proteins include variants of SEQ ID NO: 125. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 125. Other preferred fragments

lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 125 while retaining at least one epitope of SEQ ID NO: 125. The first 26 N-terminal amino acids of SEQ ID NO: 125 can usefully be omitted. Other fragments omit one or more protein domains.

# sta091

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**[0323]** The 'sta091' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta091 is SAOUHSC\_00685 and has amino acid sequence SEQ ID NO: 126 (GI:88194450).

- 10 [0324] Useful sta091 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 126 and/or may 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: 126; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 126, 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 or more). These sta091 proteins include variants of SEQ ID
- NO: 126. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 126. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 126 while retaining at least one epitope of SEQ ID NO: 126. The first 15 N-terminal amino acids of SEQ ID NO: 126 can usefully be omitted. Other fragments omit one or more protein domains.

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sta092

**[0325]** The 'sta092' antigen is annotated as 'M23/M37 peptidase domain protein'. In the NCTC 8325 strain sta092 is SAOUHSC\_00174 and has amino acid sequence SEQ ID NO: 127 (GI:88193984).

- [0326] Useful sta092 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 127 and/or may 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: 127; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 127, 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 or more). These sta092 proteins include variants of SEQ
- <sup>30</sup> ID NO: 127. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 127. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 127 while retaining at least one epitope of SEQ ID NO: 127. The first 25 N-terminal amino acids of SEQ ID NO: 127 can usefully be omitted. Other fragments omit one or more protein domains.

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sta093

**[0327]** The 'sta093' antigen is annotated as 'protein'. In the NCTC 8325 strain sta093 is SAOUHSC\_01854 and has amino acid sequence SEQ ID NO: 128 (GI:88195552).

- <sup>40</sup> [0328] Useful sta093 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 128 and/or may 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: 128; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 128, 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). These sta093 proteins include variants
- <sup>45</sup> of SEQ ID NO: 128. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 128. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 128 while retaining at least one epitope of SEQ ID NO: 128. Other fragments omit one or more protein domains.
- 50 sta094

**[0329]** The 'sta094' antigen is annotated as 'protein'. In the NCTC 8325 strain sta094 is SAOUHSC\_01512 and has amino acid sequence SEQ ID NO: 129 (GI:88195226).

[0330] Useful sta094 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID
<sup>55</sup> NO: 129 and/or may 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: 129; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 129, 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). These sta094 proteins include variants

of SEQ ID NO: 129. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 129. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 129 while retaining at least one epitope of SEQ ID NO: 129. The first 17 N-terminal amino acids of SEQ ID NO: 129 can usefully be omitted. Other fragments omit one or more protein domains.

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sta095

[0331] The 'sta095' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta095 is SAOUHSC\_
 00383 and has amino acid sequence SEQ ID NO: 130 (GI:88194180). In the Newman strain it is nwmn\_0388 (GI: 151220600).

**[0332]** Useful sta095 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 130 and/or may 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: 130; and/or (b)

comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 130, 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 or more). These sta095 proteins include variants of SEQ ID NO: 130. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 130. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 130 while retaining at least one epitope of SEQ ID NO: 130. The first 32 N-terminal amino acids of SEQ ID NO: 130 can usefully be omitted.

Other fragments omit one or more protein domains.

sta096

- [0333] The 'sta096' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta096 is SAOUHSC\_00384 and has amino acid sequence SEQ ID NO: 131 (GI:88194181).
  [0334] Useful sta096 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 131 and/or may 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: 131; and/or (b)
  comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 131, 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 or more). These sta096 proteins include variants of SEQ ID NO: 131. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 131. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 131 while retaining at least one epitope of SEQ ID NO: 131. The first 30 N-terminal amino acids of SEQ ID NO: 131 can usefully be omitted.
- Other fragments omit one or more protein domains.

sta097

- 40 [0335] The 'sta097' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta097 is SAOUHSC\_00386 and has amino acid sequence SEQ ID NO: 132 (GI:88194182).
  [0336] Useful sta097 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 132 and/or may 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: 132; and/or (b)
- <sup>45</sup> comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 132, 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). These sta097 proteins include variants of SEQ ID NO: 132. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 132. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 132 while
- <sup>50</sup> retaining at least one epitope of SEQ ID NO: 132. The first 30 N-terminal amino acids of SEQ ID NO: 132 can usefully be omitted. Other fragments omit one or more protein domains.

sta098

<sup>55</sup> **[0337]** The 'sta098' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta098 is SAOUHSC\_ 00389 and has amino acid sequence SEQ ID NO: 133 (GI:88194184). In the Newman strain it is nwmn\_0391 (GI: 151220603).

[0338] Useful sta098 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID

NO: 133 and/or may 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: 133; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 133, 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). These sta098 proteins include variants of SEQ ID NO: 133. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 133. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 133 while retaining at least one epitope of SEQ ID NO: 133. The first 30 N-terminal amino acids of SEQ ID NO: 133 can usefully be omitted. Other fragments omit one or more protein domains.

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sta099

**[0339]** The 'sta099' antigen is annotated as 'superantigen-like protein 5'. In the NCTC 8325 strain sta099 is SAOUHSC\_00390 and has amino acid sequence SEQ ID NO: 134 (GI:88194185).

- <sup>15</sup> [0340] Useful sta099 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 134 and/or may 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: 134; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 134, 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 or more). These sta099 proteins include variants of
- SEQ ID NO: 134. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 134. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 134 while retaining at least one epitope of SEQ ID NO: 134. The first 30 N-terminal amino acids of SEQ ID NO: 134 can usefully be omitted. Other fragments omit one or more protein domains.

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sta100

**[0341]** The 'sta100' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta100 is SAOUHSC\_ 00391 and has amino acid sequence SEQ ID NO: 135 (GI:88194186).

- <sup>30</sup> [0342] Useful sta100 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 135 and/or may 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: 135; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 135, 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 or more). These sta100 proteins include variants of
- <sup>35</sup> SEQ ID NO: 135. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 135. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 135 while retaining at least one epitope of SEQ ID NO: 135. The first 30 N-terminal amino acids of SEQ ID NO: 135 can usefully be omitted. Other fragments omit one or more protein domains.

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sta101

**[0343]** The 'sta101' antigen is annotated as 'superantigen-like protein 7'. In the NCTC 8325 strain sta101 is SAOUHSC\_ 00392 and has amino acid sequence SEQ ID NO: 136 (GI:88194187). In the Newman strain it is nwmn\_0394 (GI: 151220606).

**[0344]** Useful sta101 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 136 and/or may 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: 136; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 136, 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 or more). These sta101 proteins include variants of SEQ ID NO: 136. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 136. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 136 while retaining at least one epitope of SEQ ID NO: 136. The first 30 N-terminal amino acids of SEQ ID NO: 136 can usefully be omitted.

<sup>&</sup>lt;sup>55</sup> Other fragments omit one or more protein domains.

### sta102

**[0345]** The 'sta102' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta102 is SAOUHSC\_00393 and has amino acid sequence SEQ ID NO: 137 (GI:88194188).

- <sup>5</sup> [0346] Useful sta102 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 137 and/or may 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: 137; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 137, 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 or more). These sta102 proteins include variants of
- <sup>10</sup> SEQ ID NO: 137. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 137. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 137 while retaining at least one epitope of SEQ ID NO: 137. The first 17 N-terminal amino acids of SEQ ID NO: 137 can usefully be omitted. Other fragments omit one or more protein domains.
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sta103

**[0347]** The 'sta103' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta103 is SAOUHSC\_ 00394 and has amino acid sequence SEQ ID NO: 138 (GI:88194189).

- 20 [0348] Useful sta103 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 138 and/or may 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: 138; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 138, 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 or more). These sta103 proteins include variants of
- SEQ ID NO: 138. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 138. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 138 while retaining at least one epitope of SEQ ID NO: 138. The first 23 N-terminal amino acids of SEQ ID NO: 138 can usefully be omitted. Other fragments omit one or more protein domains.

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sta104

**[0349]** The 'sta104' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta104 is SAOUHSC\_ 00395 and has amino acid sequence SEQ ID NO: 139 (GI:88194190).

- <sup>35</sup> [0350] Useful sta104 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 139 and/or may 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: 139; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 139, 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 or more). These sta104 proteins include variants of
- <sup>40</sup> SEQ ID NO: 139. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 139. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 139 while retaining at least one epitope of SEQ ID NO: 139. Other fragments omit one or more protein domains.
- <sup>45</sup> sta105

**[0351]** The 'sta105' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta105 is SAOUHSC\_ 00399 and has amino acid sequence SEQ ID NO: 140 (GI:88194194). In the Newman strain it is nwmn\_0400 (GI: 151220612).

- 50 [0352] Useful sta105 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 140 and/or may 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: 140; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 140, 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 or more). These sta105 proteins include variants of
- SEQ ID NO: 140. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 140. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 140 while retaining at least one epitope of SEQ ID NO: 140. The first 30 N-terminal amino acids of SEQ ID NO: 140 can usefully be omitted.

Other fragments omit one or more protein domains.

sta106

- <sup>5</sup> [0353] The 'sta106' antigen is annotated as 'hypothetical protein'. In the NCTC 8325 strain sta106 is SAOUHSC\_01115 and has amino acid sequence SEQ ID NO: 141 (GI:88194861).
  [0354] Useful sta106 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 141 and/or may 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: 141; and/or (b)
- <sup>10</sup> comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 141, 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 or more). These sta106 proteins include variants of SEQ ID NO: 141. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 141. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 141 while retaining at
- <sup>15</sup> least one epitope of SEQ ID NO: 141. The first 16 N-terminal amino acids of SEQ ID NO: 141 can usefully be omitted. Other fragments omit one or more protein domains.

sta107

- [0355] The 'sta107' antigen is annotated as 'hypothetical protein'. In the NCTC 8325 strain sta107 is SAOUHSC\_00354 and has amino acid sequence SEQ ID NO: 177 (GI:88194153).
  [0356] Useful sta107 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 177 and/or may 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: 177; and/or (b)
  <sup>25</sup> comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 177, 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 or more). These sta107 proteins include variants of SEQ ID NO: 177. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 177. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 177 while retaining
- <sup>30</sup> at least one epitope of SEQ ID NO: 177. The first 35 N-terminal amino acids of SEQ ID NO: 177 can usefully be omitted. Other fragments omit one or more protein domains.

sta108

- <sup>35</sup> [0357] The 'sta108' antigen is annotated as 'hypothetical protein'. In the NCTC 8325 strain sta108 is SAOUHSC\_00717 and has amino acid sequence SEQ ID NO: 178 (GI:88194482).
   [0358] Useful sta108 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID
- NO: 178 and/or may 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: 178; and/or (b)
  comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 178, 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 or more). These sta108 proteins include variants of SEQ ID NO: 178. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 178. Other preferred fragments lack one or more variants of (b) comprise an epitope from SEQ ID NO: 178. Other preferred fragments lack one or more variants of (a, a, b, b, b, c, b) and b. (b) and b. (c, a, b) a
- more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 178 while retaining at
   least one epitope of SEQ ID NO: 178. The first 20 N-terminal amino acids of SEQ ID NO: 178 can usefully be omitted. Other fragments omit one or more protein domains.

sta109

- [0359] The 'sta109' antigen is annotated as 'N-acetylmuramoyl-L-alanine amidase '. In the NCTC 8325 strain sta109 is SAOUHSC\_02979 and has amino acid sequence SEQ ID NO: 179 (GI:88196599).
  [0360] Useful sta109 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 179 and/or may 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: 179; and/or (b)
- <sup>55</sup> comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 179, 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). These sta109 proteins include variants of SEQ ID NO: 179. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 179. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or

more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 179 while retaining at least one epitope of SEQ ID NO: 179. The first 27 N-terminal amino acids of SEQ ID NO: 179 can usefully be omitted. Other fragments omit one or more protein domains.

# 5 sta110

**[0361]** The 'sta110' antigen is annotated as 'hypothetical protein'. In the NCTC 8325 strain sta110 is SAOUHSC\_ 01039 and has amino acid sequence SEQ ID NO: 180 (GI:88194791).

- [0362] Useful sta110 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 180 and/or may 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: 180; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 180, 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 or more). These sta110 proteins include variants of SEQ ID NO: 180. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 180. Other preferred fragments lack
- <sup>15</sup> one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 180 while retaining at least one epitope of SEQ ID NO: 180. The first 19 N-terminal amino acids of SEQ ID NO: 180 can usefully be omitted. Other fragments omit one or more protein domains.

20 sta111

**[0363]** The 'sta111' antigen is annotated as 'hypothetical protein'. In the NCTC 8325 strain sta111 is SAOUHSC\_ 01005 and has amino acid sequence SEQ ID NO: 181 (GI:88194760).

- [0364] Useful sta111 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID
  NO: 181 and/or may 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: 181; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 181, 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 or more). These sta111 proteins include variants of SEQ ID NO: 181. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 181. Other preferred fragments lack one or
- <sup>30</sup> more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 181 while retaining at least one epitope of SEQ ID NO: 181. The first 20 N-terminal amino acids of SEQ ID NO: 181 can usefully be omitted. Other fragments omit one or more protein domains.
- 35 sta112

**[0365]** The 'sta112' antigen is annotated as a putative 'ABC transporter, substrate-binding protein'. In the NCTC 8325 strain sta112 is SAOUHSC\_00634 and has amino acid sequence SEQ ID NO: 182 (GI:88194402).

- [0366] Useful sta112 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID
  NO: 182 and/or may 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: 182; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 182, 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). These sta112 proteins include variants of SEQ ID NO: 182. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 182. Other preferred fragments
- <sup>45</sup> lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 182 while retaining at least one epitope of SEQ ID NO: 182. The first 17 N-terminal amino acids of SEQ ID NO: 182 can usefully be omitted. Other fragments omit one or more protein domains.

[0367] A Sta112 antigen can usefully be included in a composition in combination with a Sta073 [74].

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sta113

**[0368]** The 'sta113' antigen is annotated as 'hypothetical protein'. In the NCTC 8325 strain sta113 is SAOUHSC\_ 00728 and has amino acid sequence SEQ ID NO: 183 (GI:88194493).

[0369] Useful sta113 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 183 and/or may 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: 183; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 183, wherein 'n' is 7 or more (*e.g.* 8, 10, 100).

12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta113 proteins include variants of SEQ ID NO: 183. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 183. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 183 while retaining at least one epitope of SEQ ID NO: 183. The first 173 N-terminal amino acids of SEQ ID NO: 183 can usefully be omitted. Other fragments omit one or more protein domains.

sta114

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<sup>10</sup> **[0370]** The 'sta114' antigen is annotated as 'hypothetical protein'. In the NCTC 8325 strain sta114 is SAOUHSC\_ 00810 and has amino acid sequence SEQ ID NO: 184 (GI:88194570).

**[0371]** Useful sta114 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 184 and/or may 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: 184; and/or (b)

comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 184, 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 or more). These sta114 proteins include variants of SEQ ID NO: 184. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 184. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 184 while retaining at least one epitope of SEQ ID NO: 184. Other fragments omit one or more protein domains.

sta115

[0372] The 'sta115' antigen is annotated as 'hypothetical protein'. In the NCTC 8325 strain sta115 is SAOUHSC\_ 00817 and has amino acid sequence SEQ ID NO: 185 (GI:88194576).

**[0373]** Useful sta115 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 185 and/or may 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: 185; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 185, 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 or more). These sta115 proteins include variants of SEQ ID NO: 185. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 185. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 185 while retaining at least one epitope of SEQ ID NO: 185. The first 18 N-terminal amino acids of SEQ ID NO: 185 can usefully be omitted.
 Other fragments omit one or more protein domains.

sta116

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**[0374]** The 'sta116' antigen is annotated as 'formyl peptide receptor-like 1 inhibitory protein'. In the NCTC 8325 strain sta116 is SAOUHSC\_01112 and has amino acid sequence SEQ ID NO: 186 (GI:88194858).

- **[0375]** Useful sta116 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 186 and/or may 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: 186; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 186, 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 or more). These sta116 proteins include variants of SEQ ID NO: 186. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 186. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 186 while retaining at least one epitope of SEQ ID NO: 186. The first 20 N-terminal amino acids of SEQ ID NO: 186 can usefully be omitted.
  Other fragments omit one or more protein domains.

sta117

[0376] The 'sta117' antigen is annotated as 'truncated beta-hemolysin'. In the NCTC 8325 strain sta117 is SAOUHSC\_ 02240 and has amino acid sequence SEQ ID NO: 187 (GI:88195913).

**[0377]** Useful sta117 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 187 and/or may 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: 187; and/or (b)

comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 187, 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). These sta117 proteins include variants of SEQ ID NO: 187. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 187. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 187 while retaining at least one epitope of SEQ ID NO: 187. Other fragments omit one or more protein domains.

sta118

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10 [0378] The 'sta118' antigen is annotated as 'cell division protein FtsZ'. In the NCTC 8325 strain sta118 is SAOUHSC\_ 01150 and has amino acid sequence SEQ ID NO: 188 (GI:88194892).

**[0379]** Useful sta118 antigens can elicit an antibody *(e.g.* when administered to a human) that recognises SEQ ID NO: 188 and/or may 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: 188; and/or (b)

<sup>15</sup> comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 188, 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). These sta118 proteins include variants of SEQ ID NO: 188. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 188. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 188 while
20 retaining at least one epitope of SEQ ID NO: 188. Other fragments omit one or more protein domains.

sta119

sta120

[0380] The 'sta119' antigen is annotated as 'thioredoxin'. In the NCTC 8325 strain sta119 is SAOUHSC\_01100 and has amino acid sequence SEQ ID NO: 200 (GI:88194846).

**[0381]** Useful sta119 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 200 and/or may 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: 200; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 200, wherein 'n' is 7 or more (*e.g.* 8, 10,

<sup>30</sup> 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100 or more). These sta119 proteins include variants of SEQ ID NO: 200. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 200. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 200 while retaining at least one epitope of SEQ ID NO: 200. Other fragments omit one or more protein domains.

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**[0382]** The 'sta120' antigen is annotated as ' alkyl hydroperoxide reductase subunit C'. In the NCTC 8325 strain sta120 is SAOUHSC\_00365 and has amino acid sequence SEQ ID NO: 201 (GI:88194163).

- <sup>40</sup> [0383] Useful sta120 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 201 and/or may 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: 201; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 201, 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 or more). These sta120 proteins include variants of SEQ
- <sup>45</sup> ID NO: 201. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 201. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 201 while retaining at least one epitope of SEQ ID NO: 201. Other fragments omit one or more protein domains.
- 50 NW\_6

**[0384]** The 'NW\_6' antigen is annotated as 'secreted von Willebrand factor-binding protein precursor'. In the Newman strain NW\_6 is NWMN\_0757 and has amino acid sequence SEQ ID NO: 142 (GI: 151220969).

[0385] Useful NW\_6 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID
NO: 142 and/or may 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: 142; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 142, 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). These NW\_6 proteins include variants

of SEQ ID NO: 142. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 142. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 142 while retaining at least one epitope of SEQ ID NO: 142. The first 13 N-terminal amino acids of SEQ ID NO: 142 can usefully be omitted. Other fragments omit one or more protein domains.

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 $NW_9$ 

**[0386]** The 'NW\_9' antigen is annotated as 'lipoprotein'. In the Newman strain NW\_9 is NWMN\_0958 and has amino acid sequence SEQ ID NO: 143 (GI: 151221170).

**[0387]** Useful NW\_9 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 143 and/or may 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: 143; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 143, 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 or more). These NW\_9 proteins include variants of SEQ ID NO: 143. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 143. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 143 while retaining at least one epitope of SEQ ID NO: 143. The first 19 N-terminal amino acids of SEQ ID NO: 143 can usefully be omitted.
20 Other fragments omit one or more protein domains.

NW\_10

[0388] The 'NW\_10' antigen is annotated as 'fibrinogen binding-related protein'. In the Newman strain NW\_10 is NWMN\_1066 and has amino acid sequence SEQ ID NO: 144 (GI: 151221278).

**[0389]** Useful NW\_10 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 144 and/or may 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: 144; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 144, 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 or more). These NW\_10 proteins include variants of SEQ ID NO: 144. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 144. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 144 while retaining at least one epitope of SEQ ID NO: 144. The first 20 N-terminal amino acids of SEQ ID NO: 144 can usefully be omitted.
 Other fragments omit one or more protein domains.

NW\_7

[0390] The 'NW\_7' antigen is annotated as 'staphylococcal complement inhibitor SCIN'. In the Newman strain NW\_ 7 is NWMN\_1876 and has amino acid sequence SEQ ID NO: 145 (GI:151222088).

- **[0391]** Useful NW\_7 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 145 and/or may 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: 145; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 145, 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 or more). These NW\_7 proteins include variants of SEQ ID NO: 145. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 145. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 145 while retaining at least one epitope of SEQ ID NO: 145. The first 17 N-terminal amino acids of SEQ ID NO: 145 can usefully be omitted.
  Other fragments omit one or more protein domains.

NW\_8

[0392] The 'NW\_8' antigen is annotated as 'chemotaxis-inhibiting protein CHIPS'. In the Newman strain NW\_8 is NWMN\_1877 and has amino acid sequence SEQ ID NO: 146 (GI:151222089).

**[0393]** Useful NW\_8 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 146 and/or may 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: 146; and/or (b)

comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 146, 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 or more). These NW\_8 proteins include variants of SEQ ID NO: 146. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 146. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 146 while retaining at least one epitope of SEQ ID NO: 146. The first 19 N-terminal amino acids of SEQ ID NO: 146 can usefully be omitted. Other fragments omit one or more protein domains.

# NW\_2

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**[0394]** The 'NW\_2' antigen is annotated as 'enterotoxin type A precursor'. In the Newman strain NW\_2 is NWMN\_ 1883 and has amino acid sequence SEQ ID NO: 147 (GI: 151222095).

- <sup>15</sup> 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO: 147; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 147, 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). These NW\_2 proteins include variants of SEQ ID NO: 147. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 147. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or
- 20 more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 147 while retaining at least one epitope of SEQ ID NO: 147. The first 16 N-terminal amino acids of SEQ ID NO: 147 can usefully be omitted. Other fragments omit one or more protein domains.

#### NW\_1

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**[0396]** The 'NW\_1' antigen is annotated as 'lipoprotein'. In the Newman strain NW\_1 is NWMN\_1924 and has amino acid sequence SEQ ID NO: 148 (GI: 151222136).

**[0397]** Useful NW\_1 antigens can elicit an antibody (*e.g.* when administered to a human) that recognises SEQ ID NO: 148 and/or may 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: 148; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 148, 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 or more). These NW\_1 proteins include variants of SEQ ID NO: 148. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 148. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 148 while retaining at least one epitope of SEQ ID NO: 148. The first 17 N-terminal amino acids of SEQ ID NO: 148 can usefully be omitted.
- least one epitope of SEQ ID NO: 148. The first 17 N-terminal amino acids of SEQ ID NO: 148 can usefully be omitted. Other fragments omit one or more protein domains.

NW\_5

**[0398]** The 'NW\_5' antigen is annotated as 'cell wall surface anchor family protein'. In the Newman strain NW\_5 is NWMN\_2392 and has amino acid sequence SEQ ID NO: 149 (GI:151222604).

[0399] Useful NW\_5 antigens can elicit an antibody (e.g. when administered to a human) that recognises SEQ ID NO: 149 and/or may 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: 149; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 149, 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). These NW\_5 proteins include variants of SEQ ID NO: 149. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 149. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino

<sup>50</sup> acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 149 while retaining at least one epitope of SEQ ID NO: 149. The first 52 N-terminal amino acids of SEQ ID NO: 149 can usefully be omitted. Other fragments omit one or more protein domains.

# Hybrid polypeptides

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**[0400]** Antigens used in the invention may be present in the composition as individual separate polypeptides. Where more than one antigen is used, however, they do not have to be present as separate polypeptides. Instead, at least two (e.g. 2, 3, 4, 5, or more) antigens can be expressed as a single polypeptide chain (a 'hybrid' polypeptide). Hybrid

polypeptides offer two main advantages: first, a polypeptide that may be unstable or poorly expressed on its own can be assisted by adding a suitable hybrid partner that overcomes the problem; second, commercial manufacture is simplified as only one expression and purification need be employed in order to produce two polypeptides which are both antigenically useful.

- <sup>5</sup> **[0401]** The hybrid polypeptide may comprise two or more polypeptide sequences from the first antigen group. The hybrid polypeptide may comprise one or more polypeptide sequences from the first antigen group and one or more polypeptide sequences from the second antigen group. Moreover, the hybrid polypeptide may comprise two or more polypeptide sequences from each of the antigens listed above, or two or more variants of the same antigen in the cases in which the sequence has partial variability across strains.
- <sup>10</sup> **[0402]** Hybrids consisting of amino acid sequences from two, three, four, five, six, seven, eight, nine, or ten antigens are useful. In particular, hybrids consisting of amino acid sequences from two, three, four, or five antigens are preferred, such as two or three antigens.

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**[0403]** Different hybrid polypeptides may be mixed together in a single formulation. Hybrids may be combined with non-hybrid antigens selected from the first, second or third antigen groups. Within such combinations, an antigen may be present in more than one hybrid polypeptide and/or as a non-hybrid polypeptide. It is preferred, however, that an antigen is present either as a hybrid or as a non-hybrid, but not as both.

**[0404]** The hybrid polypeptides can also be combined with conjugates or non-*S.aureus* antigens as described above. **[0405]** Hybrid polypeptides can be represented by the formula  $NH_2$ -A-{-X-L-}<sub>n</sub>-B-COOH, wherein: X is an amino acid sequence of a *S.aureus* antigen, as described above; L is an optional linker amino acid sequence; A is an optional N-

terminal amino acid sequence; B is an optional C-terminal amino acid sequence; n is an integer of 2 or more (e.g. 2, 3, 4, 5, 6, etc.). Usually n is 2 or 3.

**[0406]** If a -X- moiety has a leader peptide sequence in its wild-type form, this may be included or omitted in the hybrid protein. In some embodiments, the leader peptides will be deleted except for that of the -X- moiety located at the N-terminus of the hybrid protein *i.e.* the leader peptide of  $X_1$  will be retained, but the leader peptides of  $X_2 \dots X_n$  will be omitted. This is equivalent to deleting all leader peptides and using the leader peptide of  $X_1$  as moiety -A-.

- omitted. This is equivalent to deleting all leader peptides and using the leader peptide of X<sub>1</sub> as moiety -A-.
   [0407] For each n instances of {-X-L-}, linker amino acid sequence -L- may be present or absent. For instance, when n=2 the hybrid may be NH<sub>2</sub>-X<sub>1</sub>-L<sub>1</sub>-X<sub>2</sub>-L<sub>2</sub>-COOH, NH<sub>2</sub>-X<sub>1</sub>-X<sub>2</sub>-COOH, NH<sub>2</sub>-X<sub>1</sub>-L<sub>1</sub>-X<sub>2</sub>-COOH, NH<sub>2</sub>-X<sub>1</sub>-X<sub>2</sub>-COOH, NH<sub>2</sub>-X<sub>1</sub>-X<sub>2</sub>-COOH, NH<sub>2</sub>-X<sub>1</sub>-X<sub>2</sub>-COOH, NH<sub>2</sub>-X<sub>1</sub>-X<sub>1</sub>-X<sub>2</sub>-COOH, NH<sub>2</sub>-X<sub>1</sub>-X<sub>1</sub>-X<sub>2</sub>-COOH, NH<sub>2</sub>-X<sub>1</sub>-X<sub>2</sub>-COOH, NH<sub>2</sub>-X<sub>1</sub>-X<sub>1</sub>-X<sub>2</sub>-COOH, etc. Linker amino acid sequence(s) -L- will typically be short (*e.g.* 20 or fewer amino acids *i.e.* 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples comprise short peptide sequences which facilitate cloning, poly-glycine
- <sup>30</sup> linkers (i.e. comprising Gly<sub>n</sub> where n = 2, 3, 4, 5, 6, 7, 8, 9, 10 or more), and histidine tags (*i.e.* His<sub>n</sub> where n = 3, 4, 5, 6, 7, 8, 9, 10 or more). Other suitable linker amino acid sequences will be apparent to those skilled in the art. A useful linker is GSGGGG (SEQ ID NO: 171) or GSGSGGGG (SEQ ID NO: 172), with the Gly-Ser dipeptide being formed from a *Bam*HI restriction site (or two of them, to form the SEQ ID NO: 230 tetrapeptide), thus aiding cloning and manipulation, and the (Gly)<sub>4</sub> tetrapeptide (SEQ ID NO: 227) being a typical poly-glycine linker. Other suitable linkers, particularly for use as the final L, are ASGGGS (SEQ ID NO: 173 *e.g.* encoded by SEQ ID NO: 174) or a Leu-Glu dipeptide.
- <sup>35</sup> use as the final  $L_n$  are ASGGGS (SEQ ID NO: 173 *e.g.* encoded by SEQ ID NO: 174) or a Leu-Glu dipeptide. **[0408]** -A- is an optional N-terminal amino acid sequence. This will typically be short (e.g. 40 or fewer amino acids *i.e.* 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include leader sequences to direct protein trafficking, or short peptide sequences which facilitate cloning or purification (*e.g.* histidine tags *i.e.* His<sub>n</sub> where n = 3, 4, 5, 6, 7, 8, 9, 10 or more). Other suitable
- <sup>40</sup> N-terminal amino acid sequences will be apparent to those skilled in the art. If X<sub>1</sub> lacks its own N-terminus methionine,
   -A-is preferably an oligopeptide (*e.g.* with 1, 2, 3, 4, 5, 6, 7 or 8 amino acids) which provides a N-terminus methionine
   *e.g.* Met-Ala-Ser, or a single Met residue.

**[0409]** -B- is an optional C-terminal amino acid sequence. This will typically be short (*e.g.* 40 or fewer amino acids *i.e.* 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9,

- <sup>45</sup> 8, 7, 6, 5, 4, 3, 2, 1). Examples include sequences to direct protein trafficking, short peptide sequences which facilitate cloning or purification (*e.g.* comprising histidine tags *i.e.* His<sub>n</sub> where n = 3, 4, 5, 6, 7, 8, 9, 10 or more, such as SEQ ID NO: 226), or sequences which enhance protein stability. Other suitable C-terminal amino acid sequences will be apparent to those skilled in the art.
- [0410] One hybrid polypeptide of the invention may include both EsxA and EsxB antigens. These may be in either order, N- to C- terminus. SEQ ID NOs: 151 ('EsxAB'; encoded by SEQ ID NO: 169) and 152 ('EsxBA') are examples of such hybrids, both having hexapeptide linkers ASGGGS (SEQ ID NO: 173). Another 'EsxAB' hybrid comprises SEQ ID NO: 241, which may be provided with a N-terminus methionine (e.g. SEQ ID NO: 250).

**[0411]** Another hybrid polypeptide of the invention may include both SdrD and SdrE antigens. These may be in either order, N- to C- terminus. SEQ ID NO: 168 ('SdrED') is an example of such a hybrid, having a hexapeptide linker ASGGGS (SEQ ID NO: 173).

**[0412]** Another hybrid polypeptide of the invention may include both ClfB and SdrD antigens. These may be in either order, N- to C- terminus. SEQ ID NO: 202 ('ClfB-SdrD') is an example of such a hybrid, having a hexapeptide linker ASGGGS (SEQ ID NO: 173). SEQ ID NO: 203 ('SdrD-ClfB') is another example of such a hybrid, having a hexapeptide

linker ASGGGS (SEQ ID NO: 173). SEQ ID NO: 211 ('ClfB-N3-sdrD-N3') is another example of such a hybrid, where the N3 fragments of ClfB and SdrD are joined by hexapeptide linker ASGGGS (SEQ ID NO: 173).

[0413] Another hybrid polypeptide of the invention may include both IsdA and EsxA antigens. These may be in either order, N- to C- terminus. SEQ ID NO: 204 ('IsdA-EsxA') is an example of such a hybrid, having a hexapeptide linker
 <sup>5</sup> ASGGGS (SEQ ID NO: 173). SEQ ID NO: 209 ('isdA40-184-esxA') is another example of such a hybrid, in which IsdA<sub>40-184</sub> is joined to EsxA via linker ASGGGS (SEQ ID NO: 173).

**[0414]** Another hybrid polypeptide of the invention may include both IsdA and sta006 antigens. These may be in either order, N- to C- terminus. SEQ ID NO: 221 ('isdA40-184-sta006') is an example of such a hybrid, in which IsdA<sub>40-184</sub> is joined to Sta006 via hexapeptide linker ASGGGS (SEQ ID NO: 173).

<sup>10</sup> **[0415]** Another hybrid polypeptide of the invention may include both Hla and sta006 antigens. These may be in either order, N- to C- terminus. SEQ ID NO: 222 ('HIaH35L-sta006') is an example of such a hybrid, in which a H35L mutant of H1a is joined to Sta006 via hexapeptide linker ASGGGS (SEQ ID NO: 173).

[0416] Another hybrid polypeptide of the invention may include both Hla and Emp antigens. These may be in either order, N- to C- terminus. SEQ ID NO: 205 ('HlaH35L-Emp') is an example of such a hybrid, in which a H35L mutant Hla

- <sup>15</sup> is joined to Emp via linker ASGGGS (SEQ ID NO: 173). SEQ ID NO: 206 ('Hla27-76-Emp') is another example of such a hybrid, in which a Hla fragment is joined to Emp via linker ASGGGS (SEQ ID NO: 173); SEQ ID NO: 207 is a H35L mutant of SEQ ID NO: 206. SEQ ID NO: 208 ('HlaPSGS-Emp') is another example of such a hybrid, in which a Hla mutant is joined to Emp via linker ASGGGS (SEQ ID NO: 173).
- [0417] Another hybrid polypeptide of the invention may include IsdA and EsxA and EsxB antigens. These may be in any order, N- to C- terminus. SEQ ID NO: 210 ('isdA40-184-esxAB') is an example of such a triple hybrid, in which IsdA<sub>40-184</sub> is joined to EsxAB via linker ASGGGS (SEQ ID NO: 173). The EsxAB already includes the same linker, so SEQ ID NO: 210 includes two of these linkers. SEQ ID NO: 212 ('IsdA-esxAB') is another example of such a triple hybrid, in which IsdA is joined to EsxAB via linker ASGGGS (SEQ ID NO: 173).
- [0418] Another hybrid polypeptide of the invention may include Hla and EsxA and EsxB antigens. These maybe in any order, N- to C- terminus. SEQ ID NO: 220 ('HIaH35L-esxAB') is an example of such a triple hybrid, in which a H35L mutant of H1a is joined to EsxAB via linker ASGGGS (SEQ ID NO: 173). The EsxAB already includes the same linker, so SEQ ID NO: 220 includes two of these linkers. Another example of a hybrid polypeptide including Hla and EsxA and EsxB antigens is SEQ ID NO: 237 ('HIaH35L-esxAB' as used in the examples), in which a H35L mutant of H1a is joined to EsxA via linker APTARG (SEQ ID NO: 239) to replace its N-terminus, then to EsxB via linker ASGGGS (SEQ ID NO:
- <sup>30</sup> 173) to replace its N-terminus. This hybrid can be provided with a suitable N-terminal sequence such as SEQ ID NO: 240. [0419] Another hybrid polypeptide of the invention may include sta006 and EsxA and EsxB antigens. These may be in any order, N- to C- terminus. SEQ ID NO: 223 ('sta006-esxAB') is an example of such a triple hybrid, in which sta006 is joined to EsxAB via linker ASGGGS (SEQ ID NO: 173). The EsxAB already includes the same linker, so SEQ ID NO: 223 includes two of these linkers. Another example of a hybrid polypeptide including sta006 and EsxA and EsxB antigens
- is SEQ ID NO: 238 ('sta006-esxAB' as used in the examples), in which a sta006 is joined to EsxA via linker APTARG (SEQ ID NO: 239) to replace its N-terminus, then to EsxB via linker ASGGGS (SEQ ID NO: 173) to replace its N-terminus. This hybrid can be provided with a suitable N-terminal sequence such as SEQ ID NO: 240.
   [0420] Usefully, these hybrid polypeptides can elicit an antibody (e.g. when administered to a human) that recognise
- each of the wild-type staphylococcal proteins (e.g. as shown in the sequence listing) represented in the hybrid e.g. which
   recognise both wild-type EsxA and wild-type EsxB, or which recognise both wild-type SdrD and wild-type SdrE, or which
   recognise both wild-type SdrD and wild-type ClfB, or which recognise both wild-type IsdA and wild-type EsxA, or which
   recognise both wild-type IsdA and wild-type sta006, or which recognise both wild-type Hla and wild-type sta006, or which recognise both wild-type Hla and wild-type Emp, or which recognise wild-type IsdA and wild-type EsxA and wild-type
   sxB, or which recognise wild-type Hla and wild-type Hla and wild-type EsxA and wild-type EsxA
- <sup>45</sup> and wild-type EsxA and wild-type EsxB.

# Polypeptides used with the invention

[0421] Polypeptides used with the invention can take various forms (*e.g.* native, fusions, glycosylated, non-glycosylat <sup>50</sup> ed, lipidated, non-lipidated, phosphorylated, non-phosphorylated, myristoylated, non-myristoylated, monomeric, mul timeric, particulate, denatured, *etc.*).

**[0422]** Polypeptides used with the invention can be prepared by various means (*e.g.* recombinant expression, purification from cell culture, chemical synthesis, *etc.*). Recombinantly-expressed proteins are preferred, particularly for hybrid polypeptides.

<sup>55</sup> **[0423]** Polypeptides used with the invention are preferably provided in purified or substantially purified form i.e. substantially free from other polypeptides (*e.g.* free from naturally-occurring polypeptides), particularly from other staphylococcal or host cell polypeptides, and are generally at least about 50% pure (by weight), and usually at least about 90% pure *i.e.* less than about 50%, and more preferably less than about 10% (*e.g.* 5%) of a composition is made up of other

expressed polypeptides. Thus the antigens in the compositions are separated from the whole organism with which the molecule is expressed.

- [0424] Polypeptides used with the invention are preferably staphylococcal polypeptides.
- [0425] 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 labeling component. Also included 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.

**[0426]** The invention provides polypeptides comprising a sequence -P-Q- or -Q-P-, wherein: -P- is an amino acid sequence as defined above and -Q- is not a sequence as defined above *i. e.* the invention provides fusion proteins. Where the N-terminus codon of -P- is not ATG, but this codon is not present at the N-terminus of a polypeptide, it will be translated as the standard amino acid for that codon rather than as a Met. Where this codon is at the N-terminus of

- <sup>15</sup> a polypeptide, however, it will be translated as Met. Examples of -Q- moieties include, but are not limited to, histidine tags (*i.e.* His<sub>n</sub> where n = 3, 4, 5, 6, 7, 8, 9, 10 or more), maltose-binding protein, or glutathione-S-transferase (GST). **[0427]** The invention also provides a process for producing a polypeptide of the invention, comprising the step of culturing a host cell transformed with nucleic acid of the invention under conditions which induce polypeptide expression. **[0428]** Although expression of the polypeptides of the invention may take place in a *Staphylococcus*, the invention
- will usually use a heterologous host for expression (recombinant expression). The heterologous host may be prokaryotic (e.g. a bacterium) or eukaryotic. It may be *E.coli*, but other suitable hosts include *Bacillus subtilis*, *Vibrio cholerae*, *Salmonella typhi*, *Salmonella typhimurium*, *Neisseria lactamica*, *Neisseria cinerea*, *Mycobacteria* (e.g. *M.tuberculosis*), yeasts, *etc.* Compared to the wild-type *S.aureus* genes encoding polypeptides of the invention, it is helpful to change codons to optimise expression efficiency in such hosts without affecting the encoded amino acids.
- <sup>25</sup> **[0429]** The invention provides a process for producing a polypeptide of the invention, comprising the step of synthesising at least part of the polypeptide by chemical means.

#### Nucleic acids

<sup>30</sup> **[0430]** The invention also provides nucleic acid encoding polypeptides and hybrid polypeptides of the invention. It also provides nucleic acid comprising a nucleotide sequence that encodes one or more polypeptides or hybrid polypeptides of the invention.

**[0431]** The invention also provides nucleic acid comprising nucleotide sequences having sequence identity to such nucleotide sequences. Identity between sequences is preferably determined by the Smith-Waterman homology search

- <sup>35</sup> algorithm as described above. Such nucleic acids include those using alternative codons to encode the same amino acid. [0432] The invention also provides nucleic acid which can hybridize to these nucleic acids. Hybridization reactions can be performed under conditions of different "stringency". Conditions that increase stringency of a hybridization reaction of widely known and published in the art (*e.g.* page 7.52 of reference 276). Examples of relevant conditions include (in order of increasing stringency): incubation temperatures of 25°C, 37°C, 50°C, 55°C and 68°C; buffer concentrations of
- <sup>40</sup> 10 x SSC, 6 x SSC, 1 x SSC, 0.1 x SSC (where SSC is 0.15 M NaCl and 15 mM citrate buffer) and their equivalents using other buffer systems; formamide concentrations of 0%, 25%, 50%, and 75%; incubation times from 5 minutes to 24 hours; 1, 2, or more washing steps; wash incubation times of 1, 2, or 15 minutes; and wash solutions of 6 x SSC, 1 x SSC, 0.1 x SSC, or de-ionized water. Hybridization techniques and their optimization are well known in the art (*e.g.* see refs 75, 76, 276, 278, *etc.*].
- <sup>45</sup> **[0433]** In some embodiments, nucleic acid of the invention hybridizes to a target under low stringency conditions; in other embodiments it hybridizes under intermediate stringency conditions; in preferred embodiments, it hybridizes under high stringency conditions. An exemplary set of low stringency hybridization conditions is 50°C and 10 x SSC. An exemplary set of intermediate stringency hybridization conditions is 55°C and 1 x SSC. An exemplary set of high stringency hybridization conditions is 68°C and 0.1 x SSC.
- <sup>50</sup> [0434] The invention includes nucleic acid comprising sequences complementary to these sequences (e.g. for antisense or probing, or for use as primers).
  [0435] Nucleic acids of the invention can be used in hybridisation reactions (*e.g.* Northern or Southern blots, or in nucleic acid microarrays or 'gene chips') and amplification reactions (*e.g.* PCR, SDA, SSSR, LCR, TMA, NASBA, *etc.*) and other nucleic acid techniques.
- <sup>55</sup> **[0436]** Nucleic acid according to the invention can take various forms (*e.g.* single-stranded, double-stranded, vectors, primers, probes, labelled *etc.*). Nucleic acids of the invention may be circular or branched, but will generally be linear. Unless otherwise specified or required, any embodiment of the invention that utilizes a nucleic acid may utilize both the double-stranded form and each of two complementary single-stranded forms which make up the double-stranded form.

Primers and probes are generally single-stranded, as are antisense nucleic acids.

**[0437]** Nucleic acids of the invention are preferably provided in purified or substantially purified form *i. e.* substantially free from other nucleic acids (*e.g.* free from naturally-occurring nucleic acids), particularly from other staphylococcal or host cell nucleic acids, generally being at least about 50% pure (by weight), and usually at least about 90% pure. Nucleic acids of the invention are preferably staphylococcal nucleic acids.

- **[0438]** 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.*
- **[0439]** Nucleic acid of the invention may be attached to a solid support *(e.g.* a bead, plate, filter, film, slide, microarray support, resin, *etc.)*. Nucleic acid of the invention may be labelled *e.g.* with a radioactive or fluorescent label, or a biotin label. This is particularly useful where the nucleic acid is to be used in detection techniques *e.g.* where the nucleic acid is a primer or as a probe.

**[0440]** The term "nucleic acid" includes in general means a polymeric form of nucleotides of any length, which contain deoxyribonucleotides, ribonucleotides, and/or their analogs. It includes DNA, RNA, DNA/RNA hybrids. It also includes

- <sup>15</sup> DNA or RNA analogs, such as those containing modified backbones (*e.g.* peptide nucleic acids (PNAs) or phosphorothioates) or modified bases. Thus the invention includes mRNA, tRNA, rRNA, ribozymes, DNA, cDNA, recombinant nucleic acids, branched nucleic acids, plasmids, vectors, probes, primers, *etc.* Where nucleic acid of the invention takes the form of RNA, it may or may not have a 5' cap.
- [0441] Nucleic acids of the invention may be part of a vector *i.e.* part of a nucleic acid construct designed for transduction/ transfection of one or more cell types. Vectors may be, for example, "cloning vectors" which are designed for isolation, propagation and replication of inserted nucleotides, "expression vectors" which are designed for expression of a nucleotide sequence in a host cell, "viral vectors" which is designed to result in the production of a recombinant virus or viruslike particle, or "shuttle vectors", which comprise the attributes of more than one type of vector. Preferred vectors are plasmids. A "host cell" includes an individual cell or cell culture which can be or has been a recipient of exogenous
- <sup>25</sup> nucleic acid. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in total DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation and/or change. Host cells include cells transfected or infected *in vivo* or *in vitro* with nucleic acid of the invention. [0442] Where a nucleic acid is DNA, it will be appreciated that "U" in a RNA sequence will be replaced by "T" in the DNA. Similarly, where a nucleic acid is RNA, it will be appreciated that "T" in a DNA sequence will be replaced by "U"
- <sup>30</sup> in the RNA.

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**[0443]** The term "complement" or "complementary" when used in relation to nucleic acids refers to Watson-Crick base pairing. Thus the complement of C is G, the complement of G is C, the complement of A is T (or U), and the complement of T (or U) is A. It is also possible to use bases such as I (the purine inosine) e.g. to complement pyrimidines (C or T). **[0444]** Nucleic acids of the invention can be used, for example: to produce polypeptides; as hybridization probes for

- <sup>35</sup> the detection of nucleic acid in biological samples; to generate additional copies of the nucleic acids; to generate ribozymes or antisense oligonucleotides; as single-stranded DNA primers or probes; or as triple-strand forming oligonucleotides. [0445] The invention provides a process for producing nucleic acid of the invention, wherein the nucleic acid is synthesised in part or in whole using chemical means.
- [0446] The invention provides vectors comprising nucleotide sequences of the invention (e.g. cloning or expression vectors) and host cells transformed with such vectors.
  - **[0447]** Nucleic acid amplification according to the invention may be quantitative and/or real-time.
  - [0448] For certain embodiments of the invention, nucleic acids are preferably at least 7 nucleotides in length (e.g. 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45, 50, 55, 60, 65, 70, 75, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 225, 250, 275, 300 nucleotides or longer).

**[0449]** For certain embodiments of the invention, nucleic acids are preferably at most 500 nucleotides in length (e.g. 450, 400, 350, 300, 250, 200, 150, 140, 130, 120, 110, 100, 90, 80, 75, 70, 65, 60, 55, 50, 45, 40, 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 nucleotides or shorter).

[0450] Primers and probes of the invention, and other nucleic acids used for hybridization, are preferably between 10 and 30 nucleotides in length (*e.g.* 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides).

#### Strains and variants

- <sup>55</sup> **[0451]** Antigens are defined above by reference to existing nomenclature (*e.g.* "ClfA"), to "sta" numbers or to "NW\_" numbers. Table 1 herein relates these three naming/numbering systems to existing
  - **[0452]** SAOUHSC numbering and/or NWMN numbering. SAOUHSC numbering refers to the genome of *S.aureus* strain NCTC 8325 (sequenced by Oklahoma University Health Sciences Center and disclosed in GenBank as

CP000253.1; GI:87201381), and individual SAOUHSC numbers are given as "locus\_tag" entries in the genome sequence's "features" section. Similarly, NWMN numbering refers to the genome of *S.aureus* strain Newman (isolated in 1952 from a human infection, and having robust virulence phenotype) disclosed in GenBank as AP009351.1 (GI: 150373012) and individual NWMN numbers are given as "locus\_tag" entries in the genome sequence's "features" section. Functional annotations for each antigen are also given in the databases.

- <sup>5</sup> section. Functional annotations for each antigen are also given in the databases. [0453] Table 1 also includes the GI number for each antigen of the invention. Thus an exemplary amino acid and nucleotide sequence for any of these antigens can easily be found in public sequence databases from the NCTC 8325 and/or Newman strain, but the invention is not limited to sequences from the NCTC 8325 and Newman strains. Genome sequences of several other strains of *S.aureus* are available, including those of MRSA strains N315 and Mu50 [77],
- MW2, N315, COL, MRSA252, MSSA476, RF122, USA300 (very virulent), JH1 and JH9. Standard search and alignment techniques can be used to identify in any of these (or other) further genome sequences the homolog of any particular sequence from the Newman or NCTC 8325 strain. Moreover, the available sequences from the Newman and NCTC 8325 strains can be used to design primers for amplification of homologous sequences from other strains. Thus the invention is not limited to these two strains, but rather encompasses such variants and homologs from other strains of
- S.aureus, as well as non-natural variants. In general, suitable variants of a particular SEQ ID NO include its allelic variants, its polymorphic forms, its homologs, its orthologs, its paralogs, its mutants, *etc.*[0454] Thus, for instance, polypeptides used with the invention may, compared to the SEQ ID NO herein, include one or more (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, *etc.*) amino acid substitutions, such as conservative substitutions (*i. e.* substitutions of one amino acid with another which has a related side chain). Genetically-encoded amino acids are generally divided
- into four families: (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. Phenylalanine, tryptophan, and tyrosine are sometimes classified jointly as aromatic amino acids. In general, substitution of single amino acids within these families does not have a major effect on the biological activity. The polypeptides may also include one or more (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, *etc.*) single
- amino acid deletions relative to the SEQ ID NO sequences. The polypeptides may also include one or more (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, etc.) insertions (e.g. each of 1, 2, 3, 4 or 5 amino acids) relative to the SEQ ID NO sequences.
  [0455] Similarly, a polypeptide used with the invention may comprise an amino acid sequence that:

is identical (i. e. 100% identical) to a sequence disclosed in the sequence listing;

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shares sequence identity (*e.g.* 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) with a sequence disclosed in the sequence listing;

has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 (or more) single amino acid alterations (deletions, insertions, substitutions), which may be at separate locations or may be contiguous, as compared to the sequences of (a) or (b); and

when aligned with a particular sequence from the sequence listing using a pairwise alignment algorithm, each moving window of x amino acids from N-terminus to C-terminus (such that for an alignment that extends to *p* amino acids, where p>x, there are p-x+1 such windows) has at least *x*·*y* identical aligned amino acids, where: *x* is selected from 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 150, 200; *y* is selected from 0.50, 0.60, 0.70, 0.75, 0.80, 0.85, 0.90, 0.91, 0.92, 0.93, 0.94, 0.95, 0.96, 0.97, 0.98, 0.99; and if *x*·*y* is not an integer then it is rounded up to the nearest integer. The preferred pairwise alignment algorithm is the Needleman-Wunsch global alignment algorithm [78], 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 [79].

**[0456]** Where hybrid polypeptides are used, the individual antigens within the hybrid *(i.e.* individual -X-moieties) may be from one or more strains. Where n=2, for instance,  $X_2$  may be from the same strain as  $X_1$  or from a different strain. Where n=3, the strains might be (i)  $X_1=X_2=X_3$  (ii)  $X_1=X_2\neq X_3$  (iii)  $X_1\neq X_2=X_3$  (iv)  $X_1\neq X_2\neq X_3$  or (v)  $X_1=X_3\neq X_2$ , *etc.* 

- <sup>50</sup> **[0457]** Within group (c), deletions or substitutions may be at the N-terminus and/or C-terminus, or may be between the two termini. Thus a truncation is an example of a deletion. Truncations may involve deletion of up to 40 (or more) amino acids at the N-terminus and/or C-terminus. N-terminus truncation can remove leader peptides *e.g.* to facilitate recombinant expression in a heterologous host. C-terminus truncation can remove anchor sequences *e.g.* to facilitate recombinant expression in a heterologous host.
- <sup>55</sup> **[0458]** In general, when an antigen comprises a sequence that is not identical to a complete *S.aureus* sequence from the sequence listing (*e.g.* when it comprises a sequence listing with <100% sequence identity thereto, or when it comprises a fragment thereof) it is preferred in each individual instance that the antigen can elicit an antibody which recognises the respective complete *S.aureus* sequence.

### Mutant bacteria

**[0459]** The invention also provides a *S.aureus* bacterium in which one or more of the antigens from the various antigen groups of the invention has/have been knocked out. Techniques for producing knockout bacteria are well known, and knockout *S.aureus* strains have been reported. A knockout mutation may be situated in the coding region of the gene or may lie within its transcriptional control regions (*e.g.* within its promoter). A knockout mutation will reduce the level of mRNA encoding the antigen to <1% of that produced by the wild-type bacterium, preferably <0.5%, more preferably <0.1%, and most preferably to 0%.

[0460] The invention also provides a *S.aureus* in which one or more of the antigens from the various antigen groups of the invention has a mutation which inhibits its activity. The gene encoding the antigen will have a mutation that changes the encoded amino acid sequence. Mutation may involve deletion, substitution, and/or insertion, any of which may be involve one or more amino acids.

**[0461]** The invention also provides a bacterium, such as a *S.aureus* bacterium, which hyper-expresses an antigen of the invention.

<sup>15</sup> **[0462]** The invention also provides a bacterium, such as a *S. aureus* bacterium, that constitutively expresses an antigen of the invention. The invention also provides a meningococcus comprising a gene encoding an antigen of the invention, wherein the gene is under the control of an inducible promoter.

#### Immunogenic compositions and medicaments

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**[0463]** Immunogenic compositions of the invention may be useful as vaccines. Vaccines according to the invention may either be prophylactic (*i.e.* to prevent infection) or therapeutic (*i.e.* to treat infection), but will typically be prophylactic. **[0464]** Compositions may thus be pharmaceutically acceptable. They will usually include components in addition to the antigens e.g. they typically include one or more pharmaceutical carrier(s) and/or excipient(s). A thorough discussion

<sup>25</sup> of such components is available in reference 273.

**[0465]** Compositions will generally be administered to a mammal in aqueous form. Prior to administration, however, the composition may have been in a non-aqueous form. For instance, although some vaccines are manufactured in aqueous form, then filled and distributed and administered also in aqueous form, other vaccines are lyophilised during manufacture and are reconstituted into an aqueous form at the time of use. Thus a composition of the invention may

<sup>30</sup> be dried, such as a lyophilised formulation.

**[0466]** The composition may include preservatives such as thiomersal or 2-phenoxyethanol. It is preferred, however, that the vaccine should be substantially free from (*i. e.* less than  $5 \mu g/ml$ ) mercurial material *e.g.* thiomersal-free. Vaccines containing no mercury are more preferred. Preservative-free vaccines are particularly preferred.

[0467] To improve thermal stability, a composition may include a temperature protective agent. Further details of such agents are provided below.

**[0468]** To control tonicity, it is preferred to include a physiological salt, such as a sodium salt. Sodium chloride (NaCl) is preferred, which may be present at between 1 and 20 mg/ml *e.g.* about  $10\pm 2$ mg/ml NaCl. Other salts that may be present include potassium chloride, potassium dihydrogen phosphate, disodium phosphate dehydrate, magnesium chloride, calcium chloride, *etc.* 

<sup>40</sup> **[0469]** Compositions will generally have an osmolality of between 200 mOsm/kg and 400 mOsm/kg, preferably between 240-360 mOsm/kg, and will more preferably fall within the range of 290-310 mOsm/kg.

**[0470]** Compositions may include one or more buffers. Typical buffers include: a phosphate buffer; a Tris buffer; a borate buffer; a succinate buffer; a histidine buffer (particularly with an aluminum hydroxide adjuvant); or a citrate buffer. Buffers will typically be included in the 5-20mM range.

<sup>45</sup> [0471] The pH of a composition will generally be between 5.0 and 8.1, and more typically between 6.0 and 8.0 *e.g.*6.5 and 7.5, or between 7.0 and 7.8.

[0472] The composition is preferably sterile. The composition is preferably non-pyrogenic *e.g.* containing <1 EU (endotoxin unit, a standard measure) per dose, and preferably <0.1 EU per dose. The composition is preferably gluten free.</li>
 [0473] The composition may include material for a single immunisation, or may include material for multiple immuni-

<sup>50</sup> sations (*i.e.* a 'multidose' kit). The inclusion of a preservative is preferred in multidose arrangements. As an alternative (or in addition) to including a preservative in multidose compositions, the compositions may be contained in a container having an aseptic adaptor for removal of material.

**[0474]** Human vaccines are typically administered in a dosage volume of about 0.5ml, although a half dose (*i.e.* about 0.25ml) may be administered to children.

<sup>55</sup> **[0475]** Immunogenic compositions of the invention may also comprise one or more immunoregulatory agents. Preferably, one or more of the immunoregulatory agents include one or more adjuvants. The adjuvants may include a TH1 adjuvant and/or a TH2 adjuvant, further discussed below.

[0476] Thus the invention provides an immunogenic composition comprising a combination of:

(1) one or more antigen(s) selected from the first, second, third and fourth antigen groups (as defined above); and (2) an adjuvant, such as an aluminium hydroxide adjuvant (for example, one or more antigens may be adsorbed to aluminium hydroxide).

<sup>5</sup> **[0477]** For instance, the invention provides an immunogenic composition comprising a combination of a sta006 antigen and an adjuvant, such as an aluminium hydroxide adjuvant. Similarly, the invention provides an immunogenic composition comprising a combination of a sta011 antigen and an adjuvant, such as an aluminium hydroxide adjuvant. These compositions are ideally buffered *e.g.* with a histidine buffer.

[0478] Adjuvants which may be used in compositions of the invention include, but are not limited to:

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# A. Mineral-containing compositions

**[0479]** Mineral containing compositions suitable for use as adjuvants in the invention include mineral salts, such as aluminium salts and calcium salts (or mixtures thereof). Calcium salts include calcium phosphate (*e.g.* the "CAP" particles disclosed in ref. 80). Aluminum salts include hydroxides, phosphates, sulfates, *etc.*, with the salts taking any suitable form (*e.g.* gel, crystalline, amorphous, *etc.*). Adsorption to these salts is preferred (*e.g.* all antigens may be adsorbed). The mineral containing compositions may also be formulated as a particle of metal salt [81].

[0480] The adjuvants known as aluminum hydroxide and aluminum phosphate may be used. These names are conventional, but are used for convenience only, as neither is a precise description of the actual chemical compound which is present (*e.g.* see chapter 9 of reference 82)). The invention can use any of the "hydroxide" or "phosphate" adjuvants that are in general use as adjuvants. The adjuvants known as "aluminium hydroxide" are typically aluminium oxyhydroxide salts, which are usually at least partially crystalline. The adjuvants known as "aluminium hydroxyphosphate" are typically aluminium hydroxyphosphates, often also containing a small amount of sulfate (*i. e.* aluminium hydroxyphosphate sulfate). They may be obtained by precipitation, and the reaction conditions and concentrations during precipitation influence

- the degree of substitution of phosphate for hydroxyl in the salt. [0481] A fibrous morphology (*e.g.* as seen in transmission electron micrographs) is typical for aluminium hydroxide adjuvants. The pl of aluminium hydroxide adjuvants is typically about 11 *i.e.* the adjuvant itself has a positive surface charge at physiological pH. Adsorptive capacities of between 1.8-2.6 mg protein per mg Al<sup>+++</sup> at pH 7.4 have been reported for aluminium hydroxide adjuvants.
- <sup>30</sup> [0482] Aluminium phosphate adjuvants generally have a PO<sub>4</sub>/Al molar ratio between 0.3 and 1.2, preferably between 0.8 and 1.2, and more preferably 0.95±0.1. The aluminium phosphate will generally be amorphous, particularly for hydroxyphosphate salts. A typical adjuvant is amorphous aluminium hydroxyphosphate with PO<sub>4</sub>/Al molar ratio between 0.84 and 0.92, included at 0.6mg Al<sup>3+</sup>/ml. The aluminium phosphate will generally be particulate (e.g. plate-like morphology as seen in transmission electron micrographs). Typical diameters of the particles are in the range 0.5-20µm
- (e.g. about 5-10µm) after any antigen adsorption. Adsorptive capacities of between 0.7-1.5 mg protein per mg Al<sup>+++</sup> at pH 7.4 have been reported for aluminium phosphate adjuvants.
   [0483] The point of zero charge (PZC) of aluminium phosphate is inversely related to the degree of substitution of phosphate for hydroxyl, and this degree of substitution can vary depending on reaction conditions and concentration of

<sup>40</sup> ions in solution (more phosphate = more acidic PZC) or by adding a buffer such as a histidine buffer (makes PZC more basic). Aluminium phosphates used according to the invention will generally have a PZC of between 4.0 and 7.0, more preferably between 5.0 and 6.5 e.g. about 5.7.

**[0484]** As shown below, adsorption of *S.aureus* protein antigens (except IsdA, Sta019 and Sta073) to an aluminium hydroxide adjuvant is advantageous, particularly in a multi-protein combination (in which all antigens may be adsorbed). A histidine buffer can usefully be included in such adjuvanted compositions.

A histidine buffer can usefully be included in such adjuvanted compositions.
 **[0485]** Suspensions of aluminium salts used to prepare compositions of the invention may contain a buffer (*e.g.* a phosphate or a histidine or a Tris buffer), but this is not always necessary. The suspensions are preferably sterile and pyrogen-free. A suspension may include free aqueous phosphate ions *e.g.* present at a concentration between 1.0 and 20 mM, preferably between 5 and 15 mM, and more preferably about 10 mM. The suspensions may also comprise sodium chloride.

**[0486]** The invention can use a mixture of both an aluminium hydroxide and an aluminium phosphate. In this case there may be more aluminium phosphate than hydroxide *e.g.* a weight ratio of at least 2:1 *e.g.*  $\geq$ 5:1,  $\geq$ 6:1,  $\geq$ 7:1,  $\geq$ 8:1,  $\geq$ 9:1, *etc.* 

[0487] The concentration of Al<sup>+++</sup> in a composition for administration to a patient is preferably less than 10mg/ml *e.g.* <sup>55</sup> ≤5 mg/ml, ≤4 mg/ml, ≤3 mg/ml, ≤2 mg/ml, ≤1 mg/ml, *etc.* A preferred range is between 0.3 and 1mg/ml. A maximum of 0.85mg/dose is preferred.

### B. Oil Emulsions

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**[0488]** Oil emulsion compositions suitable for use as adjuvants in the invention include squalene-water emulsions, such as MF59 [Chapter 10 of ref. 82; see also ref. 83] (5% Squalene, 0.5% Tween 80, and 0.5% Span 85, formulated into submicron particles using a microfluidizer). Complete Freund's adjuvant (CFA) and incomplete Freund's adjuvant (IFA) may also be used.

**[0489]** Various oil-in-water emulsion adjuvants are known, and they typically include at least one oil and at least one surfactant, with the oil(s) and surfactant(s) being biodegradable (metabolisable) and biocompatible. The oil droplets in the emulsion are generally less than 5  $\mu$ m in diameter, and ideally have a sub-micron diameter, with these small sizes being achieved with a microfluidiser to provide stable emulsions. Droplets with a size less than 220nm are preferred as

they can be subjected to filter sterilization. [0490] The emulsion can comprise oils such as those from an animal (such as fish) or vegetable source. Sources for vegetable oils include nuts, seeds and grains. Peanut oil, soybean oil, coconut oil, and olive oil, the most commonly available, exemplify the nut oils. Jojoba oil can be used *e.g.* obtained from the jojoba bean. Seed oils include safflower

- <sup>15</sup> oil, cottonseed oil, sunflower seed oil, sesame seed oil and the like. In the grain group, corn oil is the most readily available, but the oil of other cereal grains such as wheat, oats, rye, rice, teff, triticale and the like may also be used. 6-10 carbon fatty acid esters of glycerol and 1,2-propanediol, while not occurring naturally in seed oils, may be prepared by hydrolysis, separation and esterification of the appropriate materials starting from the nut and seed oils. Fats and oils from mammalian milk are metabolizable and may therefore be used in the practice of this invention. The procedures for
- 20 separation, purification, saponification and other means necessary for obtaining pure oils from animal sources are well known in the art. Most fish contain metabolizable oils which may be readily recovered. For example, cod liver oil, shark liver oils, and whale oil such as spermaceti exemplify several of the fish oils which may be used herein. A number of branched chain oils are synthesized biochemically in 5-carbon isoprene units and are generally referred to as terpenoids. Shark liver oil contains a branched, unsaturated terpenoids known as squalene, 2,6,10,15,19,23-hexamethyl-
- 26 2,6,10,14,18,22-tetracosahexaene, which is particularly preferred herein. Squalane, the saturated analog to squalene, is also a preferred oil. Fish oils, including squalene and squalane, are readily available from commercial sources or may be obtained by methods known in the art. Other preferred oils are the tocopherols (see below). Mixtures of oils can be used.
   [0491] Surfactants can be classified by their 'HLB' (hydrophile/lipophile balance). Preferred surfactants of the invention have a HLB of at least 10, preferably at least 15, and more preferably at least 16. The invention can be used with
- <sup>30</sup> surfactants including, but not limited to: the polyoxyethylene sorbitan esters surfactants (commonly referred to as the Tweens), especially polysorbate 20 and polysorbate 80; copolymers of ethylene oxide (EO), propylene oxide (PO), and/or butylene oxide (BO), sold under the DOWFAX<sup>™</sup> tradename, such as linear EO/PO block copolymers; octoxynols, which can vary in the number of repeating ethoxy (oxy-1,2-ethanediyl) groups, with octoxynol-9 (Triton X-100, or t-octylphenoxypolyethoxyethanol) being of particular interest; (octylphenoxy)polyethoxyethanol (IGEPAL CA-630/NP-40);
- <sup>35</sup> phospholipids such as phosphatidylcholine (lecithin); nonylphenol ethoxylates, such as the Tergitol<sup>™</sup> NP series; polyoxyethylene fatty ethers derived from lauryl, cetyl, stearyl and oleyl alcohols (known as Brij surfactants), such as triethyleneglycol monolauryl ether (Brij 30); and sorbitan esters (commonly known as the SPANs), such as sorbitan trioleate (Span 85) and sorbitan monolaurate. Non-ionic surfactants are preferred. Preferred surfactants for including in the emulsion are Tween 80 (polyoxyethylene sorbitan monooleate), Span 85 (sorbitan trioleate), lecithin and Triton X-100.
- <sup>40</sup> **[0492]** Mixtures of surfactants can be used e.g. Tween 80/Span 85 mixtures. A combination of a polyoxyethylene sorbitan ester such as polyoxyethylene sorbitan monooleate (Tween 80) and an octoxynol such as t-octylphenoxypolyethoxyethanol (Triton X-100) is also suitable. Another useful combination comprises laureth 9 plus a polyoxyethylene sorbitan ester and/or an octoxynol.
- [0493] Preferred amounts of surfactants (% by weight) are: polyoxyethylene sorbitan esters (such as Tween 80) 0.01 to 1%, in particular about 0.1 %; octyl- or nonylphenoxy polyoxyethanols (such as Triton X-100, or other detergents in the Triton series) 0.001 to 0.1 %, in particular 0.005 to 0.02%; polyoxyethylene ethers (such as laureth 9) 0.1 to 20 %, preferably 0.1 to 10 % and in particular 0.1 to 1 % or about 0.5%.

**[0494]** Preferred emulsion adjuvants have an average droplets size of <1  $\mu$ m e.g.  $\leq$ 750nm,  $\leq$ 500nm,  $\leq$ 400nm,  $\leq$ 300nm,  $\leq$ 250nm,  $\leq$ 220nm,  $\leq$ 220nm, or smaller. These droplet sizes can conveniently be achieved by techniques such as microfluidisation.

[0495] Specific oil-in-water emulsion adjuvants useful with the invention include, but are not limited to:

● A submicron emulsion of squalene, Tween 80, and Span 85. The composition of the emulsion by volume can be about 5% squalene, about 0.5% polysorbate 80 and about 0.5% Span 85. In weight terms, these ratios become 4.3% squalene, 0.5% polysorbate 80 and 0.48% Span 85. This adjuvant is known as 'MF59' [84-86], as described in more detail in Chapter 10 of ref. 87 and chapter 12 of ref. 88. The MF59 emulsion advantageously includes citrate ions e.g. 10mM sodium citrate buffer.

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• An emulsion of squalene, a tocopherol, and polysorbate 80 (Tween 80). The emulsion may include phosphate buffered saline. It may also include Span 85 (*e.g.* at 1%) and/or lecithin. These emulsions may have from 2 to 10% squalene, from 2 to 10% tocopherol and from 0.3 to 3% Tween 80, and the weight ratio of squalene:tocopherol is preferably  $\leq$ 1 as this provides a more stable emulsion. Squalene and Tween 80 may be present volume ratio of about 5:2 or at a weight ratio of about 11:5. One such emulsion can be made by dissolving Tween 80 in PBS to give a 2% solution, then mixing 90ml of this solution with a mixture of (5g of DL- $\alpha$ -tocopherol and 5ml squalene), then microfluidising the mixture. The resulting emulsion may have submicron oil droplets *e.g.* with an average diameter of between 100 and 250nm, preferably about 180nm. The emulsion may also include a 3-de-O-acylated monophosphoryl lipid A (3d-MPL). Another useful emulsion of this type may comprise, per human dose, 0.5-10 mg squalene, 0.5-11 mg tocopherol, and 0.1-4 mg polysorbate 80 [89].

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• An emulsion of squalene, a tocopherol, and a Triton detergent (*e.g.* Triton X-100). The emulsion may also include a 3d-MPL (see below). The emulsion may contain a phosphate buffer.

- An emulsion comprising a polysorbate (e.g. polysorbate 80), a Triton detergent (e.g. Triton X-100) and a tocopherol (e.g. an α-tocopherol succinate). The emulsion may include these three components at a mass ratio of about 75: 11:10 (e.g. 750µg/ml polysorbate 80, 110µg/ml Triton X-100 and 100µg/ml α-tocopherol succinate), and these concentrations should include any contribution of these components from antigens. The emulsion may also include squalene. The emulsion may also include a 3d-MPL (see below). The aqueous phase may contain a phosphate buffer.
  - An emulsion of squalane, polysorbate 80 and poloxamer 401 ("Pluronic<sup>™</sup> L121"). The emulsion can be formulated in phosphate buffered saline, pH 7.4. This emulsion is a useful delivery vehicle for muramyl dipeptides, and has been used with threonyl-MDP in the "SAF-1" adjuvant [90] (0.05-1% Thr-MDP, 5% squalane, 2.5% Pluronic L121 and 0.2% polysorbate 80). It can also be used without the Thr-MDP, as in the "AF" adjuvant [91] (5% squalane, 1.25% Pluronic L121 and 0.2% polysorbate 80). Microfluidisation is preferred.
    - An emulsion comprising squalene, an aqueous solvent, a polyoxyethylene alkyl ether hydrophilic nonionic surfactant (e.g. polyoxyethylene (12) cetostearyl ether) and a hydrophobic nonionic surfactant (e.g. a sorbitan ester or mannide ester, such as sorbitan monoleate or 'Span 80'). The emulsion is preferably thermoreversible and/or has at least 90% of the oil droplets (by volume) with a size less than 200 nm [92]. The emulsion may also include one or more of: alditol; a cryoprotective agent (e.g. a sugar, such as dodecylmaltoside and/or sucrose); and/or an alkylpolyglycoside. The emulsion may include a TLR4 agonist [93]. Such emulsions may be lyophilized.
  - An emulsion of squalene, poloxamer 105 and Abil-Care [94]. The final concentration (weight) of these components in adjuvanted vaccines are 5% squalene, 4% poloxamer 105 (pluronic polyol) and 2% Abil-Care 85 (Bis-PEG/PPG-16/16 PEG/PPG-16/16 dimethicone; caprylic/capric triglyceride).
    - An emulsion having from 0.5-50% of an oil, 0.1-10% of a phospholipid, and 0.05-5% of a non-ionic surfactant. As described in reference 95, preferred phospholipid components are phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, sphingomyelin and cardiolipin. Submicron droplet sizes are advantageous.
    - A submicron oil-in-water emulsion of a non-metabolisable oil (such as light mineral oil) and at least one surfactant (such as lecithin, Tween 80 or Span 80). Additives may be included, such as QuilA saponin, cholesterol, a saponinlipophile conjugate (such as GPI-0100, described in reference 96, produced by addition of aliphatic amine to desacylsaponin via the carboxyl group of glucuronic acid), dimethyidioctadecylammonium bromide and/or N,N-dioctadecyl-N,N-bis (2-hydroxyethyl)propanediamine.
    - An emulsion in which a saponin (*e.g.* QuilA or QS21) and a sterol (*e.g.* a cholesterol) are associated as helical micelles [97].
      - An emulsion comprising a mineral oil, a non-ionic lipophilic ethoxylated fatty alcohol, and a non-ionic hydrophilic surfactant (*e.g.* an ethoxylated fatty alcohol and/or polyoxyethylene-polyoxypropylene block copolymer) [98].
- An emulsion comprising a mineral oil, a non-ionic hydrophilic ethoxylated fatty alcohol, and a non-ionic lipophilic surfactant (*e.g.* an ethoxylated fatty alcohol and/or polyoxyethylene-polyoxypropylene block copolymer) [98].
  - [0496] In some embodiments an emulsion may be mixed with antigen extemporaneously, at the time of delivery, and
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thus the adjuvant and antigen may be kept separately in a packaged or distributed vaccine, ready for final formulation at the time of use. In other embodiments an emulsion is mixed with antigen during manufacture, and thus the composition is packaged in a liquid adjuvanted form,. The antigen will generally be in an aqueous form, such that the vaccine is finally prepared by mixing two liquids. The volume ratio of the two liquids for mixing can vary (e.g. between 5:1 and 1:

<sup>5</sup> 5) but is generally about 1:1. Where concentrations of components are given in the above descriptions of specific emulsions, these concentrations are typically for an undiluted composition, and the concentration after mixing with an antigen solution will thus decrease.

**[0497]** Where a composition includes a tocopherol, any of the  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\epsilon$  or  $\xi$  tocopherols can be used, but  $\alpha$ -tocopherols are preferred. The tocopherol can take several forms *e.g.* different salts and/or isomers. Salts include organic

- <sup>10</sup> salts, such as succinate, acetate, nicotinate, *etc.* D- $\alpha$ -tocopherol and DL- $\alpha$ -tocopherol can both be used. Tocopherols are advantageously included in vaccines for use in elderly patients (*e.g.* aged 60 years or older) because vitamin E has been reported to have a positive effect on the immune response in this patient group [99]. They also have antioxidant properties that may help to stabilize the emulsions [100]. A preferred  $\alpha$ -tocopherol is DL- $\alpha$ -tocopherol, and the preferred salt of this tocopherol is the succinate. The succinate salt has been found to cooperate with TNF-related ligands *in vivo*.
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### C. Saponin formulations [chapter 22 of ref. 82]

**[0498]** Saponin formulations may also be used as adjuvants in the invention. Saponins are a heterogeneous group of sterol glycosides and triterpenoid glycosides that are found in the bark, leaves, stems, roots and even flowers of a wide range of plant species. Saponin from the bark of the *Quillaia saponaria* Molina tree have been widely studied as

- wide range of plant species. Saponin from the bark of the Quillaia saponaria Molina tree have been widely studied as adjuvants. Saponin can also be commercially obtained from Smilax ornata (sarsaprilla), Gypsophilla paniculata (brides veil), and Saponaria officianalis (soap root). Saponin adjuvant formulations include purified formulations, such as QS21, as well as lipid formulations, such as ISCOMs. QS21 is marketed as Stimulon™.
- [0499] Saponin compositions have been purified using HPLC and RP-HPLC. Specific purified fractions using these techniques have been identified, including QS7, QS17, QS18, QS21, QH-A, QH-B and QH-C. Preferably, the saponin is QS21. A method of production of QS21 is disclosed in ref. 101. Saponin formulations may also comprise a sterol, such as cholesterol [102].

**[0500]** Combinations of saponins and cholesterols can be used to form unique particles called immunostimulating complexs (ISCOMs) [chapter 23 of ref. 82]. ISCOMs typically also include a phospholipid such as phosphatidyleth-

<sup>30</sup> anolamine or phosphatidylcholine. Any known saponin can be used in ISCOMs. Preferably, the ISCOM includes one or more of QuilA, QHA & QHC. ISCOMs are further described in refs. 102-104. Optionally, the ISCOMS may be devoid of additional detergent [105].

[0501] A review of the development of saponin based adjuvants can be found in refs. 106 & 107.

# 35 D. Virosomes and virus-like particles

**[0502]** Virosomes and virus-like particles (VLPs) can also be used as adjuvants in the invention. These structures generally contain one or more proteins from a virus optionally combined or formulated with a phospholipid. They are generally non-pathogenic, non-replicating and generally do not contain any of the native viral genome. The viral proteins may be recombinantly produced or isolated from whole viruses. These viral proteins suitable for use in virosomes or VLPs include proteins derived from influenza virus (such as HA or NA), Hepatitis B virus (such as core or capsid proteins), Hepatitis E virus, measles virus, Sindbis virus, Rotavirus, Foot-and-Mouth Disease virus, Retrovirus, Norwalk virus, human Papilloma virus, HIV, RNA-phages, Qß-phage (such as coat proteins), GA-phage, fr-phage, AP205 phage, and Ty (such as retrotransposon Ty protein pl). VLPs are discussed further in refs. 108-113. Virosomes are discussed further in, for example, ref. 114

E. Bacterial or microbial derivatives

 [0503] Adjuvants suitable for use in the invention include bacterial or microbial derivatives such as non-toxic derivatives
 of enterobacterial lipopolysaccharide (LPS), Lipid A derivatives, immunostimulatory oligonucleotides and ADP-ribosylating toxins and detoxified derivatives thereof.

**[0504]** Non-toxic derivatives of LPS include monophosphoryl lipid A (MPL) and 3-O-deacylated MPL (3dMPL). 3dMPL is a mixture of 3 de-O-acylated monophosphoryl lipid A with 4, 5 or 6 acylated chains. A preferred "small particle" form of 3 De-O-acylated monophosphoryl lipid A is disclosed in ref. 115. Such "small particles" of 3dMPL are small enough

to be sterile filtered through a 0.22µm membrane [115]. Other non-toxic LPS derivatives include monophosphoryl lipid A mimics, such as aminoalkyl glucosaminide phosphate derivatives *e.g.* RC-529 [116,117].
 [0505] Lipid A derivatives include derivatives of lipid A from *Escherichia coli* such as OM-174. OM-174 is described for example in refs. 118 & 119.

**[0506]** Immunostimulatory oligonucleotides suitable for use as adjuvants in the invention include nucleotide sequences containing a CpG motif (a dinucleotide sequence containing an unmethylated cytosine linked by a phosphate bond to a guanosine). Double-stranded RNAs and oligonucleotides containing palindromic or poly(dG) sequences have also been shown to be immunostimulatory.

- <sup>5</sup> **[0507]** The CpG's can include nucleotide modifications/analogs such as phosphorothioate modifications and can be double-stranded or single-stranded. References 120, 121 and 122 disclose possible analog substitutions *e.g.* replacement of guanosine with 2'-deoxy-7-deazaguanosine. The adjuvant effect of CpG oligonucleotides is further discussed in refs. 123-128.
- [0508] The CpG sequence may be directed to TLR9, such as the motif GTCGTT or TTCGTT [129]. The CpG sequence may be specific for inducing a Th1 immune response, such as a CpG-A ODN, or it may be more specific for inducing a B cell response, such a CpG-B ODN. CpG-A and CpG-B ODNs are discussed in refs. 130-132. Preferably, the CpG is a CpG-A ODN.

**[0509]** Preferably, the CpG oligonucleotide is constructed so that the 5' end is accessible for receptor recognition. Optionally, two CpG oligonucleotide sequences may be attached at their 3' ends to form "immunomers". See, for example, refs. 129 & 133-135.

**[0510]** A useful CpG adjuvant is CpG7909, also known as ProMune<sup>TM</sup> (Coley Pharmaceutical Group, Inc.). Another is CpG1826. As an alternative, or in addition, to using CpG sequences, TpG sequences can be used [136], and these oligonucleotides may be free from unmethylated CpG motifs. The immunostimulatory oligonucleotide may be pyrimidine-rich. For example, it may comprise more than one consecutive thymidine nucleotide (*e.g.* TTTT, as disclosed in ref.

- 136), and/or it may have a nucleotide composition with >25% thymidine (e.g. >35%, >40%, >50%, >60%, >80%, etc.). For example, it may comprise more than one consecutive cytosine nucleotide (e.g. CCCC, as disclosed in ref. 136), and/or it may have a nucleotide composition with >25% cytosine (e.g. >35%, >40%, >50%, >60%, >80%, etc.). These oligonucleotides may be free from unmethylated CpG motifs. Immunostimulatory oligonucleotides will typically comprise at least 20 nucleotides. They may comprise fewer than 100 nucleotides.
- 25 [0511] A particularly useful adjuvant based around immunostimulatory oligonucleotides is known as IC-31™ [137]. Thus an adjuvant used with the invention may comprise a mixture of (i) an oligonucleotide (e.g. between 15-40 nucleotides) including at least one (and preferably multiple) Cpl motifs (*i.e.* a cytosine linked to an inosine to form a dinucleotide), and (ii) a polycationic polymer, such as an oligopeptide (e.g. between 5-20 amino acids) including at least one (and preferably multiple) Lys-Arg-Lys tripeptide sequence(s). The oligonucleotide may be a deoxynucleotide comprising 26-
- <sup>30</sup> mer sequence 5'-(IC)<sub>13</sub>-3' (SEQ ID NO: 175). The polycationic polymer may be a peptide comprising 11-mer amino acid sequence KLKLLLLKLK (SEQ ID NO: 176). The oligonucleotide and polymer can form complexes *e.g.* as disclosed in references 138 & 139.

**[0512]** Bacterial ADP-ribosylating toxins and detoxified derivatives thereof may be used as adjuvants in the invention. Preferably, the protein is derived from *E.coli* (*E.coli* heat labile enterotoxin "LT"), cholera ("CT"), or pertussis ("PT"). The

- <sup>35</sup> use of detoxified ADP-ribosylating toxins as mucosal adjuvants is described in ref. 140 and as parenteral adjuvants in ref. 141. The toxin or toxoid is preferably in the form of a holotoxin, comprising both A and B subunits. Preferably, the A subunit contains a detoxifying mutation; preferably the B subunit is not mutated. Preferably, the adjuvant is a detoxified LT mutant such as LT-K63, LT-R72, and LT-G192. The use of ADP-ribosylating toxins and detoxified derivatives thereof, particularly LT-K63 and LT-R72, as adjuvants can be found in refs. 142-149. A useful CT mutant is or CT-E29H [150].
- <sup>40</sup> Numerical reference for amino acid substitutions is preferably based on the alignments of the A and B subunits of ADPribosylating toxins set forth in ref. 151, specifically incorporated herein by reference in its entirety.

#### F. Human immunomodulators

<sup>45</sup> [0513] Human immunomodulators suitable for use as adjuvants in the invention include cytokines, such as interleukins (e.g. IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12 [152], etc.) [153], interferons (e.g. interferon-γ), macrophage colony stimulating factor, and tumor necrosis factor. A preferred immunomodulator is IL-12.

#### G. Bioadhesives and Mucoadhesives

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**[0514]** Bioadhesives and mucoadhesives may also be used as adjuvants in the invention. Suitable bioadhesives include esterified hyaluronic acid microspheres [154] or mucoadhesives such as cross-linked derivatives of poly(acrylic acid), polyvinyl alcohol, polyvinyl pyrollidone, polysaccharides and carboxymethylcellulose. Chitosan and derivatives thereof may also be used as adjuvants in the invention [155].

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H. Microparticles

[0515] Microparticles may also be used as adjuvants in the invention. Microparticles (i.e. a particle of ~100nm to ~

150 $\mu$ m in diameter, more preferably ~200nm to ~30 $\mu$ m in diameter, and most preferably ~500nm to ~10 $\mu$ m in diameter) formed from materials that are biodegradable and non-toxic (*e.g.* a poly( $\alpha$ -hydroxy acid), a polyhydroxybutyric acid, a polyorthoester, a polyanhydride, a polycaprolactone, *etc.*), with poly(lactide-co-glycolide) are preferred, optionally treated to have a negatively-charged surface (*e.g.* with SDS) or a positively-charged surface (*e.g.* with a cationic detergent, such as CTAB).

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I. Liposomes (Chapters 13 & 14 of ref. 82)

[0516] Examples of liposome formulations suitable for use as adjuvants are described in refs. 156-158.

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J. Polyoxyethylene ether and polyoxyethylene ester formulations

**[0517]** Adjuvants suitable for use in the invention include polyoxyethylene ethers and polyoxyethylene esters [159]. Such formulations further include polyoxyethylene sorbitan ester surfactants in combination with an octoxynol [160] as well as polyoxyethylene alkyl ethers or ester surfactants in combination with at least one additional non-ionic surfactant such as an octoxynol [161]. Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether (laureth 9), polyoxyethylene-9-steoryl ether, polyoxytheylene-8-steoryl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether.

20 K. Phosphazenes

**[0518]** A phosphazene, such as poly[di(carboxylatophenoxy)phosphazene] ("PCPP") as described, for example, in references 162 and 163, may be used.

<sup>25</sup> L. Muramyl peptides

**[0519]** Examples of muramyl peptides suitable for use as adjuvants in the invention include N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-normuramyl-L-alanyl-D-isoglutamine (nor-MDP), and N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-*sn*-glycero-3-hydroxyphosphoryloxy)-ethylamine MTP-PE).

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### M. Imidazoquinolone Compounds.

**[0520]** Examples of imidazoquinolone compounds suitable for use adjuvants in the invention include Imiquimod ("R-837") [164,165], Resiquimod ("R-848") [166], and their analogs; and salts thereof (*e.g.* the hydrochloride salts). Further details about immunostimulatory imidazoquinolines can be found in references 167 to 171.

#### N. Substituted ureas

[0521] Substituted ureas useful as adjuvants include compounds of formula I, II or III, or salts thereof:

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as defined in reference 172, such as 'ER 803058', 'ER 803732', 'ER 804053', ER 804058', 'ER 804059', 'ER 804442', 'ER 804680', 'ER 804764', ER 803022 or 'ER 804057' e.g.:



#### <sup>30</sup> O. Further adjuvants

**[0522]** Further adjuvants that may be used with the invention include:

• An aminoalkyl glucosaminide phosphate derivative, such as RC-529 [173,174].

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**[0523]** Cyclic diguanylate ('c-di-GMP'), which has been reported as a useful adjuvant for *S. aureus* vaccines [175]. **[0524]** A thiosemicarbazone compound, such as those disclosed in reference 176. Methods of formulating, manufacturing, and screening for active compounds are also described in reference 176. The thiosemicarbazones are particularly effective in the stimulation of human peripheral blood mononuclear cells for the production of cytokines, such as TNF- $\alpha$ . **[0525]** A tryptanthrin compound, such as those disclosed in reference 177. Methods of formulating, manufacturing, and screening for active compounds are also described in reference 177. The thiosemicarbazones are particularly effective in the stimulation of human peripheral blood mononuclear cells for the production of cytokines, such as TNF- $\alpha$ .

A nucleoside analog, such as: (a) Isatorabine (ANA-245; 7-thia-8-oxoguanosine):

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and prodrugs thereof; (b) ANA975; (c) ANA-025-1; (d) ANA380; (e) the compounds disclosed in references 178 to 180Loxoribine (7-allyl-8-oxoguanosine) [181].

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- Compounds disclosed in reference 182, including: Acylpiperazine compounds, Indoledione compounds, Tetrahyd-• raisoquinoline (THIQ) compounds, Benzocyclodione compounds, Aminoazavinyl compounds, Aminobenzimidazole quinolinone (ABIQ) compounds [183,184], Hydrapthalamide compounds, Benzophenone compounds, Isoxazole compounds, Sterol compounds, Quinazilinone compounds, Pyrrole compounds [185], Anthraguinone compounds, Quinoxaline compounds, Triazine compounds, Pyrazalopyrimidine compounds, and Benzazole compounds [186].
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- Compounds containing lipids linked to a phosphate-containing acyclic backbone, such as the TLR4 antagonist E5564 [187,188]:
- 10 A polyoxidonium polymer [189,190] or other N-oxidized polyethylene-piperazine derivative.
  - Methyl inosine 5'-monophosphate ("MIMP") [191]. •
  - A polyhydroxlated pyrrolizidine compound [192], such as one having formula:
    - CHOH
- where R is selected from the group comprising hydrogen, straight or branched, unsubstituted or substituted, saturated 25 or unsaturated acyl, alkyl (e.g. cycloalkyl), alkenyl, alkynyl and aryl groups, or a pharmaceutically acceptable salt or derivative thereof. Examples include, but are not limited to: casuarine, casuarine-6-α-D-glucopyranose, 3-epi-casuarine, 7-epi-casuarine, 3,7-diepi-casuarine, etc.
- A CDId ligand, such as an  $\alpha$ -glycosylceramide [193-200] (e.g.  $\alpha$ -galactosylceramide), phytosphingosine-containing 30 α-glycosylceramides, OCH, KRN7000 [(2S,3S,4R)-1-O-(α-D-galactopyranosyl)-2-(N-hexacosanoylamino)-1,3,4octadecanetriol], CRONY-101, 3"-O-sulfo-galactosylceramide, etc.
  - A gamma inulin [201]or derivative thereof, such as algammulin.

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OPO(OH)2 CH<sub>3</sub>C H<sub>2</sub>)<sub>9</sub>CH<sub>3</sub> (HO)2OPO Hſ CH<sub>3</sub>(CH<sub>2</sub>)<sub>6</sub> (CH<sub>2</sub>)<sub>6</sub>CH<sub>3</sub> o 40 CH30 45

Adjuvant combinations

50 the following adjuvant compositions may be used in the invention: (1) a saponin and an oil-in-water emulsion [202]; (2) a saponin (e.g. QS21) + a non-toxic LPS derivative (e.g. 3dMPL) [203]; (3) a saponin (e.g. QS21) + a non-toxic LPS derivative (e.g. 3dMPL) + a cholesterol; (4) a saponin (e.g. QS21) + 3dMPL + IL-12 (optionally + a sterol) [204]; (5) combinations of 3dMPL with, for example, QS21 and/or oil-in-water emulsions [205]; (6) SAF, containing 10% squalane,

0.4% Tween 80<sup>™</sup>, 5% pluronic-block polymer L121, and thr-MDP, either microfluidized into a submicron emulsion or 55 vortexed to generate a larger particle size emulsion. (7) Ribi™ adjuvant system (RAS), (Ribi Immunochem) containing 2% squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (Detox™); and (8) one or more mineral salts (such as an aluminum salt) + a non-toxic derivative of LPS (such as 3dMPL).

[0526] The invention may also comprise combinations of one or more of the adjuvants identified above. For example,

[0527] Other substances that act as immunostimulating agents are disclosed in chapter 7 of ref. 82.

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**[0528]** The use of an aluminium hydroxide and/or aluminium phosphate adjuvant is particularly preferred, and antigens are generally adsorbed to these salts. Calcium phosphate is another preferred adjuvant. Other preferred adjuvant combinations include combinations of Th1 and Th2 adjuvants such as CpG & alum or resignimod & alum. A combination of aluminium phosphate and 3dMPL may be used.

**[0529]** The compositions of the invention may elicit both a cell mediated immune response as well as a humoral immune response. This immune response will preferably induce long lasting (e.g. neutralising) antibodies and a cell mediated immunity that can quickly respond upon exposure to pnuemococcus.

[0530] Two types of T cells, CD4 and CD8 cells, are generally thought necessary to initiate and/or enhance cell mediated immunity and humoral immunity. CD8 T cells can express a CD8 co-receptor and are commonly referred to as Cytotoxic T lymphocytes (CTLs). CD8 T cells are able to recognized or interact with antigens displayed on MHC Class I molecules.

**[0531]** CD4 T cells can express a CD4 co-receptor and are commonly referred to as T helper cells. CD4 T cells are able to recognize antigenic peptides bound to MHC class II molecules. Upon interaction with a MHC class II molecule,

<sup>15</sup> the CD4 cells can secrete factors such as cytokines. These secreted cytokines can activate B cells, cytotoxic T cells, macrophages, and other cells that participate in an immune response. Helper T cells or CD4+ cells can be further divided into two functionally distinct subsets: TH1 phenotype and TH2 phenotypes which differ in their cytokine and effector function.

[0532] Activated TH1 cells enhance cellular immunity (including an increase in antigen-specific CTL production) and

- are therefore of particular value in responding to intracellular infections. Activated TH1 cells may secrete one or more of IL-2, IFN-γ, and TNF-β. A TH1 immune response may result in local inflammatory reactions by activating macrophages, NK (natural killer) cells, and CD8 cytotoxic T cells (CTLs). A TH1 immune response may also act to expand the immune response by stimulating growth of B and T cells with IL-12. TH1 stimulated B cells may secrete IgG2a.
   [0533] Activated TH2 cells enhance antibody production and are therefore of value in responding to extracellular
- <sup>25</sup> infections. Activated TH2 cells may secrete one or more of IL-4, IL-5, IL-6, and IL-10. A TH2 immune response may result in the production of IgGI, IgE, IgA and memory B cells for future protection.
   [0534] An enhanced immune response may include one or more of an enhanced TH1 immune response and a TH2 immune response.
- **[0535]** A TH1 immune response may include one or more of an increase in CTLs, an increase in one or more of the cytokines associated with a TH1 immune response (such as IL-2, IFN-γ, and TNF-β), an increase in activated macro-phages, an increase in NK activity, or an increase in the production of IgG2a. Preferably, the enhanced TH1 immune response will include an increase in IgG2a production.

**[0536]** A TH1 immune response may be elicited using a TH1 adjuvant. A TH1 adjuvant will generally elicit increased levels of IgG2a production relative to immunization of the antigen without adjuvant. TH1 adjuvants suitable for use in

- <sup>35</sup> the invention may include for example saponin formulations, virosomes and virus like particles, non-toxic derivatives of enterobacterial lipopolysaccharide (LPS), immunostimulatory oligonucleotides. Immunostimulatory oligonucleotides, such as oligonucleotides containing a CpG motif, are preferred TH1 adjuvants for use in the invention. [0537] A TH2 immune response may include one or more of an increase in one or more of the cytokines associated with a TH2 immune response (such as IL-4, IL-5, IL-6 and IL-10), or an increase in the production of IgGI, IgE, IgA and
- 40 memory B cells. Preferably, the enhanced TH2 immune resonse will include an increase in IgGI production. [0538] A TH2 immune response may be elicited using a TH2 adjuvant. A TH2 adjuvant will generally elicit increased levels of IgG1 production relative to immunization of the antigen without adjuvant. TH2 adjuvants suitable for use in the invention include, for example, mineral containing compositions, oil-emulsions, and ADP-ribosylating toxins and detoxified derivatives thereof. Mineral containing compositions, such as aluminium salts are preferred TH2 adjuvants for use
  - in the invention. **[0539]** Preferably, the invention includes a composition comprising a combination of a TH1 adjuvant and a TH2 adjuvant. Preferably, such a composition elicits an enhanced TH1 and an enhanced TH2 response, i.e., an increase in the production of both IgGI and IgG2a production relative to *immunization* without an adjuvant. Still more preferably, the composition comprising a combination of a TH1 and a TH2 adjuvant elicits an increased TH1 and/or an increased
- TH2 immune response relative to immunization with a single adjuvant (*i.e.*, relative to immunization with a TH1 adjuvant alone or immunization with a TH2 adjuvant alone).
  [0540] The immune response may be one or both of a TH1 immune response and a TH2 response. Preferably, immune response provides for one or both of an enhanced TH1 response and an enhanced TH2 response.
- [0541] The enhanced immune response may be one or both of a systemic and a mucosal immune response. Preferably, the immune response provides for one or both of an enhanced systemic and an enhanced mucosal immune response. Preferably the mucosal immune response is a TH2 immune response. Preferably, the mucosal immune response includes an increase in the production of IgA.

[0542] S. aureus infections can 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 *(e.g. a lyophilised composition or a spray-freeze dried composition)*. 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

- <sup>5</sup> a tablet or capsule, as a spray, 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. The composition may be in kit form, designed such that a combined composition is reconstituted just prior to administration to a patient. Such kits may comprise one or more antigens in liquid form and one or more lyophilised antigens.
- [0543] Where a composition is to be prepared extemporaneously prior to use (*e.g.* where a component is presented in lyophilised form) and is presented as a kit, the kit may comprise two vials, or it may comprise one ready-filled syringe and one vial, with the contents of the syringe being used to reactivate the contents of the vial prior to injection.
   [0544] Immunogenic compositions used as vaccines comprise an immunologically effective amount of antigen(s), as
- well as any other components, as needed. By 'immunologically effective amount', it is meant that the administration of that amount to an individual, either in a single dose or as part of a series, is effective for treatment or prevention. This amount varies depending upon the health and physical condition of the individual to be treated, age, the taxonomic group of individual to be treated (e.g. non-human primate, primate, etc.), the capacity of the individual's immune system to synthesise antibodies, the degree of protection desired, the formulation of the vaccine, the treating doctor's assessment of the medical situation, and other relevant factors. It is expected that the amount will fall in a relatively broad range that
- can be determined through routine trials. Where more than one antigen is included in a composition then two antigens may be present at the same dose as each other or at different doses.
   [0545] As mentioned above, a composition may include a temperature protective agent, and this component may be particularly useful in adjuvanted compositions (particularly those containing a mineral adjuvant, such as an aluminium salt). As described in reference 206, a liquid temperature protective agent may be added to an aqueous vaccine com-
- <sup>25</sup> position to lower its freezing point *e.g.* to reduce the freezing point to below 0°C. Thus the composition can be stored below 0°C, but above its freezing point, to inhibit thermal breakdown. The temperature protective agent also permits freezing of the composition while protecting mineral salt adjuvants against agglomeration or sedimentation after freezing and thawing, and may also protect the composition at elevated temperatures *e.g.* above 40°C. A starting aqueous vaccine and the liquid temperature protective agent may be mixed such that the liquid temperature protective agent
- <sup>30</sup> forms from 1-80% by volume of the final mixture. Suitable temperature protective agents should be safe for human administration, readily miscible/soluble in water, and should not damage other components (*e.g.* antigen and adjuvant) in the composition. Examples include glycerin, propylene glycol, and/or polyethylene glycol (PEG). Suitable PEGs may have an average molecular weight ranging from 200-20,000 Da. In a preferred embodiment, the polyethylene glycol can have an average molecular weight of about 300 Da ('PEG-300').
- <sup>35</sup> **[0546]** The invention provides an immunogenic composition comprising: (i) one or more antigen(s) selected from the first, second, third or fourth antigen groups; and (ii) a temperature protective agent. This composition may be formed by mixing (i) an aqueous composition comprising one or more antigen(s) selected from the first, second, third or fourth antigen groups, with (ii) a temperature protective agent. The mixture may then be stored *e.g.* below 0°C, from 0-20°C, from 20-35°C, from 35-55°C, or higher. It may be stored in liquid or frozen form. The mixture may be lyophilised. The
- 40 composition may alternatively be formed by mixing (i) a dried composition comprising one or more antigen(s) selected from the first, second, third or fourth antigen groups, with (ii) a liquid composition comprising the temperature protective agent. Thus component (ii) can be used to reconstitute component (i).

#### Methods of treatment, and administration of the vaccine

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**[0547]** The invention also provides a method for raising an immune response in a mammal comprising the step of administering an effective amount of a composition of the invention. The immune response is preferably protective and preferably involves antibodies and/or cell-mediated immunity. The method may raise a booster response.

**[0548]** The invention also provides at least two antigens of the invention for combined use as a medicament *e.g.* for use in raising an immune response in a mammal.

**[0549]** The invention also provides the use of at least two antigens of the invention in the manufacture of a medicament for raising an immune response in a mammal.

**[0550]** By raising an immune response in the mammal by these uses and methods, the mammal can be protected against *S.aureus* infection, including a nosocomial infection. More particularly, the mammal may be protected against a skin infection, pneumonia, meningitis, osteomyelitis endocarditis, toxic shock syndrome, and/or septicaemia.

<sup>55</sup> a skin infection, pneumonia, meningitis, osteomyelitis endocarditis, toxic shock syndrome, and/or septicaemia. [0551] The invention also provides a kit comprising a first component and a second component wherein neither the first component nor the second component is a composition of the invention as described above, but wherein the first component and the second component can be combined to provide a composition of the invention as described above.

The kit may further include a third component comprising one or more of the following: instructions, syringe or other delivery device, adjuvant, or pharmaceutically acceptable formulating solution.

**[0552]** The invention also provides a delivery device pre-filled with an immunogenic composition of the invention.

- **[0553]** The mammal is preferably a human. Where the vaccine is for prophylactic use, the human is preferably a child (*e.g.* a toddler or infant) or a teenager; where the vaccine is for therapeutic use, the human is preferably a teenager or an adult. A vaccine intended for children may also be administered to adults *e.g.* to assess safety, dosage, immunogenicity, *etc.* Other mammals which can usefully be immunised according to the invention are cows, dogs, horses, and pigs.
- **[0554]** One way of checking efficacy of therapeutic treatment involves monitoring *S.aureus* infection after administration of the compositions of the invention. One way of checking efficacy of prophylactic treatment involves monitoring immune responses, systemically (such as monitoring the level of IgGI and IgG2a production) and/or mucosally (such as monitoring the level of IgA production), against the antigens in the compositions of the invention after administration of the composition. Typically, antigen-specific serum antibody responses are determined post-immunisation but prechallenge whereas antigen-specific mucosal antibody responses are determined post-immunisation and post-challenge.
- <sup>15</sup> **[0555]** Another way of assessing the immunogenicity of the compositions of the present invention is to express the proteins recombinantly for screening patient sera or mucosal secretions by immunoblot and/or microarrays. A positive reaction between the protein and the patient sample indicates that the patient has mounted an immune response to the protein in question. This method may also be used to identify immunodominant antigens and/or epitopes within antigens. **[0556]** The efficacy of vaccine compositions can also be determined *in vivo* by challenging animal models of *S.aureus*
- 20 infection, e.g., guinea pigs or mice, with the vaccine compositions. In particular, there are three useful animal models for the study of *S.aureus* infectious disease, namely: (i) the murine abscess model [207], (ii) the murine lethal infection model [207] and (iii) the murine pneumonia model [208]. The abscess model looks at abscesses in mouse kidneys after intravenous challenge. The lethal infection model looks at the number of mice which survive after being infected by a normally-lethal dose of *S.aureus* by the intravenous or intraperitoneal route. The pneumonia model also looks at the
- <sup>25</sup> survival rate, but uses intranasal infection. A useful vaccine may be effective in one or more of these models. For instance, for some clinical situations it may be desirable to protect against pneumonia, without needing to prevent hematic spread or to promote opsonisation; in other situations the main desire may be to prevent hematic spread. Different antigens, and different antigen combinations, may contribute to different aspects of an effective vaccine.
- [0557] 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 mucosally, such as by rectal, oral (*e.g.* tablet, spray), vaginal, topical, transdermal or transcutaneous, intranasal, ocular, aural, pulmonary or other mucosal administration.
   [0558] The invention may be used to elicit systemic and/or mucosal immunity, preferably to elicit an enhanced systemic

and/or mucosal immunity.
 <sup>35</sup> [0559] Preferably the enhanced systemic and/or mucosal immunity is reflected in an enhanced TH1 and/or TH2

immune response. Preferably, the enhanced immune response includes an increase in the production of IgGI and/or IgG2a and/or IgA.

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**[0560]** Dosage can be by 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. In a multiple dose schedule the various doses may be given by the same or different routes *e.g.* a parenteral prime and mucosal boost, a mucosal prime and parenteral boost, *etc.* Multiple doses will typically be administered at least 1 week apart (*e.g.* about 2 weeks, about 3 weeks, about

4 weeks, about 6 weeks, about 8 weeks, about 10 weeks, about 12 weeks, about 16 weeks, *etc.*). [0561] Vaccines prepared according to the invention may be used to treat both children and adults. Thus a human

- patient may be less than 1 year old, 1-5 years old, 5-15 years old, 15-55 years old, or at least 55 years old. Preferred
   patients for receiving the vaccines are the elderly (*e.g.* ≥50 years old, ≥60 years old, and preferably ≥65 years), the young (*e.g.* ≤5 years old), hospitalised patients, healthcare workers, armed service and military personnel, pregnant women, the chronically ill, or immunodeficient patients. The vaccines are not suitable solely for these groups, however, and may be used more generally in a population.
- [0562] Vaccines produced by the invention may be administered to patients at substantially the same time as (e.g. during the same medical consultation or visit to a healthcare professional or vaccination centre) other vaccines e.g. at substantially the same time as an influenza vaccine, a measles vaccine, a mumps vaccine, a rubella vaccine, a MMR vaccine, a varicella vaccine, a MMRV vaccine, a diphtheria vaccine, a tetanus vaccine, a pertussis vaccine, a DTP vaccine, a conjugated *H.influenzae* type b vaccine, an inactivated poliovirus vaccine, a hepatitis B virus vaccine, a meningococcal conjugate vaccine (such as a tetravalent A-C-W135-Y vaccine), a respiratory syncytial virus vaccine,
- 55 etc. Further non-staphylococcal vaccines suitable for co-administration may include one or more antigens listed on pages 33-46 of reference 51.

# Nucleic acid immunisation

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**[0563]** The immunogenic compositions described above include polypeptide antigens from *S.aureus*. In all cases, however, the polypeptide antigens can be replaced by nucleic acids (typically DNA) encoding those polypeptides, to give compositions, methods and uses based on nucleic acid immunisation. Nucleic acid immunisation is now a developed field (*e.g.* see references 209 to 216 *etc.*).

**[0564]** The nucleic acid encoding the immunogen is expressed *in vivo* after delivery to a patient and the expressed immunogen then stimulates the immune system. The active ingredient will typically take the form of a nucleic acid vector comprising: (i) a promoter; (ii) a sequence encoding the immunogen, operably linked to the promoter; and optionally (iii)

- a selectable marker. Preferred vectors may further comprise (iv) an origin of replication; and (v) a transcription terminator downstream of and operably linked to (ii). In general, (i) & (v) will be eukaryotic and (iii) & (iv) will be prokaryotic.
   [0565] Preferred promoters are viral promoters e.g. from cytomegalovirus (CMV). The vector may also include transcriptional regulatory sequences (e.g. enhancers) in addition to the promoter and which interact functionally with the promoter. Preferred vectors include the immediate-early CMV enhancer/promoter, and more preferred vectors also
- <sup>15</sup> include CMV intron A. The promoter is operably linked to a downstream sequence encoding an immunogen, such that expression of the immunogen-encoding sequence is under the promoter's control.
   [0566] Where a marker is used, it preferably functions in a microbial host (e.g. in a prokaryote, in a bacteria, in a yeast). The marker is preferably a prokaryotic selectable marker (e.g. transcribed under the control of a prokaryotic

yeast). The marker is preferably a prokaryotic selectable marker (e.g. transcribed under the control of a prokaryotic promoter). For convenience, typical markers are antibiotic resistance genes.

<sup>20</sup> **[0567]** The vector of the invention is preferably an autonomously replicating episomal or extrachromosomal vector, such as a plasmid.

**[0568]** The vector of the invention preferably comprises an origin of replication. It is preferred that the origin of replication is active in prokaryotes but not in eukaryotes.

[0569] Preferred vectors thus include a prokaryotic marker for selection of the vector, a prokaryotic origin of replication, but a eukaryotic promoter for driving transcription of the immunogen-encoding sequence. The vectors will therefore (a) be amplified and selected in prokaryotic hosts without polypeptide expression, but (b) be expressed in eukaryotic hosts without being amplified. This arrangement is ideal for nucleic acid immunization vectors.

**[0570]** The vector of the invention may comprise a eukaryotic transcriptional terminator sequence downstream of the coding sequence. This can enhance transcription levels. Where the coding sequence does not have its own, the vector of the invention preferably comprises a polyadenylation sequence. A preferred polyadenylation sequence is from bovine growth hormone.

**[0571]** The vector of the invention may comprise a multiple cloning site

**[0572]** In addition to sequences encoding the immunogen and a marker, the vector may comprise a second eukaryotic coding sequence. The vector may also comprise an IRES upstream of said second sequence in order to permit translation

<sup>35</sup> of a second eukaryotic polypeptide from the same transcript as the immunogen. Alternatively, the immunogen-coding sequence may be downstream of an IRES.

**[0573]** The vector of the invention may comprise unmethylated CpG motifs *e.g.* unmethylated DNA sequences which have in common a cytosine preceding a guanosine, flanked by two 5' purines and two 3' pyrimidines. In their unmethylated form these DNA motifs have been demonstrated to be potent stimulators of several types of immune cell.

- 40 [0574] Vectors may be delivered in a targeted way. Receptor-mediated DNA delivery techniques are described in, for example, references 217 to 222. Therapeutic compositions containing a nucleic acid are administered in a range of about 100ng to about 200mg of DNA for local administration in a gene therapy protocol. Concentration ranges of about 500 ng to about 50 mg, about 1µg to about 2 mg, about 5µg to about 500µg, and about 20µg to about 100µg of DNA can also be used during a gene therapy protocol. Factors such as method of action (e.g. for enhancing or inhibiting
- <sup>45</sup> levels of the encoded gene product) and efficacy of transformation and expression are considerations which will affect the dosage required for ultimate efficacy. Where greater expression is desired over a larger area of tissue, larger amounts of vector or the same amounts re-administered in a successive protocol of administrations, or several administrations to different adjacent or close tissue portions may be required to effect a positive therapeutic outcome. In all cases, routine experimentation in clinical trials will determine specific ranges for optimal therapeutic effect.
- [0575] Vectors can be delivered using gene delivery vehicles. The gene delivery vehicle can be of viral or non-viral origin (see generally references 223 to 226).
   [0576] Viral-based vectors for delivery of a desired nucleic acid and expression in a desired cell are well known in the art. Exemplary viral-based vehicles include, but are not limited to, recombinant retroviruses (e.g. references 227 to 237),
- alphavirus-based vectors (*e.g.* Sindbis virus vectors, Semliki forest virus (ATCC VR-67; ATCC VR-1247), Ross River
   virus (ATCC VR-373; ATCC VR-1246) and Venezuelan equine encephalitis virus (ATCC VR-923; ATCC VR-1250; ATCC VR 1249; ATCC VR-532); hybrids or chimeras of these viruses may also be used), poxvirus vectors (e.g. vaccinia, fowlpox, canarypox, modified vaccinia Ankara, *etc.*), adenovirus vectors, and adeno-associated virus (AAV) vectors (*e.g.* see refs. 238 to 243). Administration of DNA linked to killed adenovirus [244] can also be employed.
**[0577]** Non-viral delivery vehicles and methods can also be employed, including, but not limited to, polycationic condensed DNA linked or unlinked to killed adenovirus alone *[e.g.* 244], ligand-linked DNA [245], eukaryotic cell delivery vehicles cells *[e.g.* refs. 246 to 250] and nucleic charge neutralization or fusion with cell membranes. Naked DNA can also be employed. Exemplary naked DNA introduction methods are described in refs. 251 and 252. Liposomes *(e.g.* 

<sup>5</sup> immunoliposomes) that can act as gene delivery vehicles are described in refs. 253 to 257. Additional approaches are described in references 258 & 259.

**[0578]** Further non-viral delivery suitable for use includes mechanical delivery systems such as the approach described in ref. 259. Moreover, the coding sequence and the product of expression of such can be delivered through deposition of photopolymerized hydrogel materials or use of ionizing radiation *[e.g.* refs. 260 & 261]. Other conventional methods for gene delivery that can be used for delivery of the coding sequence include, for example, use of hand-held gene

for gene delivery that can be used for delivery of the coding sequence include, for example, use of hand-held gene transfer particle gun [262] or use of ionizing radiation for activating transferred genes [260 & 261].
[0579] Delivery DNA using PLG {poly(lactide-co-glycolide)} microparticles is a particularly preferred method *e.g.* by adsorption to the microparticles, which are optionally treated to have a negatively-charged surface *(e.g.* treated with

SDS) or a positively-charged surface (e.g. treated with a cationic detergent, such as CTAB).

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S.epidermidis

[0580] Although the invention focuses on *S.aureus*, the inventors also realise that the sta006 and sta011 antigens have homologs in *S.epidermidis*. For example, SEQ ID NO: 234 is the 'iron (Fe+3) ABC superfamily ATP binding cassette transporter, binding protein' from *S.epidermidis* strain M23864:W1, with 73% identity to SEQ ID NO: 42 (sta006), and SEQ ID NO: 235 is the 'putative lipoprotein' from *S.epidermidis* strain RP62A, with 67% identity to SEQ ID NO: 47 (sta011). *S.epidermidis* is commonly present on human skin and can sometimes cause illness. Infection is usually associated with medical devices, such as catheters, and is a cause of nosocomial infections. The results disclosed herein for sta006 and sta011 against *S.aureus* suggest that the homologous proteins in *S. epidermidis* could be useful for immunising against this pathogen.

[0581] The invention provides an immunogenic composition comprising:

(i) a polypeptide comprising 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: 234; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 234, 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); and/or

(ii) a polypeptide comprising 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: 235; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 235, 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).

**[0582]** The composition may also include an adjuvant. These compositions are particularly useful for immunising a mammal (including a human) against *S.epidermidis* infection.

**[0583]** Preferred fragments of (b) comprise an epitope from SEQ ID NO: 234 or 235, respectively. Other preferred fragments lack one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 234/235 while retaining at least one epitope of SEQ ID NO: 234/235.

<sup>45</sup> **[0584]** More generally, the invention provides the use of the sta006 and/or sta011 homolog from any *Staphylococcus* species for immunising a mammal against that species.

### Antibodies

- <sup>50</sup> [0585] Antibodies against *S. aureus* antigens can be used for passive immunisation. Thus the invention provides an antibody which is specific for an antigen in the first, second, third or fourth antigen groups. The invention also provides the use of such antibodies in therapy. The invention also provides the use of such antibodies in the manufacture of a medicament. The invention also provides a method for treating a mammal comprising the step of administering an effective amount of an antibody of the invention. As described above for immunogenic compositions, these methods and uses allow a mammal to be protected against *S. aureus* infection.
- <sup>55</sup> and uses allow a mammal to be protected against S.aureus infection. [0586] The term "antibody" includes intact immunoglobulin molecules, as well as fragments thereof which are capable of binding an antigen. These include hybrid (chimeric) antibody molecules [263, 264]; F(ab')2 and F(ab) fragments and Fv molecules; non-covalent heterodimers [265, 266]; single-chain Fv molecules (sFv) [267]; dimeric and trimeric antibody

fragment constructs; minibodies [268, 269]; humanized antibody molecules [270-272]; and any functional fragments obtained from such molecules, as well as antibodies obtained through non-conventional processes such as phage display. Preferably, the antibodies are monoclonal antibodies. Methods of obtaining monoclonal antibodies are well known in the art. Humanised or fully-human antibodies are preferred.

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#### General

**[0587]** The practice of the present invention will employ, unless otherwise indicated, conventional methods of chemistry, biochemistry, molecular biology, immunology and pharmacology, within the skill of the art. Such techniques are explained fully in the literature. See, *e.g.*, references 273-280, *etc.* 

**[0588]** "GI" numbering is used above. A GI number, or "GenInfo Identifier", is a series of digits assigned consecutively to each sequence record processed by NCBI when sequences are added to its databases. The GI number bears no resemblance to the accession number of the sequence record. When a sequence is updated (*e.g.* for correction, or to add more annotation or information) then it receives a new GI number. Thus the sequence associated with a given GI number is never changed.

- **[0589]** Where the invention concerns an "epitope", this epitope may be a B-cell epitope and/or a T-cell epitope. Such epitopes can be identified empirically (*e.g.* using PEPSCAN [281,282] or similar methods), or they can be predicted (*e.g.* using the Jameson-Wolf antigenic index [283], matrix-based approaches [284], MAPITOPE [285], TEPITOPE [286,287], neural networks [288], OptiMer & EpiMer [289, 290], ADEPT [291], Tsites [292], hydrophilicity [293], antigenic
- 20 index [294] or the methods disclosed in references 295-299, etc.). Epitopes are the parts of an antigen that are recognised by and bind to the antigen binding sites of antibodies or T-cell receptors, and they may also be referred to as "antigenic determinants".

**[0590]** Where an antigen "domain" is omitted, this may involve omission of a signal peptide, of a cytoplasmic domain, of a transmembrane domain, of an extracellular domain, *etc.* 

<sup>25</sup> **[0591]** 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.

[0592] The term "about" in relation to a numerical value x is optional and means, for example,  $x \pm 10\%$ .

[0593] References to a percentage sequence identity between two amino acid sequences means that, when aligned, that percentage of amino acids are the same in comparing the two sequences. This alignment and the percent homology or sequence identity can be determined using software programs known in the art, for example those described in section 7.7.18 of ref. 300. A preferred alignment is determined by the Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 2, BLOSUM matrix of 62. The Smith-

# 35 BRIEF DESCRIPTION OF DRAWINGS

Waterman homology search algorithm is disclosed in ref. 301.

### [0594]

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Figure 1 shows bacterial counts (Log cfu/ml) after challenge of mice previously immunised with the indicated antigens.

Figures 2 to 4 show survival (%) after challenge of mice previously immunised with various mixtures of antigens over 14 days. In Figure 2, the six groups from SA-10-a are, from top to bottom at day 14. groups (i), (iii) & (iv) together, (ii), IsdB, then the negative control. In Figure 3, the six groups from SA-10-a are, from top to bottom at day 14. groups (i), (iii) & (iv) together, (ii), IsdB, then the negative control. In Figure 3, the six groups from SA-10-b are, from top to bottom at day 14.

groups (iii), (i), (iv), (ii) and IsdB together, then the negative control. In Figure 4, the six groups from SA-14 are, from top to bottom at day 14. groups (iv), (ii), (i), (iii), negative control, and IsdB.

<sup>50</sup> Figure 5 shows collected data on mouse survival from four different experiments after challenge of mice previously immunised with various compositions (PBS negative control; IsdB antigen; and "Combo-1" and "Combo-2" antigen combinations of the invention). Individual symbols show the survival duration of individual mice; the horizontal bar for each group shows the median survival duration; the percentage figures are survival 14 days after challenge; and the p values at the top are t-Test comparisons of median survival durations between groups.

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Figure 6 shows the number of colony forming units (cfu) in mouse kidneys after infection with 9x10<sup>6</sup> cfu of Newman strain in the abscess model. Horizontal bars are averages per group, and the figure beneath each group is the log reduction relative to the PBS control group.

Figure 7 shows bacterial count (log CFU/ml) in kidneys of mice in an abscess model experiment. Mice were challenged with the following strains: (A) MW2; (B) LAC; (C) Staph19; or (D) MU50. Each point is an individual animal and the bar shows the median count per group. Mice had been immunised as shown on the x-axis label.

<sup>5</sup> Figure 8 shows the formation of Sta011 oligomers in the presence of increasing concentrations of Ca<sup>++</sup> ions. Numbers indicate mM concentrations, and a \* indicates the presence of 50mM EDTA.

Figure 9 shows IgG titers against (A) EsxAB (B) Sta006 (C) HIa-H35L (D) Sta011. Each graph has three groups, with a pair of bars per group. The right-hand bar in a pair shows pre-immune IgG and the left-hand bar shows post-immune IgG. The three groups are the compositions used for immunising and, from left to right, are: negative control of adjuvant alone; the Combo 1 combination; and the relevant antigen alone.

Figure 10 shows bacterial counts values (log CFU/ml) in mice after challenge with the indicated strains. Each point is an individual animal and the bar shows the median CFU. The P value beneath the IsdB and Combo columns is a comparison against the adjuvant-only control.

Figure 11 shows the area of abscesses (mm<sup>2</sup>) in mice after challenge with Newman strain.

Figure 12 shows days of survival of mice after challenge with four different strains: Newman ( $\bigcirc$ ), ST-80 ( $\square$ ), USA300-20 FPR3757 ( $\Delta$ ) or USA300-Lac (x) strains. Each point is an individual animal, the bar shows the median survival, and the heading number shows the % of animals surviving after 15 days. Mice received aluminium hydroxide adjuvant alone, IsdB or Combo1.

Figure 13 shows the median survival (days) of mice after challenge. The mice had been immunised with the antigens
 indicated on the X-axis. Each point is an individual animal and the bar shows the median survival. The heading numbers show the % of animals surviving after 15 days.

### MODES FOR CARRYING OUT THE INVENTION

### 30 Antigen selection

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**[0595]** *S.aureus* proteins have been selected for use as vaccine components based on various criteria.

[0596] IsdA is a surface protein involved in iron uptake. It is detectable with a high molecular weight (>250kDa) in immunoblots of whole cell lysates and cell wall fractions of *S. aureus*. Furthermore, labelled anti-IsdA antibodies revealed extracellular structures. These structures were seen in a variety of growth and infection conditions, including iron positive

- conditions (in which IsdA expression is reported to be suppressed). The structures have a tail up to  $4\mu$ m long, with a typical orientation parallel to the mammalian cell surface. Detached IsdA-positive structures were observed to adhere on the surface of epithelial cells, but lose cell junction localization. Epithelia/bacteria interaction may stimulate expression of the structures. In addition, the inventors have found that IsdA is well conserved between different strains (present in
- 40 36/36 strains tested; see below), thus offering protection across a broad population of circulating strains. Iron uptake is important for virulence, so the protein is likely to be available for immune attack at pathological stages of the bacterial life cycle. The inventors have found that the protein is not cytotoxic to human cells (see below). The protein can also adsorb reasonably well to aluminium hydroxide (see below), which is useful for stable formulation for delivery to humans. It is useful for providing an immune response to prevent hematic spread of the bacterium.
- 45 [0597] EsxA and EsxB are small acidic dimeric secreted proteins. The inventors have found that EsxA is highly conserved between different strains (present in 36/36 strains tested; see below), while EsxB is present in 25/36 strains. The proteins are involved in persisting an infection and so are likely to be available for immune attack at pathological stages of the bacterial life cycle. The inventors have found that a fusion of EsxA and EsxB ('EsxAB') is not cytotoxic to human cells (see below). It can also adsorb well to aluminium hydroxide (see below), which is useful for stable formulation
- <sup>50</sup> for delivery to humans. Thus the antigens are useful for providing an immune response to prevent hematic spread of the bacterium.

**[0598]** Hla is a pore-forming secreted toxin. This protein is well conserved between different strains (present in 36/36 strains tested; see below), thus offering protection across a broad population of circulating strains. It is an important virulence factor so is likely to be available for immune attack at pathological stages of the bacterial life cycle. It is not

<sup>55</sup> cytotoxic to human cells (see below). The protein can adsorb reasonably well to aluminium hydroxide (see below), which is useful for stable formulation for delivery to humans. It is useful for providing an immune response to prevent pneumonia.
 [0599] Spa is a surface protein involved in Fc binding. The inventors have found that this protein is well conserved between different strains (present in 36/36 strains tested), thus offering protection across a broad population of circulating

strains. It is important for virulence so is likely to be available for immune attack at pathological stages of the bacterial life cycle. The protein can also adsorb reasonably well to aluminium hydroxide (see below), which is useful for stable formulation for delivery to humans. It is useful for providing an immune response to prevent hematic spread of the bacterium.

- <sup>5</sup> **[0600]** Sta006 (also known as FhuD2) is a surface protein involved in iron uptake. The inventors have found that this protein is well conserved between different strains (present in 36/36 strains tested; see below), thus offering protection across a broad population of circulating strains. The inventors have found that the protein is not cytotoxic to human cells (see below). The protein can also adsorb well to aluminium hydroxide (see below), which is useful for stable formulation for delivery to humans. It is useful for providing an immune response to prevent hematic spread of the bacterium.
- 10 **[0601]** Sta011 is a surface lipoprotein. The inventors have found that this protein is well conserved between different strains (present in 36/36 strains tested; see below), thus offering protection across a broad population of circulating strains. The inventors have found that the protein is not cytotoxic to human cells (see below). The protein can also adsorb reasonably well to aluminium hydroxide (see below), which is useful for stable formulation for delivery to humans. It is useful for providing an immune response to prevent hematic spread of the bacterium. This protein has been shown
- <sup>15</sup> to assemble into oligomers in the presence of Ca<sup>++</sup> ions, but not Mg<sup>++</sup> ions (see Figure 8). These experiments used 5µg recombinant tag-free Sta011, incubated at 37°C for 25 minutes with increasing CaCl<sub>2</sub> concentrations from 0.5-50mM, then analysed by gel electrophoresis on a clear native gel. A mobility shift (indicating oligomerisation) was evident from 2mM Ca<sup>++</sup>, and particularly >5mM. These levels compare to blood Ca<sup>++</sup> concentrations of about 1.2mM, serum concentrations of about 11mM, and milk concentrations of about 32mM. EDTA reversed the shift.
- [0602] Surface digestion [302] and/or analysis of secreted proteins revealed peptide fragments from ClfA, ClfB, coA, eap, ebhA, ebpS, efb, emp, FnBA, FnBB, hla, IsdA, IsdB, IsdH, ukD, lukS, sdrD, sdrE, sasB, sasD, sasF, spa, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta019, sta023, sta024, sta028, sta036, sta040, sta049, sta050, sta054, sta057, sta064, sta065, sta073, sta095, sta096, sta098, sta100, sta101, sta102, sta103, sta105, sta107, sta108, sta109, sta111, sta112, sta113, sta115, sta116, sta117, sta118, sta120, NW\_06, NW\_07, NW\_
   08 NW, 09 and NW, 10 e a, SEQ ID NOS: 228 and 229 were identified as fragments of sta019
- 08, NW\_09 and NW\_10 *e.g.* SEQ ID NOs: 228 and 229 were identified as fragments of sta019.
   [0603] Conjugated capsular saccharides are useful for providing opsonic immunity. Serotypes 5 and 8 cover about 85% of clinical isolates.

### Strain coverage

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**[0604]** A panel of 36 clinical isolates was used to represent circulating strains, including strains belonging to the five clonal lineages representing the vast majority of worldwide circulating CA-MRSA (community-associated methicillin-resistant *S.aureus*). HA-MRSA (hospital-associated MRSA) and non-MRSA strains were also included. Overall the panel included 9 HA-MRSA strains, 7 CA-MRSA strains, 2 MRSA strains, and 18 other strains.

- <sup>35</sup> **[0605]** Genes encoding IsdA, Hla, EsxA, Sta006, Sta011, Spa, and ClfB were present in all 36 strains. The gene for EsxB was absent from 11/36 strains, and the gene for SdrD was absent from 6/36 strains.
- [0606] The encoded IsdA sequences were 95-100% identical across the panel, and the protein was expressed in iron-limited conditions in the stationary growth phase. The encoded SdrD sequences were 95-100% identical in the 30/36 SdrD<sup>+ve</sup> panel members. The encoded EsxA sequences were 100% identical across the panel; the encoded EsxB sequences were 95-100% identical in the 25 EsxB<sup>+ve</sup> strains. The encoded ClfB sequences were 93-100% identical across the panel, and this protein was also found to be highly surface-exposed in the early exponential growth phase. [0607] Conservation in the encoded amino acid sequences were as follows (% identity):

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Antigen	IsdA	ClfB	SdrD	Spa	Hla	EsxA	EsxB	Sta006
%	95-100	97-100	88-100	98-100	97-100	100	95-100	99.7-100

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**[0608]** A larger panel of 61 strains was screened for the presence of genes encoding HIa and Sta006, as well as for their expression. This panel covered both MRSA and MSSA strains, a variety of geographical origins, and a variety of ST and clonal complex types. 9/61 strains did not express HIa, whereas all but one strain expressed Sta006 (data for the 61st strain were inconclusive). Thus a vaccine based on HIa alone is unlikely to give adequate coverage for a universal vaccine, but this problem could be overcome by addition of Sta006.

### Cytotoxicity and cell binding studies

**[0609]** The analysis of the potential cellular cytotoxicity by *S.aureus* recombinant antigens Hla, Hla-H35L, IsdA, IsdB, sta006, sta011 and EsxAB was conducted on HBMECs and A549 cells. Annexin V and propidium iodide staining were

used to measure the percentage of early and late apoptotic cells by flow cytometry. Endothelial cells were grown in 24 well plates up to fully confluent. Cells were then incubated for 24 hours with three different concentration of recombinant antigens (10μg/ml, 1μg/ml, 0.1 μg/ml). The combination of TNF-α and cycloheximide (CHX), which has been reported to induce apoptosis in endothelial cells, was used as a positive control. Incubation with PBS buffer alone was a negative control. Analysis was then performed by FACS.

- [0610] None of the antigens induced a cytotoxic effect on HBMECs or A549 cells. Indeed, the percentage of live cell population compared to control cells remained essentially constant up to 24 hours of incubation. In contrast, the combination of TNF- $\alpha$  and CHX induced a 25% increase in the number of apoptotic cells.
- [0611] HBMECs were also used as an *in vitro* model for testing the binding of *S.aureus* recombinant antigens to 10 human endothelial cells. HBMECs were grown up to confluence at 37°C in humidified atmosphere in RPMI 1640 medium supplemented with 10% heat-inactivated fetal calf serum, 10% NuSerum, 2mM glutamine, 1 mM pyruvate, 1% nonessential amino acids, 1% MEM vitamins, 100 units/ml penicillin, and 100 µg/ml streptomycin. Binding of recombinant antigens to the cells was tested by indirect immunofluorescence and analyzed by FACS. The cells positive for binding were measured as net mean intensity of fluorescence respect to negative controls, identified as unspecific antibody
- 15 recognition. Binding experiments were performed at 4°C. Mouse polyclonal antibodies specific for each of the recombinant antigens were used as primary antibodies and binding was detected by R-Phycoerythrin-conjugated goat anti-mouse IgG secondary antibody. As negative control, HBMECs were incubated with primary polyclonal antibodies detected by fluorescence-labeled secondary antibody or fluorescence-labeled secondary antibody alone. Binding of a known surfaced-exposed GBS antigen was used as positive control.
- 20 [0612] Hla and Hla-H35L were the only antigens able to strongly bind to endothelial cells. The haemolytic activity of these two antigens was also tested.

[0613] De-fibrinated sheep and rabbit blood were used to measure their haemolytic activity by spectrophotometric assay. The blood was incubated at 37°C for 30 minutes with serial dilution 1:4 of the two proteins. Incubation with water, to cause osmotic lysis, and incubation with a S.pyogenes protein, were positive controls; as negative control, the blood was incubated with PBS+ BSA 0.5%.

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[0614] Recombinant native HIa, but not its H35L mutant form, showed haemolytic activity on rabbit erythrocytes. The mutant was at least 150-fold less haemolytic than wild-type. Both proteins had no haemolytic activity on sheep blood. [0615] Thus the S.aureus recombinant vaccine candidates do not show any cytotoxicity both on A549 epithelial cell line and HBMEC endothelial cell line. Importantly, HIa, a secreted toxin known to form pores into the plasma membrane

30 of host cells, could bind A549 cells but did not induce cytotoxicity on them; it was also able to induce haemolysis of rabbit erythrocytes. In contrast, recombinant Hla-H35L, a variant toxin with a single amino acid substitution that cannot form cytolytic pores, did not induce cellular damage in both human cell lines and rabbit erythrocytes. These findings indicate that this mutant form of HIa may be more safely used in a vaccine composition. None of the other antigens showed the capacity to bind to host cells.

### Adjuvant formulation

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[0616] Selected S.aureus protein antigen candidates have been formulated with aluminium hydroxide, either individually or as a combination of proteins, with or without capsular polysaccharide conjugate(s). The formulations have been optimized for pH and osmolarity.

[0617] The antigens were EsxA-B, Sta006, Sta011, Hla-H35L, SdrD, IsdA, IsdA<sub>40-184</sub>, Sta019, Sta021, Sta073, ClfB<sub>45-552</sub>, SdrD<sub>53-592</sub>, SasF, and IsdB. These are formulated as monovalent antigens at 100µg/ml, or as combinations at 50µg/ml each. Capsular saccharide conjugates from type 5 or type 8 strains are added at 5µg/ml, 10µg/ml or 25µg/ml. Aluminium hydroxide was used at 2mg/ml, in a 10mM histidine buffer (pH 6.5) and with 9mg/ml NaCl.

45 [0618] All monovalent and combination formulations, with or without conjugates, could be adjusted with respect to a desired pH and osmolality. The formulations had pH in the range 6.2-7.3, and osmolality in the range 248-360 mOsm/kg. Glycerol was excluded from formulations as it had a negative impact on osmolality.

[0619] All proteins tested, in various monovalent and combination formulations, adsorbed well to the aluminium hydroxide adjuvant, except for IsdA, IsdA<sub>40-184</sub>, Sta019, and Sta073.

- 50 [0620] The individual Sta006, Sta011, EsxA-B and HIa-H35L proteins were completely adsorbed, and could be desorbed without altering their pre-adsorption electrophoretic profile. [0621] Each antigen in a combination of Sta006, Sta011, EsxA-B and Hla-H35L was completely adsorbed, with no inter-antigen competition for the adjuvant. The antigens in a combination of Sta006, Sta011, EsxA-B and IsdA40-184 were also completely adsorbed, except for  $IsdA_{40-184}$ , which behaved in the same way as the monovalent protein. For
- 55 both combinations, the antigens could be desorbed without altering their pre-adsorption electrophoretic profile. **[0622]** The additional presence of type 5 and/or type 8 conjugates also did not change the adsorption or desorption characteristics of the antigens e.g. in combination with Sta006+Sta011+EsxA-B.

[0623] A short stability study (2 weeks at 4°C) was performed to evaluate the stability of monovalent formulations and

to evaluate antigen integrity. All tested formulations were stable for their pH and osmolality. All antigens remained completely adsorbed to the adjuvant. All antigens maintained their desorption characteristics. There was no evidence of increased degradation or aggregation of antigens after desorption.

### 5 Efficacy testing

**[0624]** Individual antigens sta006, sta011, sta012, sta017, sta019, sta021 and sta028 were tested for their ability to protect against IV challenge by  $1.2 \times 10^7$  cfu of Newman strain (type 5). Results are shown in Figure 1. All antigens reduced bacterial numbers compared with the control, and the best results were seen with sta006, sta011 and sta019.

- 10 [0625] Further individual antigens were tested: (i) NW\_10; (ii) IsdA<sub>40-184</sub>; (iii) Sta002; (iv) Sta003; (v) Sta073; (vi) Sta101; (vii) Sta014; (viii) HIa-PSGS; (ix) SdrD<sub>CnaB</sub>. The increase in survival, compared to the negative control group, 15 days after challenge was: (i) 50%; (ii) 19%; (iii) 37%; (iv) 43%; (v) 25%; (vi) 12%; (vii) 25%; (viii) 56%; (ix) 39%. [0626] Two hybrid polypeptides were also tested: (i) HIaH35L-EsxAB; (ii) Sta006-EsxAB. The increase in survival after challenge, compared to the negative control group, was: (i) 25%; (ii) 25%.
- <sup>15</sup> [0627] Table 2 gives a summary of results obtained with various antigens in the abscess model. [0628] Experiment SA-10-a tested the efficacy of antigen combinations. Six groups of twelve CD-1 mice received a negative control (PBS), IsdB, or one of the following combinations, adjuvanted with aluminium hydroxide: (i) EsxAB + Hla-H35L; (ii) Sta006 + Sta011 + EsxAB; (iii) Sta006 + Sta011 + EsxAB; (iii) Sta006 + Sta011 + EsxAB; (iii) Sta006 + Sta011 + IsdA<sub>40-184</sub> + EsxAB. Two administrations were given, at days 0 and 14. At day 24 mice received 3x10<sup>8</sup> cfu of Newman strain
- 20 staphylococcus and survival in each group was assessed every 24 hours for two weeks. Results are shown in Figure 2. After 14 days, 25% of animals in the positive control group had survived, but 50% of animals in group (ii) had survived, as had 58% of animals in groups (iii) & (iv), and 75% in group (i).
  20 Staphylococcus and survival in each group was assessed every 24 hours for two weeks. Results are shown in Figure 2. After 14 days, 25% of animals in the positive control group had survived, but 50% of animals in group (ii) had survived, as had 58% of animals in groups (iii) & (iv), and 75% in group (i).

**[0629]** Experiment SA-10-b used the same methods to test: (i)  $ClfB_{45-552}$  + HIa-H35L + Sta006 + EsxAB; (ii)  $ClfB_{45-552}$ 

- + Sta011 + Sta006 + EsxAB; (iii) ClfB<sub>45-552</sub> + IsdA<sub>40-184</sub> + Sta006 + EsxAB; or (iv) SdrD<sub>53-592</sub> + IsdA<sub>40-184</sub> + Sta006 + EsxAB. Results are shown in Figure 3. After 14 days, 25% of animals in the positive control group and in group (ii) had survived, but 33% of animals in group (iv) had survived, 75% of animals in group (i), and 83% of animals in group (iii).
  [0630] Further combinations were also used to immunise mice. The combinations were typically adjuvanted with aluminium hydroxide (see above) and were administered on days 0 and 14. The immunisations were in CD1 mice, 12 per group. On day 24 the mice were challenged with a lethal dose of live bacteria and survival was then followed for 14
- further days. For comparison, PBS was used as a negative control and IsdB as a positive control [2].
   [0631] Experiment SA-11 tested: (i) a type 5 conjugate combined with EsxAB + Sta006 + Sta011; (ii) EsxAB + Sta019 + Sta006 + Sta011; (iii) a type 5 conjugate + HIa-H35L + Sta006 + Sta011; (iv) EsxAB + HIa-H35L + Sta006 + Sta011; or (v) EsxAB + IsdA<sub>40-184</sub> + Sta006 + Sta011. 14 days after challenge all of the negative control animals had died, but 42% of positive control animals had survived. Survival results in the test groups were as follows: (i) 67%; (ii) 42%; (iii) 75%; (iv) 33%; and (v) 25%.

**[0632]** Experiment SA-12 tested: (i) Hla-H35L + IsdA<sub>40-184</sub> + Sta006 + Sta011; (ii) Hla-H35L + EsxAB + Sta006 + Sta011; (iii) EsxAB + IsdA<sub>40-184</sub> + Sta006 + Sta011; (iv) EsxAB + IsdA + Sta006 + Sta011. 14 days after challenge 8% of the negative control animals and 17% of positive control animals had survived. Survival results in the test groups were as follows: (i) 50%; (ii) 50%; (iii) 25%; (iv) 33%.

- 40 [0633] Experiment SA-14 tested: (i) EsxAB + Hla-H35L + Sta006 + Sta011; (ii) EsxAB + IsdA<sub>40-184</sub> + Sta006 + Sta011; (iii) Sta006 + Sta011 + Sta019 + EsxAB; (iv) Sta006 + Sta011 + Sta019 + Hla-H35L. 14 days after challenge with 5x10<sup>8</sup> CFU of Newman strain, 18% of the negative control animals and 9% of positive control animals had survived; survival results in the test groups were as follows: (i) 58%; (ii) 67%; (iii) 42%; (iv) 83%. Survival numbers over 14 days are shown in Figure 4, showing that all combinations performed better than the two controls on every post-challenge day.
- <sup>45</sup> [0634] Experiment SA-17a tested: (i) EsxAB + Sta006 + Sta011 + serotype 5 conjugate + serotype 8 conjugate; (ii) EsxAB + Sta073 + Sta011 + serotype 5 conjugate + serotype 8 conjugate; (iii) EsxAB + Hla-H35L + Sta011 + Sta073. Compared to the negative control, the increase in survival 15 days after challenge with Newman strain was: (i) 17%; (ii) 42%; (iii) 34%. The median survival in groups (ii) and (iii) was the full 15 days, and was 12 days in group (i). [0635] Further antigen combination experiments tested: (a) serotype 5 conjugate + serotype 8 conjugate + EsxAB +
- Sta006 + Sta011; (b) Sta002+Sta003+Sta021+NW-10; (c) EsxAB+ HlaH35L + Sta006 + Sta019; and (d) EsxAB + Sta006+Sta019. Compared to the negative control, the increase in survival after challenge with Newman strain was: (a) 37%; (b) 36%; (c) 13%.; and (d) 0%.

**[0636]** Survival data from studies SA-10, SA-11, SA-12 and SA-14 were combined to assess the efficacy of two combinations when compared to PBS or IsdB. "Combo-1" was EsxAB+HIa-H35L+Sta006+Sta011 (with polypeptides

<sup>55</sup> comprising SEQ ID NOs: 241, 150, 246 & 247). "Combo-2" was EsxAB+IsdA<sub>40-184</sub>+Sta006+Sta011. The median survival times for each group of 48 mice after 14 days were compared. Whereas the PBS and IsdB groups had a median survival time of 1 day, mice in the "Combo-1" and "Combo-2" groups had a median survival time of 14 days. The differences in median survival duration were compared by a t-test: survival in the "Combo-1" group was statistically superior to both

the PBS group (p<0.0001) and the IsdB group (p<0.0001); survival in the "Combo-2" group was statistically superior to both the PBS group (p<0.0001) and the IsdB group (p=0.0049). These data are shown in Figure 5.

**[0637]** Figure 6 shows data with Combo-1 and Combo-2 in the abscess model. Kidneys of mice are isolated after challenge and are then homogenised and plated. The cfu count indicates the level of abscess formation. Figure 6 shows

<sup>5</sup> data from a single experiment. The numbers beneath the data show the log reduction relative to the PBS group. The reduction is bigger in the two combination groups than with IsdB alone, with U-test (one tail) values of 0.0001 for Combo-1 and 0.0005 for Combo-2. The same effect was seen in the two combination groups in a second experiment in which an IsdB group was not included.

[0638] Further experiments compared protection achieved with Combo-1, IsdB or PBS against challenge with three different strains: Staph-19, FPR3757(USA300) and Lac(USA300). There were 44 mice per group and results were as follows (see also Figure 12), including one-tailed p-values for the survival proportion, where: P1 compares Combo-1 with PBS; P2 compares Combo-1 with IsdB; and P3 compared PBS with IsdB:

	Staph	-19	FPR3	757	Lac	
Survival	%	Days	%	Days	%	Days
PBS	20	1	45	8	47	7
IsdB	32	1	52	15	61	15
Combo-1	80	15	91	15	89	15
P1	<0.0001	-	<0.0001	-	0.0001	-
P2	<0.0001	-	<0.0004	-	0.0052	-
P3	0.1715	-	0.2137	-	0.1789	-

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**[0639]** Further experiments showed that immunisation with adjuvanted Combo 1 reduced CFU counts after challenge with Newman, USA100, CC30 and USA300 strains, when compared to immunisation with adjuvant alone (aluminium hydroxide) or IsdB. Figure 10 shows CFU values (log/ml) for the four challenge strains. The lowest count, with p<0.015 in each case, was achieved with Combo 1. The area of abscess was also assessed and was also lower in the Combo1-immunised mice (e.g. Figure 11).

- **[0640]** Further experiments showed that Combo1 is highly protective against clinically relevant strains in the sepsis model, and always achieved a higher survival % than IsdB. Figure 12 shows that the median survival in Combo1-immunised mice (40 per group, 3 experiments) was the full 15 days when challenged with Newman, ST-80, FPR3757 or Lac strains, and that the proportion of mice surviving was ≥75%. In contrast, the median survival in IsdB-immunised
- 35 or Lac strains, and that the proportion of mice surviving was ≥75%. In contrast, the median survival in IsdB-immi mice was only 1 day with Newman and ST-80 challenge, with <65% survival for all four challenge strains.</p>

### Comparison of Combo1 to its individual polypeptides

40 **[0641]** Various tests were performed to compare Combo1 to its four individual polypeptides (*i.e.* EsxAB, Hla-H35L, Sta006, Sta011), as well as to IsdB or to an antigen-free negative control.

**[0642]** The opsonophagocytic activity of sera from immunised animals was tested. Sera were obtained using (i) the four individual polypeptides, (ii) all pairs of the polypeptides, (iii) all triplets, or (iv) the full Combo 1 combination. For comparison, anti-IsdB serum was used. Pre-immune and negative control sera showed no killing of Newman strain in

- 45 this assay. In a first experiment: anti-IsdB serum showed 27% killing; sera against each of the four individual polypeptides showed between 26-34% killing; all multi-polypeptide combinations showed at least 34% killing; and sera raised with Combo-1 showed 39% killing. In a second experiment sera with Combo-1 showed 43% killing but anti-IsdB serum performed slightly better; all single or multi-polypeptide sera using the Combo-1 polypeptides showed at least 26% killing. [0643] Further experiments looked at passive protection achieved by transferring into mice (20 per group, 8 week old
- 50 CD1 mice) antiserum from immunised rabbits. Four groups received 200µl of sera from rabbits immunised with one of EsxAB, Hla-H35L, Sta006, Sta011; a fifth group received 50µl of each serum (200µl in total). Two other groups received serum from IsdB-immunised rabbits or serum from rabbits immunised with saline+adjuvant. 15 minutes later the mice were challenged intraperitoneally (10<sup>8</sup> CFU of Newman strain) and then mortality was assessed after 14 days. Results were as follows:
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	EsxA-B	Sta006	Sta011	HIaH35L	Combo1	IsdB	-ve ctrl
Survival	5%	26%	0%	15%	25%	10%	5%

[0644] In further experiments the level of specific antibodies induced in CD1 mice were examined to assess the immunogenicity of the four polypeptides in Combo1. Compositions included either 20µg of each of the four single polypeptides, or 4x10µg in the combination. The compositions included an aluminium hydroxide adjuvant. Serum levels of antigen-specific IgG were determined by Luminex 4Plex assay As shown in Figure 9, all four polypeptides were highly immunogenic in CD1 mice on their own and in combination. In each case the titer against a polypeptide was higher when it was administered in the combination than when administered alone (compare middle and right pairs).

[0645] Further experiments compared protection achieved either with Combo-1 or with its four individual polypeptides. IsdB was also included for comparison. The proportions of animals surviving (40 animals per group) 15 days after challenge with Newman strain, and the average (median) survival in days, were as follows, including a one-tailed pvalue of the surviving proportion in comparison with a PBS+adjuvant negative control:

	EsxA-B	Sta006	Sta011	HIaH35L	Combo1	IsdB	PBS
Survival	34%	28%	16%	39%	59%	22%	5%
р	0.0017	0.0003	0.0064	<0.0001	<0.0001	0.0006	-
Days	1	2	1	10	15	1	0

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**[0646]** The murine abscess model was used to compare the four individual polypeptides with the Combo 1 combination. 20 In some experiments mice were immunised with IsdB for comparison. Antigens were adjuvanted with aluminium hydroxide, and adjuvant alone was used as a negative control. Figure 7 shows the numbers of bacteria in animals' kidneys after challenge with four different strains. The lowest average counts were seen for the Combo 1 combination.

[0647] Challenge experiments were performed following immunisation with (i) the four individual polypeptides, (ii) all pairs, (iii) all triplets, or (iv) the full Combo1 combination. IsdB or buffer alone were used for comparison. Survival results 25 from 24 mice per group (3 experiments) after challenge with 5x10<sup>8</sup> CFU of Newman strain are shown in Figure 13. The median survival for IsdB was only 2 days. The median survival for the individual Combo1 polypeptides ranged from 1-6 days. Pairs of the polypeptides gave median survival of 2-11 days. Triplets gave median survival of 8-15 days. The full Combo1 combination gave a median survival of the full 15 days, with 59% of mice surviving this long (cf. only 35% with IsdB).

30 [0648] It will be understood that the invention has been described by way of example only and modifications may be made whilst remaining within the scope and spirit of the invention.

TABLE 1: NOMENCLATURE CROSS-REFERENCE									
35			NCTC 8325 s	train	Newman	strain			
	SEQ ID NO	Name	SAOUHSC_#	GI	NMWN_#	GI			
	1	clfA	SAOUHSC_00812	88194572	NWMN_0756	151220968			
	2	clfB	SAOUHSC_02963	88196585	NWMN_2529	151222741			
40	3	coA	SAOUHSC_00192	88194002	NWMN_0166	151220378			
	4	eap	SAOUHSC_02161	88195840	NWMN_1872	151222084			
	5	ebhA	SAOUHSC_01447	88195168	-	-			
45	6	ebpS	SAOUHSC_01501	88195217	NWMN_1389	151221601			
	7	efb	SAOUHSC_01114	88194860	NWMN_1069	151221281			
	8	emp	SAOUHSC_00816	88194575	NWMN_0758	151220970			
	9	esaC	SAOUHSC_00264	88194069	-	-			
50	10	esxA	SAOUHSC_00257	88194063	-	-			
	11	esxB	SAOUHSC_00265	88194070	-	-			
	12	FnBA	SAOUHSC_02803	88196438	NWMN_2399	151222611			
55	13	FnBB	SAOUHSC_02802	88196437	NWMN_2397	151222609			
	14	hla	SAOUHSC_01121	88194865	NWMN_1073	151221285			
	15	hlgB	SAOUHSC_02710	88196350	-	-			

### NOMENCI ATUDE ODOGO DECEDENCE

			NCTC 8325 strain		Newman strain	
	SEQ ID NO	Name	SAOUHSC_#	GI	NMWN_#	GI
5	16	hlgC	SAOUHSC_02709	88196349	-	-
	17	isdA	SAOUHSC_01081	88194829	NWMN_1041	151221253
	18	isdB	SAOUHSC_01079	88194828	-	-
10	19	isdC	SAOUHSC_01082	88194830	-	-
	20	isdG	SAOUHSC_01089	88194836	-	-
	21	isdH	SAOUHSC_01843	88195542	NWMN_1624	151221836
	22	isdl	SAOUHSC_00130	88193943	-	-
15	23	lukD	SAOUHSC_01954	88195647	NWMN_1718	151221930
	24	lukE	SAOUHSC_01955	88195648	-	-
	25	lukF	SAOUHSC_02241	88195914	-	-
20	26	lukS	SAOUHSC_02243	88195915	NWMN_1928	151222140
	27	nuc	SAOUHSC_01316	88195046	-	-
	28	sasA	SAOUHSC_02990	88196609	-	-
	29	sasB	SAOUHSC_02404	88196065	-	-
25	30	sasC	SAOUHSC_01873	88195570	-	-
	31	sasD	SAOUHSC_00094	88193909	-	-
	32	sasF	SAOUHSC_02982	88196601	-	-
30	33	sdrC	SAOUHSC_00544	88194324	-	-
	34	sdrD	SAOUHSC_00545	88194325	-	-
	35	sdrE2	-	-	NWMN_0525	151220737
25	36	spa	SAOUHSC_00069	88193885	NWMN_0055	151220267
35	37	sta001	SAOUHSC_00025	88193846	NWMN_0022	151220234
	38	sta002	SAOUHSC_00356	88194155	NWMN_0364	151220576
	39	sta003	SAOUHSC_00400	88194195	NWMN_0401	151220613
40	40	sta004	SAOUHSC_00749	88194514	NWMN_0705	151220917
	41	sta005	SAOUHSC_01127	88194870	NWMN_1077	151221289
	42	sta006	SAOUHSC_02554	88196199	NWMN_2185	151222397
45	43	sta007	SAOUHSC_02571	88196215	NWMN_2199	151222411
	44	sta008	SAOUHSC_02650	88196290	NWMN_2270	151222482
	45	sta009	SAOUHSC_02706	88196346	NWMN_2317	151222529
	46	sta010	SAOUHSC_02887	88196515	NWMN_2469	151222681
50	47	sta011	SAOUHSC_00052	88193872	-	-
	48	sta012	SAOUHSC_00106	88193919	-	-
	49	sta013	SAOUHSC_00107	88193920	-	-
55	50	sta014	SAOUHSC_00137	88193950	-	-
	51	sta015	SAOUHSC_00170	88193980	-	-
	52	sta016	SAOUHSC_00171	88193981	-	-

			NCTC 8325 strain		Newman strain	
	SEQ ID NO	Name	SAOUHSC_#	GI	NMWN_#	GI
5	53	sta017	SAOUHSC_00186	88193996	-	-
	54	sta018	SAOUHSC_00201	88194011	-	-
	55	sta019	SAOUHSC_00248	88194055	NWMN_0210	151220422
10	56	sta020	SAOUHSC_00253	88194059	-	-
	57	sta021	SAOUHSC_00256	88194062	-	-
	58	sta022	SAOUHSC_00279	88194083	-	-
	59	sta023	SAOUHSC_00284	88194087	-	-
15	60	sta024	SAOUHSC_00300	88194101	-	-
	61	sta025	SAOUHSC_00362	88194160	-	-
	62	sta026	SAOUHSC_00404	88194198	-	-
20	63	sta027	SAOUHSC_00661	88194426	-	-
	64	sta028	SAOUHSC_00671	88194436	NWMN_0634	151220846
	65	sta029	SAOUHSC_00754	88194518	-	-
	66	sta030	SAOUHSC_00808	88194568	-	-
25	67	sta031	SAOUHSC_00860	88194617	-	-
	68	sta032	SAOUHSC_00958	88194715	-	-
	69	sta033	SAOUHSC_00987	88194744	-	-
30	70	sta034	SAOUHSC_00988	88194745	-	-
	71	sta035	SAOUHSC_00998	88194754	-	-
	72	sta036	SAOUHSC_01084	88194831	-	-
	73	sta037	SAOUHSC_01085	88194832	-	-
35	74	sta038	SAOUHSC_01088	88194835	-	-
	75	sta039	SAOUHSC_01124	88194868	-	-
	76	sta040	SAOUHSC_01125	88194869	NWMN_1076	151221288
40	77	sta041	SAOUHSC_01175	88194914	-	-
	78	sta042	SAOUHSC_01180	88194919	-	-
	79	sta043	SAOUHSC_01219	88194955	-	-
45	80	sta044	SAOUHSC_01508	88195223	-	-
45	81	sta045	SAOUHSC_01627	88195337	-	-
	82	sta046	SAOUHSC_01918	88195613	-	-
	83	sta047	SAOUHSC_01920	88195615	-	-
50	84	sta048	SAOUHSC_01949	88195642	-	-
	85	sta049	SAOUHSC_01972	88195663	NWMN_1733	151221945
	86	sta050	SAOUHSC_02127	88195808	-	-
55	87	sta051	SAOUHSC_02147	88195827	-	-
	88	sta052	SAOUHSC_02246	88195918	-	-
	89	sta053	SAOUHSC_02257	88195928	-	-

			NCTC 8325 strain		Newman strain	
	SEQ ID NO	Name	SAOUHSC_#	GI	NMWN_#	GI
5	90	sta054	SAOUHSC_02333	88195999	-	-
	91	sta055	SAOUHSC_02448	88196100	-	-
	92	sta056	SAOUHSC_02463	88196115	-	-
10	93	sta057	SAOUHSC_02576	88196220	NWMN_2203	151222415
	94	sta058	SAOUHSC_02690	88196330	-	-
	95	sta059	SAOUHSC_02708	88196348	-	-
	96	sta060	SAOUHSC_02767	88196403	-	-
15	97	sta061	SAOUHSC_02783	88196419	-	-
	98	sta062	SAOUHSC_02788	88196424	-	-
	99	sta063	SAOUHSC_02971	88196592	-	-
20	100	sta064	SAOUHSC_03006	88196625	NWMN_2569	151222781
	101	sta065	SAOUHSC_00051	88193871	-	-
	102	sta066	SAOUHSC_00172	88193982	-	-
	103	sta067	SAOUHSC_00176	88193986	-	-
25	104	sta068	SAOUHSC_00327	88194127	-	-
	105	sta069	SAOUHSC_00427	88194219	-	-
	106	sta070	SAOUHSC_00773	88194535	-	-
30	107	sta071	SAOUHSC_00854	88194612	-	-
	108	sta072	SAOUHSC_00872	88194629	-	-
	109	sta073	SAOUHSC_00994	88194750	NWMN_0922	151221134
05	110	sta074	SAOUHSC_01220	88194956	-	-
30	111	sta075	SAOUHSC_01256	88194989	-	-
	112	sta076	SAOUHSC_01263	88194996	-	-
	113	sta077	SAOUHSC_01317	88195047	-	-
40	114	sta078	SAOUHSC_01857	88195555	-	-
	115	sta079	SAOUHSC_01935	88195630	-	-
	116	sta080	SAOUHSC_01936	88195631	-	-
45	170	sta081	SAOUHSC_01938	88195633		
	117	sta082	SAOUHSC_01939	88195634	-	-
	118	sta083	SAOUHSC_01941	88195635	-	-
	119	sta084	SAOUHSC_01942	88195636	-	-
50	120	sta085	SAOUHSC_02171	88195848	-	-
	121	sta086	SAOUHSC_02327	88195993	-	-
	122	sta087	SAOUHSC_02635	88196276	-	-
55	123	sta088	SAOUHSC_02844	88196477	-	-
~~	124	sta089	SAOUHSC_02855	88196486	-	-
	125	sta090	SAOUHSC_02883	88196512	-	-

			NCTC 8325 strain		Newman strain	
	SEQ ID NO	Name	SAOUHSC_#	GI	NMWN_#	GI
5	126	sta091	SAOUHSC_00685	88194450	-	-
	127	sta092	SAOUHSC_00174	88193984	-	-
	128	sta093	SAOUHSC_01854	88195552	-	-
10	129	sta094	SAOUHSC_01512	88195226	-	-
	130	sta095	SAOUHSC_00383	88194180	NWMN_0388	151220600
	131	sta096	SAOUHSC_00384	88194181	-	-
	132	sta097	SAOUHSC_00386	88194182	-	-
15	133	sta098	SAOUHSC_00389	88194184	NWMN_0391	151220603
	134	sta099	SAOUHSC_00390	88194185	-	-
	135	sta100	SAOUHSC_00391	88194186	-	-
20	136	sta101	SAOUHSC_00392	88194187	NWMN_0394	151220606
	137	sta102	SAOUHSC_00393	88194188	-	-
	138	sta103	SAOUHSC_00394	88194189	-	-
	139	sta104	SAOUHSC_00395	88194190	-	-
25	140	sta105	SAOUHSC_00399	88194194	NWMN_0400	151220612
	141	sta106	SAOUHSC_01115	88194861	-	-
	177	sta107	SAOUHSC_00354	88194153	NWMN_0362	151220574
30	178	sta108	SAOUHSC_00717	88194482	NWMN_0677	151220889
	179	sta109	SAOUHSC_02979	88196599	NWMN_2543	151222755
	180	sta110	SAOUHSC_01039	88194791		
25	181	sta111	SAOUHSC_01005	88194760	NWMN_0931	151221143
30	182	sta112	SAOUHSC_00634	88194402	NWMN_0601	151220813
	183	sta113	SAOUHSC_00728	88194493	NWMN_0687	151220899
	184	sta114	SAOUHSC_00810	88194570		
40	185	sta115	SAOUHSC_00817	88194576	NWMN_0759	151220971
	186	sta116	SAOUHSC_01112	88194858	NWMN_1067	151221279
	187	sta117	SAOUHSC_02240	88195913	NWMN_1926	151222138
45	188	sta118	SAOUHSC_01150	88194892	NWMN_1096	151221308
+0	200	sta119	SAOUHSC_01100	88194846		
	201	sta120	SAOUHSC_00365	88194163		
	142	NW_6	-	-	NWMN_0757	151220969
50	143	NW_9	-	-	NWMN_0958	151221170
	144	NW_10	-	-	NWMN_1066	151221278
	145	NW_7	-	-	NWMN_1876	151222088
55	146	NW_8	-	-	NWMN_1877	151222089
~~	147	NW_2	-	-	NWMN_1883	151222095
	148	NW_1	-	-	NWMN_1924	151222136

(continued)

		NCTC 8325 s	strain	Newman	strain
SEQ ID NO	Name	SAOUHSC_#	GI	NMWN_#	GI
149	NW_5	-	-	NWMN_2392	15122260



# TABLE 2: ABSCESS MODEL RESULTS SUMMARY

	Immunising antigon(s)	Adiuvant	infacting strai	in & doso	Reduction**
5	Enh	Aujuvant	Marrie Ma		2 12
	FIID St. 005		Newman	1.4E+07	2.13
		aium	Newman	1.4E+07	1.20
		alum	Newman	1.4E+07	1.08
	SasD	alum	Newman	1.4E+07	0.10
10	SpA G FII	alum	Newman	$\frac{1.4E+07}{1.4E+07}$	0.41
	SasFHis	alum	Newman	$\frac{1.4E+07}{1.4E+07}$	1.33
	COA	alum	Newman	1.4E+07	1.01
	Sta028	alum	Newman	1.2E+07	1.85
	Sta017	alum	Newman	1.2E+07	1.23
15	Sta006	alum	Newman	1.2E+07	2.33
	Sta012	alum	Newman	1.2E+07	1.69
	Sta011	alum	Newman	1.2E+07	2.66
	Sta019	alum	Newman	1.2E+07	2.36
	Sta021	alum	Newman	1.2E+07	1.58
20	IsdA + EsxAB	alum	Newman	1.8E+07	0.11
	EsxAB	alum	Newman	1.8E+07	1.31
	NW_1	alum	Newman	1.8E+07	1.00
	NW_10	alum	Newman	1.8E+07	-0.65
	Sta073	alum	Newman	1.8E+07	1.46
25	Sta002	alum	Newman	1.8E+07	0.17
	Sta064	alum	Newman	1.8E+07	1.04
	Sta014	alum	Newman	1.8E+07	1.74
	Sta002	alum	Newman	1.0E+07	0.52
	Sta014	alum	Newman	1.0E+07	1.02
30	Sta064	alum	Newman	1.0E+07	1.22
	Sta006	alum	Newman	1.0E+07	0.80
	Sta073	alum	Newman	1.0E+07	0.92
	NW 1	alum	Newman	1.0E+07	0.77
	NW 10	alum	Newman	1.0E+07	2.25
35	Sta017	alum	Newman	1.0E+07	2.13
	Sta028	alum	Newman	1.0E+07	0.64
	Sta021	alum	Newman	1.0E+07	1.03
	Sta019	alum	Newman	1.0E+07	1.28
	Sta011	alum	Newman	1.0E+07	0.78
40	IsdB	alum	Newman	1.0E+07	1.22
	IsdA40-184	none	Newman	1.0E+07	0.58
	Sta006	none	Newman	1.0E+07	0.30
	Sta011	none	Newman	1.0E+07	0.62
	EsxAB	none	Newman	1.0E+07	1.09
45	Sast	none	Newman	1.0E+07	0.11
	IsdB	none	Newman	1.0E+07	0.93
	IsdA <sub>40,184</sub>	alum	Newman	1.0E+07	1.02
	Sta006	alum	Newman	1.0E+07	0.45
	Sta011	alum	Newman	1.0E+07	0.80
50	EsxAB	alum	Newman	1.0E+07	0.47
	Sast	alum	Newman	1.0E+07	-0.78
	IsdB	alum	Newman	1.0E+07	1 24
	Type 5 conjugate + Isd $\Delta_{12}$ and	alum	Newman	1 5E+07	0.34
	Type 5 conjugate	alum	Newman	1.5E+07	0.72
55	IsdA 40.104	alum	Newman	1.5E+07	1.08
		**1**111	_ ( <b>v</b> ) , 1110111		

	Type 5 conjugate	MF59	Newman	1.5E+07	0.45
	lsdB	alum	Newman	1.5E+07	1.50
	ClfB <sub>45-552</sub>	alum	Newman	1.5E+07	-0.05
5	Sta019	alum	Newman	1.5E+07	0.82
	$1sdA_{40-184} + ClfB_{45-552}$	alum	Newman	1.5E+07	0.72
	Type 8 conjugate	alum	Becker	4.0E+07	1.51
	Type 8 conjugate	MF59	Becker	4.0E+07	0.35
	Factor	alum	Newman	1.0E+07	1 54
10	combol	alum	Newman	1.0E+07	2.04
	$E_{SXAB} + I_{SdA_{40,184}} + Sta006 + Sta011$	alum	Newman	1.0E+07	0.84
	SdrD <sub>52,502</sub>	alum	Newman	1.0E+07	1 15
	Sta105	alum	Newman	1.0E+07	0.54
	Sta101	alum	Newman	1.0E+07	1 51
15	Sta116	alum	Newman	1.0E+07	1.31
	Sta106	alum	Newman	1.0E+07	1.25
-	Sta100	alum	Newman	1.0E+07	1.20
	Sta107	alum	Newman	1.0E+0.7	0.70
	Sta004	alum	Newman	1.0E+07 1.0E+07	1.32
20	$\sum_{n=1}^{\infty} A D + \sum_{n=1}^{\infty} A D + \sum_{n=1}^{\infty$	alum	Newman	1.0E+07	2.04
	ESXAB + SIa019 + SIa000 + SIa011	alum	Newman	9.0E+06	3.04
		alum	Newman	9.0E+06	2.53
	$ESXAB + ISdA_{40-184} + Sta006 + Sta011$	alum	Newman	9.0E+06	1.85
	SdrD <sub>53-592</sub>	alum	Newman	9.0E+06	1.80
25	Sta105	alum	Newman	9.0E+06	0.60
-	Sta101	alum	Newman	9.0E+06	0.83
	Sta116	alum	Newman	9.0E+06	1.96
	Sta106	alum	Newman	9.0E+06	2.56
	IsdB	alum	Newman	9.0E+06	1.37
30	Sta004	alum	Newman	9.0E+06	1.01
	Sta003	alum	Newman	9.0E+06	2.20
	IsdB	alum	Newman	1.0E+07	0.83
	Sta107	alum	Newman	1.0E+07	0.24
	SrdC <sub>51-518</sub>	alum	Newman	1.0E+07	0.84
35	SdrE <sub>53-632</sub>	alum	Newman	1.0E+07	1.08
	Hla <sub>27-76</sub>	alum	Newman	1.0E+07	0.18
	EsxAB + HlaH35L + Sta006 + Sta021	alum	Newman	1.0E+07	0.59
	EsxAB + HlaH35L + Sta006 + Sta019	alum	Newman	1.0E+07	0.85
	EsxAB + HlaH35L + Sta006 + Sta017	alum	Newman	1.0E+07	1.88
40	EsxAB + Hla27-76 + Sta006 + Sta021	alum	Newman	1.0E+07	1.49
	$Hla_{27-76} + Sta006 + Sta017 + Sta019$	alum	Newman	1.0E+07	0.00
	IsdB	alum	Newman	1.2E+07	1.07
	Sta107	alum	Newman	1.2E+07	1.35
	SrdC <sub>51-518</sub>	alum	Newman	1.2E+07	2.17
45	SdrE <sub>53-632</sub>	alum	Newman	1.2E+07	2.82
	$Hla_{27-76}$	alum	Newman	1.2E+07	0.17
	EsxAB + HlaH35L + Sta006 + Sta021	alum	Newman	1.2E+07	1.70
	EsxAB + HlaH35L + Sta006 + Sta019	alum	Newman	1.2E+07	1.20
50	EsxAB + HlaH35L + Sta006 + Sta017	alum	Newman	1.2E+07	1.52
50	$EsxAB + Hla_{27-76} + Sta006 + Sta021$	alum	Newman	1.2E+07	1.81
	Hla <sub>27-76</sub> + Sta006 + Sta017 + Sta019	alum	Newman	1.2E+07	0.89
	IsdB	alum	Mu-50	3.8E+07	0.44
	Combo1	alum	Mu-50	3.8E+07	1.73
55	IsdB	alum	USA 200	2.0E+07	1.17
	Combo1	alum	USA 200	2.0E+07	1.87

Combol         alum         USA 300         3.0E+07         2.19           5         Combol         alum         Staph19         2.7E+07         0.66           IsdB         alum         Mu-50         4.5E+07         0.76           IsdB         alum         Mu-50         4.5E+07         0.76           IsdB         alum         USA 200         1.6E+07         0.18           Combol         alum         USA 300         2.2E+07         0.21           Combol         alum         LAC         3.50E+07         2.07           Sta011         alum         MW2         3.00E+07         0.01           Sta011         alum         MW2         3.00E+07         0.01 <th></th> <th>IsdB</th> <th>alum</th> <th>USA 300</th> <th>3.0E+07</th> <th>0.09</th>		IsdB	alum	USA 300	3.0E+07	0.09
IsdB         alum         Staph19         2.7E+07         0.66           IsdB         alum         Mu-50         4.5E+07         0.98           IsdB         alum         Mu-50         4.5E+07         0.98           IsdB         alum         Mu-50         4.5E+07         0.98           IsdB         alum         Mu-50         4.5E+07         0.18           Combol         alum         USA 200         1.6E+07         0.19           IsdB         alum         USA 300         2.2E+07         0.29           IsdB         alum         USA 300         2.2E+07         0.29           IsdB         alum         USA 300         2.2E+07         0.29           IsdB         alum         LAC         3.50E+07         1.5           IsdB         alum         LAC         3.50E+07         2.1           Haf135L         alum         LAC         3.50E+07         2.1           IsdB         alum         MW2         3.00E+07         1.17           IsdB         alum         MW2         3.00E+07         1.8           IsdB         alum         MW2         3.00E+07         0.17           IsdB         a		Combo1	alum	USA 300	3.0E+07	2.19
Combol         alum         Staph19         2.7E+07         0.46           IsdB         alum         Mu-50         4.5E+07         0.76           IsdB         alum         USA 200         1.6E+07         0.18           Combol         alum         USA 200         1.6E+07         0.19           IsdB         alum         USA 300         2.2E+07         0.21           Combol         alum         USA 300         2.2E+07         0.23           IsdB         alum         USA 300         2.2E+07         0.80           IsdB         alum         LAC         3.50E+07         2.67           IsdB         alum         LAC         3.50E+07         2.67           Sta011         alum         LAC         3.50E+07         2.66           IsdB         alum         MW2         3.00E+07         1.7           IsdB		IsdB	alum	Staph19	2.7E+07	0.66
S         IsdB         alum         Mu-50         4.5E+07         0.98           Combol         alum         Mu-50         4.5E+07         0.76           IsdB         alum         USA 200         1.6E+07         0.19           IsdB         alum         USA 300         2.2E+07         0.29           IsdB         alum         USA 300         2.2E+07         0.29           IsdB         alum         Staph19         2.3E+07         0.80           Combol         alum         Staph19         2.3E+07         0.80           IsdB         alum         LAC         3.50E+07         2.67           Sta011         alum         LAC         3.50E+07         2.39           Combol         alum         MV2         3.00E+07         0.81           Ista01         alum         MV2         3.00E+07         0.81	5	Combo1	alum	Staph19	2.7E+07	0.46
Combol         alum         Mu-S0         4.5E+07         0.76           IsdB         alum         USA 200         1.6E+07         0.18           Combol         alum         USA 300         2.2E+07         0.21           Combol         alum         USA 300         2.2E+07         0.27           IsdB         alum         USA 300         2.2E+07         0.27           IsdB         alum         Staph19         2.3E+07         0.57           Combol         alum         Staph19         2.3E+07         0.57           Sta011         alum         LAC         3.50E+07         2.67           Sta012         alum         LAC         3.50E+07         2.67           Sta013         alum         LAC         3.50E+07         2.11           Sta006         alum         LAC         3.50E+07         2.66           IsdB         alum         MW2         3.00E+07         1.89           FissAB         alum         MW2         3.00E+07         0.87           Sta011         alum         MW2         3.00E+07         0.87           Sta011         alum         LAC         4.00E+07         1.95           Es		IsdB	alum	Mu-50	4.5E+07	0.98
IsdB         alum         USA 200         1.6E+07         0.18           10         IsdB         alum         USA 300         2.2E+07         0.21           Combol         alum         USA 300         2.2E+07         0.21           Combol         alum         USA 300         2.2E+07         0.21           IsdB         alum         Staph19         2.3E+07         0.80           IsdB         alum         Staph19         2.3E+07         0.80           IsdB         alum         LAC         3.50E+07         2.67           EaxAB         alum         LAC         3.50E+07         2.21           Hal435L         alum         LAC         3.50E+07         2.23           Sta010         alum         LAC         3.50E+07         2.30           EaxAB         alum         LAC         3.50E+07         2.66           IsdB         alum         MW2         3.00E+07         0.71           Sta011         alum         MW2         3.00E+07         0.87           EaxAB         alum         MW2         3.00E+07         0.91           Combol         alum         MW2         3.00E+07         0.91		Combo1	alum	Mu-50	4.5E+07	0.76
Combol         alum         USA 200         1.6E+07         0.19           IsdB         alum         USA 300         2.2E+07         -0.21           Combol         alum         USA 300         2.2E+07         -0.29           IsdB         alum         Staph19         2.3E+07         0.80           IsdB         alum         Staph19         2.3E+07         0.80           IsdB         alum         LAC         3.50E+07         1.35           EsxAB         alum         LAC         3.50E+07         2.67           Sta011         alum         LAC         3.50E+07         2.11           BidB         alum         LAC         3.50E+07         2.21           HlaH35L         alum         LAC         3.50E+07         2.17           Sta006         alum         MW2         3.00E+07         1.66           IsdB         alum         MW2         3.00E+07         1.89           HaH35L         alum         MW2         3.00E+07         0.87           Sta006         alum         MW2         3.00E+07         0.91           Combol         alum         MW2         3.00E+07         1.95           Sta006 </td <td></td> <td>IsdB</td> <td>alum</td> <td>USA 200</td> <td>1.6E+07</td> <td>0.18</td>		IsdB	alum	USA 200	1.6E+07	0.18
isdB         alum         USA 300         2.2E+07         -0.21           Combol         alum         USA 300         2.2E+07         -0.29           isdB         alum         Staph19         2.3E+07         -0.29           isdB         alum         Staph19         2.3E+07         -0.29           isdB         alum         LAC         3.50E+07         2.67           isdB         alum         LAC         3.50E+07         1.35           EaxAB         alum         LAC         3.50E+07         2.21           HaH3SL         alum         LAC         3.50E+07         2.39           Combol         alum         LAC         3.50E+07         2.39           isdB         alum         MW2         3.00E+07         0.87           sta011         alum         MW2         3.00E+07         0.87           Sta006         alum         MW2         3.00E+07         0.87           Sta011         alum         MW2         3.00E+07         0.91           Combol         alum         LAC         4.00E+07         1.54           sta011         alum         LAC         4.00E+07         1.54           sta011 <td></td> <td>Combol</td> <td>alum</td> <td>USA 200</td> <td>1.6E+07</td> <td>0.19</td>		Combol	alum	USA 200	1.6E+07	0.19
Combot         alum         USA 300         2.2E+07         4.0.29           IsdB         alum         Staph19         2.3E+07         0.57           Combot         alum         Staph19         2.3E+07         0.57           IsdB         alum         LAC         3.50E+07         2.67           Sta011         alum         LAC         3.50E+07         2.67           Sta011         alum         LAC         3.50E+07         2.11           Hiaf35L         alum         LAC         3.50E+07         0.71           Sta006         alum         LAC         3.50E+07         0.71           Sta010         alum         LAC         3.50E+07         0.71           Sta011         alum         MW2         3.00E+07         0.82           ExxAB         alum         MW2         3.00E+07         0.87           Sta011         alum         MW2         3.00E+07         0.87           Sta006         alum         MW2         3.00E+07         0.87           Sta011         alum         LAC         4.00E+07         1.54           Sta011         alum         LAC         4.00E+07         1.55           Sta006	10	IsdB	alum	USA 300	2.2E+07	-0.21
IsdB         alum         Staph19         2.3E+07         0.57           15         IsdB         alum         Staph19         2.3E+07         0.80           15         IsdB         alum         LAC         3.50E+07         2.67           16         Sta011         alum         LAC         3.50E+07         2.21           Hald135L         alum         LAC         3.50E+07         2.21           Sta006         alum         LAC         3.50E+07         2.39           Combol         alum         LAC         3.50E+07         2.39           Sta006         alum         MW2         3.00E+07         0.66           IsdB         alum         MW2         3.00E+07         0.87           Sta006         alum         LAC         4.00E+07         0.87           Sta011         alum         LAC         4.00E+07         1.55           Sta011         alum         LAC         4.00E+07		Combo1	alum	USA 300	2.2E+07	-0.29
Combol         alum         Staph19         2.3E+07         0.80           15         IsdB         alum         LAC         3.50E+07         2.67           Sta011         alum         LAC         3.50E+07         2.21           HlaH35L         alum         LAC         3.50E+07         2.21           HlaH35L         alum         LAC         3.50E+07         2.01           Sta006         alum         LAC         3.50E+07         2.66           IsdB         alum         LAC         3.50E+07         2.66           IsdB         alum         MW2         3.00E+07         1.71           Sta011         alum         MW2         3.00E+07         0.82           Sta011         alum         MW2         3.00E+07         0.87           Sta006         alum         MW2         3.00E+07         0.69           Combol         alum         MW2         3.00E+07         0.69           Sta011         alum         LAC         4.00E+07         1.51           Sta011         alum         LAC         4.00E+07         1.21           IsdB         alum         LAC         4.00E+07         1.22		IsdB	alum	Staph19	2.3E+07	0.57
IsdB         alum         LAC         3.50E+07         2.67           Sta011         alum         LAC         3.50E+07         1.35           EsxAB         alum         LAC         3.50E+07         2.11           HlaH35L         alum         LAC         3.50E+07         2.21           HlaH35L         alum         LAC         3.50E+07         2.39           Combol         alum         LAC         3.50E+07         2.66           IsdB         alum         MW2         3.00E+07         1.87           Sta011         alum         MW2         3.00E+07         0.82           EsxAB         alum         MW2         3.00E+07         0.87           Sta006         alum         MW2         3.00E+07         0.87           Sta006         alum         MW2         3.00E+07         0.87           Sta011         alum         LAC         4.00E+07         1.54           Sta011         alum         LAC         4.00E+07         1.51           Sta006         alum         LAC         4.00E+07         1.74           Combol         alum         LAC         4.00E+07         1.74           Combol		Combol	alum	Staph19	2.3E+07	0.80
Sta01         alum         LAC         3.50E+07         1.35           EsxAB         alum         LAC         3.50E+07         2.21           HaH3SL         alum         LAC         3.50E+07         2.39           20         Sta006         alum         LAC         3.50E+07         2.39           20         Sta006         alum         LAC         3.50E+07         2.39           20         Sta011         alum         LAC         3.50E+07         2.39           20         Sta011         alum         MW2         3.00E+07         0.82           EsxAB         alum         MW2         3.00E+07         0.87           Sta011         alum         MW2         3.00E+07         0.87           Sta006         alum         MW2         3.00E+07         0.87           Sta011         alum         LAC         4.00E+07         1.54           Sta010         alum         LAC         4.00E+07         1.54           Sta010         alum         LAC         4.00E+07         1.25           Sta011         alum         LAC         4.00E+07         1.22           IsdB         alum         MW2         2.75E		IsdB	alum	LAC	3 50E+07	2.67
Baska B         alum         LAC         3.50E+07         2.21           HlaH3SL         alum         LAC         3.50E+07         2.21           Sta006         alum         LAC         3.50E+07         2.21           Sta006         alum         LAC         3.50E+07         2.39           Combol         alum         LAC         3.50E+07         2.66           IsdB         alum         MW2         3.00E+07         1.17           Sta011         alum         MW2         3.00E+07         0.82           EsxAB         alum         MW2         3.00E+07         0.82           Sta006         alum         MW2         3.00E+07         0.87           Sta006         alum         MW2         3.00E+07         0.87           Sta011         alum         LAC         4.00E+07         1.54           Sta011         alum         LAC         4.00E+07         1.54           Sta010         alum         LAC         4.00E+07         1.74           Combol         alum         LAC         4.00E+07         1.74           Combol         alum         MW2         2.75E+07         1.16           Hat35L	15	Sta011	alum		3 50E+07	1 35
Hala 35L         alum         LAC         3.50E+07         0.71           Sta006         alum         LAC         3.50E+07         2.39           Combol         alum         LAC         3.50E+07         2.66           IsdB         alum         MW2         3.00E+07         0.82           EsxAB         alum         MW2         3.00E+07         0.82           EsxAB         alum         MW2         3.00E+07         0.87           Sta010         alum         MW2         3.00E+07         0.87           Sta006         alum         MW2         3.00E+07         0.91           Combol         alum         MW2         3.00E+07         0.91           Sta006         alum         MW2         3.00E+07         1.54           Sta011         alum         LAC         4.00E+07         1.54           Sta006         alum         LAC         4.00E+07         1.74           Combol         alum         LAC         4.00E+07         1.25           Sta011         alum         MW2         2.75E+07         1.25           Sta011         alum         MW2         2.75E+07         1.25           Sta011		EsxAB	alum	LAC	3 50E+07	2 21
Balance         Balance         Date         Stabbe         Stab           20         Stabbe         alum         LAC         3.50E+07         2.39           20         IsdB         alum         LAC         3.50E+07         2.66           IsdB         alum         MW2         3.00E+07         1.39           EsxAB         alum         MW2         3.00E+07         1.39           Half3SL         alum         MW2         3.00E+07         0.87           Sta006         alum         MW2         3.00E+07         0.87           Sta006         alum         MW2         3.00E+07         0.91           Combol         alum         MW2         3.00E+07         0.87           Sta010         alum         LAC         4.00E+07         1.54           Sta011         alum         LAC         4.00E+07         1.31           Hal+35L         alum         LAC         4.00E+07         1.25           Sta006         alum         LAC         4.00E+07         1.25           Sta010         alum         MW2         2.75E+07         1.26           Sta011         alum         MW2         2.75E+07         1.16			alum		3.50E+07	0.71
		Sta006	alum		3.50E+07	2 39
20         Iduation         Iduation         Interface         100000         100000         100000         1000000         1000000 <td></td> <td>Combol</td> <td>alum</td> <td></td> <td>3.50E+07</td> <td>2.66</td>		Combol	alum		3.50E+07	2.66
$45 $ $\frac{5100}{510}$	20	IsdB	alum	MW2	3.00E+07	1 17
Bakari         Bakari         MW2         Bakari         Bakari           25         EsxAB         alum         MW2         3.00E+07         0.87           26         Sta006         alum         MW2         3.00E+07         0.91           26         Combol         alum         MW2         3.00E+07         0.91           27         Sta006         alum         MW2         3.00E+07         0.91           28         Sta006         alum         LAC         4.00E+07         1.54           30         HiaH35L         alum         LAC         4.00E+07         1.74           29         EsxAB         alum         LAC         4.00E+07         1.74           20         Bta011         alum         LAC         4.00E+07         1.74           20         Sta0106         alum         MW2         2.75E+07         1.25           31         Bta011         alum         MW2         2.75E+07         1.16           11         Alum         MW2         2.75E+07         1.61           31006         alum         MW2         2.75E+07         1.16           311         alum         MW2         2.75E+07		Sta011	alum	MW2	3.00E+07	0.82
Data Barrier         Barrier         Barrier         Barrier           25         HaH35L         alum         MW2         3.00E+07         0.87           26         Sta006         alum         MW2         3.00E+07         0.91           26         Gombol         alum         MW2         3.00E+07         0.67           27         Sta006         alum         LAC         4.00E+07         1.54           28         Sta011         alum         LAC         4.00E+07         1.31           29         EsxAB         alum         LAC         4.00E+07         1.74           20         Sta006         alum         LAC         4.00E+07         1.22           20         Sta006         alum         LAC         4.00E+07         1.21           21         IsdB         alum         MW2         2.75E+07         1.22           22         Sta011         alum         MW2         2.75E+07         1.61           23         Sta006         alum         MW2         2.75E+07         1.61           24         Sta011         alum         MW2         2.75E+07         1.01           25         Sta011         alum		FsxAB	alum	MW2	3.00E+07	1 39
Sta006         alum         MW2         3.00E+07         0.91           Combol         alum         MW2         3.00E+07         0.91           Sta006         alum         MW2         3.00E+07         0.91           Sta011         alum         LAC         4.00E+07         1.54           Sta011         alum         LAC         4.00E+07         1.95           EsxAB         alum         LAC         4.00E+07         1.74           Sta006         alum         LAC         4.00E+07         1.74           Combol         alum         LAC         4.00E+07         1.74           Sta006         alum         LAC         4.00E+07         1.22           Sta006         alum         MW2         2.75E+07         1.22           Sta011         alum         MW2         2.75E+07         1.16           HH313L         alum         MW2         2.75E+07         1.16           Sta006         alum         MW2         2.75E+07         1.17           Sta011         alum         MW2         2.75E+07         1.13           Combol         alum         Mu-50         4.00E+07         0.71           Sta011		HlaH35L	alum	MW2	3.00E+07	0.87
25         30000         30000         30000         30000         30000         30000         30000         30000         30000         300000         300000         300000 <td></td> <td>Sta006</td> <td>alum</td> <td>MW2</td> <td>3.00E+07</td> <td>0.91</td>		Sta006	alum	MW2	3.00E+07	0.91
IsdB         alum         IAC         4.00E+07         1.53           30         IsdB         alum         IAC         4.00E+07         1.54           30         EsxAB         alum         IAC         4.00E+07         1.31           30         HiaH35L         alum         IAC         4.00E+07         1.31           30         HiaH35L         alum         IAC         4.00E+07         1.31           30         Sta006         alum         IAC         4.00E+07         1.74           Combol         alum         IAC         4.00E+07         2.21           1sdB         alum         MW2         2.75E+07         1.22           Sta010         alum         MW2         2.75E+07         1.25           Sta01         alum         MW2         2.75E+07         1.61           Half35L         alum         MW2         2.75E+07         1.61           Sta006         alum         MW2         2.75E+07         1.16           Sta011         alum         MW2         2.75E+07         1.16           Sta006         alum         MU-50         4.00E+07         0.71           Sta011         alum         Mu-5	25	Combol	alum	MW2	$3.00\pm07$ $3.00\pm07$	2 69
45 $45$ $40$ $40$ $40$ $40$ $40$ $40$ $40$ $40$		IsdB	alum		$\frac{3.00\pm07}{4.00\pm07}$	1.54
$40 = \begin{bmatrix} bAW1 & bAW1 & bAW & bAW1 & bAW1 & bAW2 & bAW1 & bAW2 & b$		Sta011	alum		4.00E+07	1.95
30         Harrison         adum         LAC         4.00E+07         0.75           Sta006         alum         LAC         4.00E+07         1.74           Combol         alum         LAC         4.00E+07         2.21           IsdB         alum         LAC         4.00E+07         2.21           IsdB         alum         MW2         2.75E+07         1.22           Sta011         alum         MW2         2.75E+07         1.25           EsxAB         alum         MW2         2.75E+07         1.61           HIH35L         alum         MW2         2.75E+07         1.61           Sta006         alum         MW2         2.75E+07         1.16           HIH35L         alum         MW2         2.75E+07         1.16           Sta006         alum         MW2         2.75E+07         1.13           Combol         alum         MW2         2.75E+07         1.10           EsxAB         alum         Mu-50         4.00E+07         1.72           Sta011         alum         Mu-50         4.00E+07         1.72           Sta011         alum         Staph19         5.30E+07         1.23		FsrAB	alum		4.00E+07	1.33
Statub         Balan         LAC         Hoberton         0.73           Statubo         alum         LAC         4.00E+07         0.74           Combol         alum         LAC         4.00E+07         2.21           IsdB         alum         MW2         2.75E+07         1.22           Sta011         alum         MW2         2.75E+07         1.25           35         EssAB         alum         MW2         2.75E+07         1.16           H1aH35L         alum         MW2         2.75E+07         1.61           Sta006         alum         MW2         2.75E+07         1.61           Sta011         alum         MW2         2.75E+07         1.61           Sta010         alum         MW2         2.75E+07         1.61           Sta006         alum         MW2         2.75E+07         1.97           Sta011         alum         Mu-50         4.00E+07         0.71           EsxAB         alum         Mu-50         4.00E+07         0.71           Sta006         alum         Mu-50         4.00E+07         1.72           45         Sta011         alum         Staph19         5.30E+07         2.02<	30	HlaH35I	alum		4.00E+07	0.75
	50	Sta006	alum	LAC	4 00E+07	1 74
$45 = \begin{bmatrix} 500001 & 100000000000000000000000000000$		Combol	alum	LAC	4 00E+07	2.21
		IsdB	alum	MW2	2.75E+07	1 22
35         EssAB         alum         MW2         2.75E+07         1.16           HlaH35L         alum         MW2         2.75E+07         1.61           Sta006         alum         MW2         2.75E+07         1.13           Combol         alum         MW2         2.75E+07         1.13           Combol         alum         MW2         2.75E+07         1.97           40         Sta011         alum         MW2         2.75E+07         1.97           40         Sta011         alum         MW2         2.75E+07         1.97           40         EsxAB         alum         MW2         2.75E+07         1.97           40         EsxAB         alum         Mu-50         4.00E+07         0.86           HlaH35L         alum         Mu-50         4.00E+07         0.71           Sta006         alum         Mu-50         4.00E+07         1.72           45         Sta011         alum         Staph19         5.30E+07         1.23           50         Sta006         alum         Staph19         5.30E+07         2.00           50         Sta011         alum         Mu-50         4.30E+07         0.36		Sta011	alum	MW2	2.75E+07	1.25
HlaH35L         alum         MW2         2.75E+07         1.61           Sta006         alum         MW2         2.75E+07         1.13           Combol         alum         MW2         2.75E+07         1.13           Combol         alum         MW2         2.75E+07         1.97           Sta011         alum         MU-50         4.00E+07         1.10           EsxAB         alum         Mu-50         4.00E+07         0.86           HlaH35L         alum         Mu-50         4.00E+07         0.71           Sta006         alum         Mu-50         4.00E+07         1.57           Combol         alum         Mu-50         4.00E+07         1.72           Sta011         alum         Mu-50         4.00E+07         1.72           Sta011         alum         Staph19         5.30E+07         1.23           EsxAB         alum         Staph19         5.30E+07         1.65           Sta006         alum         Staph19         5.30E+07         2.00           Combol         alum         Staph19         5.30E+07         2.02           Sta011         alum         Mu-50         4.30E+07         0.36	35	EsxAB	alum	MW2	2.75E+07	1.16
Sta006         alum         MW2         2.75E+07         1.13           40         Sta011         alum         MW2         2.75E+07         1.97           5ta011         alum         MW-50         4.00E+07         1.10           EsxAB         alum         Mu-50         4.00E+07         0.86           HlaH35L         alum         Mu-50         4.00E+07         0.71           Sta006         alum         Mu-50         4.00E+07         1.72           Sta006         alum         Mu-50         4.00E+07         1.72           Sta011         alum         Mu-50         4.00E+07         1.72           Sta011         alum         Staph19         5.30E+07         1.23           EsxAB         alum         Staph19         5.30E+07         1.19           HlaH35L         alum         Staph19         5.30E+07         2.00           Combol         alum         Staph19         5.30E+07         2.02           50         Sta011         alum         Mu-50         4.30E+07         0.36           HaH35L         alum         Mu-50         4.30E+07         0.36           HaH35L         alum         Mu-50         4.30E+		HlaH35L	alum	MW2	2.75E+07	1.61
Combol         alum         MW2         2.75E+07         1.97           40         Sta011         alum         Mu-50         4.00E+07         1.10           EsxAB         alum         Mu-50         4.00E+07         0.86           HlaH35L         alum         Mu-50         4.00E+07         0.71           Sta006         alum         Mu-50         4.00E+07         1.57           Combol         alum         Mu-50         4.00E+07         1.72           Sta011         alum         Mu-50         4.00E+07         1.72           Sta011         alum         Mu-50         4.00E+07         1.72           Sta011         alum         Staph19         5.30E+07         1.23           EsxAB         alum         Staph19         5.30E+07         1.19           HlaH35L         alum         Staph19         5.30E+07         2.00           Sta006         alum         Staph19         5.30E+07         2.02           50         Sta011         alum         Mu-50         4.30E+07         0.36           HaH35L         alum         Mu-50         4.30E+07         0.36           HaH35L         alum         Mu-50         4.30		Sta006	alum	MW2	2.75E+07	1.13
40       Sta011       alum       Mu-50       4.00E+07       1.10         EsxAB       alum       Mu-50       4.00E+07       0.86         HlaH35L       alum       Mu-50       4.00E+07       0.71         Sta006       alum       Mu-50       4.00E+07       1.57         Combol       alum       Mu-50       4.00E+07       1.72         45       Sta011       alum       Mu-50       4.00E+07       1.72         45       Sta011       alum       Mu-50       4.00E+07       1.72         45       Sta011       alum       Mu-50       4.00E+07       1.72         46       Sta011       alum       Mu-50       4.00E+07       1.72         47       Sta011       alum       Staph19       5.30E+07       1.23         48       EsxAB       alum       Staph19       5.30E+07       0.65         Sta006       alum       Staph19       5.30E+07       2.00         50       Sta011       alum       Mu-50       4.30E+07       1.33         EsxAB       alum       Mu-50       4.30E+07       0.36         HlaH35L       alum       Mu-50       4.30E+07       1.05     <		Combo1	alum	MW2	2.75E+07	1.97
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		Sta011	alum	Mu-50	4 00E+07	1.10
Ham         Num         Num <td>40</td> <td>EsxAB</td> <td>alum</td> <td>Mu-50</td> <td>4.00E+07</td> <td>0.86</td>	40	EsxAB	alum	Mu-50	4.00E+07	0.86
Sta006         alum         Mu-50         4.00E+07         1.57           Combol         alum         Mu-50         4.00E+07         1.57           45         Sta011         alum         Mu-50         4.00E+07         1.72           45         Sta011         alum         Staph19         5.30E+07         1.23           45         EsxAB         alum         Staph19         5.30E+07         1.19           HlaH35L         alum         Staph19         5.30E+07         0.65           Sta006         alum         Staph19         5.30E+07         2.00           Combol         alum         Staph19         5.30E+07         2.00           50         Sta006         alum         Staph19         5.30E+07         2.00           Combol         alum         Mu-50         4.30E+07         0.36           HaH35L         alum         Mu-50         4.30E+07         0.36           HaH35L         alum         Mu-50         4.30E+07         1.05           55         Sta010         alum         Mu-50         4.30E+07         1.34           55         Sta011         alum         Mu-50         4.30E+07         1.07		HlaH35L	alum	Mu-50	4.00E+07	0.71
Combol         alum         Mu-50         4.00E+07         1.72           45         Sta011         alum         Staph19         5.30E+07         1.23           EsxAB         alum         Staph19         5.30E+07         1.19           HlaH35L         alum         Staph19         5.30E+07         0.65           Sta006         alum         Staph19         5.30E+07         2.00           Combol         alum         Staph19         5.30E+07         2.02           50         Sta011         alum         Staph19         5.30E+07         2.02           50         Sta011         alum         Mu-50         4.30E+07         1.33           EsxAB         alum         Mu-50         4.30E+07         0.36           HlaH35L         alum         Mu-50         4.30E+07         0.11           Sta006         alum         Mu-50         4.30E+07         1.05           Combol         alum         Mu-50         4.30E+07         1.05           Sta006         alum         Mu-50         4.30E+07         1.05           Sta006         alum         Mu-50         4.30E+07         1.07           55         Sta011         alu		Sta006	alum	Mu-50	4.00E+07	1.57
45       Sta011       alum       Staph19       5.30E+07       1.23         EsxAB       alum       Staph19       5.30E+07       1.19         HlaH35L       alum       Staph19       5.30E+07       0.65         Sta006       alum       Staph19       5.30E+07       2.00         Combol       alum       Staph19       5.30E+07       2.02         50       Sta011       alum       Mu-50       4.30E+07       1.33         50       Sta011       alum       Mu-50       4.30E+07       0.36         50       Sta011       alum       Mu-50       4.30E+07       1.33         50       Sta011       alum       Mu-50       4.30E+07       1.34         51       Sta006       alum       Mu-50       4.30E+07       1.05         55       Sta010       alum       Mu-50       4.30E+07       1.05         55       Sta011       alum       Staph19       4.40E+07       1.07         55       Sta011       alum       Staph19       4.40E+07       1.07		Combol	alum	Mu-50	4.00E+07	1.72
45       EsxAB       alum       Staph19       5.30E+07       1.19         HlaH35L       alum       Staph19       5.30E+07       0.65         Sta006       alum       Staph19       5.30E+07       2.00         Combo1       alum       Staph19       5.30E+07       2.02         50       Sta011       alum       Mu-50       4.30E+07       1.33         EsxAB       alum       Mu-50       4.30E+07       0.36         HlaH35L       alum       Mu-50       4.30E+07       0.11         Sta006       alum       Mu-50       4.30E+07       1.05         Combo1       alum       Mu-50       4.30E+07       1.04         Sta006       alum       Mu-50       4.30E+07       1.05         Sta011       alum       Mu-50       4.30E+07       1.05         Sta011       alum       Mu-50       4.30E+07       1.07         Sta011       alum       Staph19       4.40E+07       1.07         EsxAB       alum       Staph19       4.40E+07       0.94	45	Sta011	alum	Staph19	5.30E+07	1.23
HlaH35L         alum         Staph19         5.30E+07         0.65           Sta006         alum         Staph19         5.30E+07         2.00           Combol         alum         Staph19         5.30E+07         2.00           50         Sta011         alum         Mu-50         4.30E+07         1.33           50         Sta011         alum         Mu-50         4.30E+07         0.36           HlaH35L         alum         Mu-50         4.30E+07         0.11           Sta006         alum         Mu-50         4.30E+07         1.05           Combol         alum         Mu-50         4.30E+07         1.05           Sta006         alum         Mu-50         4.30E+07         1.05           Sta011         alum         Mu-50         4.30E+07         1.05           Sta011         alum         Mu-50         4.30E+07         1.05           Sta011         alum         Staph19         4.40E+07         1.07           EsxAB         alum         Staph19         4.40E+07         0.94	45	EsxAB	alum	Staph19	5.30E+07	1.19
Sta006         alum         Staph19         5.30E+07         2.00           Combol         alum         Staph19         5.30E+07         2.02           50         Sta011         alum         Mu-50         4.30E+07         1.33           50         Sta011         alum         Mu-50         4.30E+07         0.36           HlaH35L         alum         Mu-50         4.30E+07         0.11           Sta006         alum         Mu-50         4.30E+07         1.05           Combol         alum         Mu-50         4.30E+07         1.05           Sta006         alum         Mu-50         4.30E+07         1.05           Sta011         alum         Mu-50         4.30E+07         1.05           Sta011         alum         Mu-50         4.30E+07         1.05           Sta011         alum         Mu-50         4.30E+07         1.07           EsxAB         alum         Staph19         4.40E+07         0.94		HlaH35L	alum	Staph19	5.30E+07	0.65
Combol         alum         Staph19         5.30E+07         2.02           50         Sta011         alum         Mu-50         4.30E+07         1.33           EsxAB         alum         Mu-50         4.30E+07         0.36           HlaH35L         alum         Mu-50         4.30E+07         0.11           Sta006         alum         Mu-50         4.30E+07         1.05           Combol         alum         Mu-50         4.30E+07         1.05           Sta010         alum         Mu-50         4.30E+07         1.05           Sta011         alum         Mu-50         4.30E+07         1.04           Sta011         alum         Staph19         4.40E+07         1.07           EsxAB         alum         Staph19         4.40E+07         0.94		Sta006	alum	Staph19	5.30E+07	2.00
50       Sta011       alum       Mu-50       4.30E+07       1.33         EsxAB       alum       Mu-50       4.30E+07       0.36         HlaH35L       alum       Mu-50       4.30E+07       0.11         Sta006       alum       Mu-50       4.30E+07       1.05         Combol       alum       Mu-50       4.30E+07       1.05         55       Sta011       alum       Staph19       4.40E+07       1.07         EsxAB       alum       Staph19       4.40E+07       0.94		Combo1	alum	Staph19	5.30E+07	2.02
EsxAB       alum       Mu-50       4.30E+07       0.36         HlaH35L       alum       Mu-50       4.30E+07       0.11         Sta006       alum       Mu-50       4.30E+07       1.05         Combol       alum       Mu-50       4.30E+07       1.34         55       Sta011       alum       Staph19       4.40E+07       1.07         EsxAB       alum       Staph19       4.40E+07       0.94	50	Sta011	alum	Mu-50	4.30E+07	1.33
HlaH35L     alum     Mu-50     4.30E+07     0.11       Sta006     alum     Mu-50     4.30E+07     1.05       Combol     alum     Mu-50     4.30E+07     1.34       55     Sta011     alum     Staph19     4.40E+07     1.07       EsxAB     alum     Staph19     4.40E+07     0.94	50	EsxAB	alum	Mu-50	4.30E+07	0.36
Sta006         alum         Mu-50         4.30E+07         1.05           Combol         alum         Mu-50         4.30E+07         1.34           55         Sta011         alum         Staph19         4.40E+07         1.07           EsxAB         alum         Staph19         4.40E+07         0.94		HlaH35L	alum	Mu-50	4.30E+07	0.11
Combol         alum         Mu-50         4.30E+07         1.34           55         Sta011         alum         Staph19         4.40E+07         1.07           EsxAB         alum         Staph19         4.40E+07         0.94		Sta006	alum	Mu-50	4.30E+07	1.05
55         Sta011         alum         Staph19         4.40E+07         1.07           EsxAB         alum         Staph19         4.40E+07         0.94		Combo1	alum	Mu-50	4.30E+07	1.34
EsxAB alum Staph19 4.40E+07 0.94	55	Sta011	alum	Staph19	4.40E+07	1.07
		EsxAB	alum	Staph19	4.40E+07	0.94

HlaH35L	alum	Staph19	4.40E+07	1.19
Sta006	alum	Staph19	4.40E+07	2.31
Combo1	alum	Staph19	4.40E+07	2.45

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\* alum = aluminium hydroxide

\*\* Log reduction in kidney CFU

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### EMBODIMENTS OF THE INVENTION

# 35

[0650]

40	1. An immunogenic composition comprising a combination of antigens, said combination comprising two or more antigens selected from the group consisting of: (1) a sta006 antigen; (2) a sta011 antigen; (3) a esxA antigen; (4) a esxB antigen; (5) a hla antigen; (6) a ebpS antigen; (7) a efb antigen; (8) a emp antigen; (9) a esaC antigen; (10) a coA antigen; (11) a eap antigen; (12) a FnBA antigen; (13) a FnBB antigen; (14) a ebhA antigen; (15) a hlgB antigen; (16) a hlgC antigen; (17) a isdA antigen; (18) a isdB antigen; (19) a isdC antigen; (20) a isdG antigen; (21)
	a isdH antigen; (22) a isdI antigen; (23) a lukD antigen; (24) a lukE antigen; (25) a lukF antigen; (26) a lukS antigen;
	(27) a nuc antigen; (28) a sasA antigen; (29) a sasB antigen; (30) a sasC antigen; (31) a sasD antigen; (32) a sasF
45	antigen; (33) a sdrC antigen; (34) a sdrD antigen; (35) a sdrE2 antigen; (36) a spa antigen; (37) a clfA antigen; (38)
	a clfB antigen; (39) a sta001 antigen; (40) a sta002 antigen; (41) a sta003 antigen; (42) a sta004 antigen; (43) a
	sta005 antigen; (44) a sta007 antigen; (45) a sta008 antigen; (46) a sta009 antigen; (47) a sta010 antigen; (48) a
	sta012 antigen; (49) a sta013 antigen; (50) a sta014 antigen; (51) a sta015 antigen; (52) a sta016 antigen; (53) a
	sta017 antigen; (54) a sta018 antigen; (55) a sta019 antigen; (56) a sta020 antigen; (57) a sta021 antigen; (58) a
50	sta022 antigen; (59) a sta023 antigen; (60) a sta024 antigen; (61) a sta025 antigen; (62) a sta026 antigen; (63) a
	sta027 antigen; (64) a sta028 antigen; (65) a sta029 antigen; (66) a sta030 antigen; (67) a sta031 antigen; (68) a
	sta032 antigen; (69) a sta033 antigen; (70) a sta034 antigen; (71) a sta035 antigen; (72) a sta036 antigen; (73) a
	sta037 antigen; (74) a sta038 antigen; (75) a sta039 antigen; (76) a sta040 antigen; (77) a sta041 antigen; (78) a
	sta042 antigen; (79) a sta043 antigen; (80) a sta044 antigen; (81) a sta045 antigen; (82) a sta046 antigen; (83) a
55	sta047 antigen; (84) a sta048 antigen; (85) a sta049 antigen; (86) a sta050 antigen; (87) a sta051 antigen; (88) a
	sta052 antigen; (89) a sta053 antigen; (90) a sta054 antigen; (91) a sta055 antigen; (92) a sta056 antigen; (93) a
	sta057 antigen; (94) a sta058 antigen; (95) a sta059 antigen; (96) a sta060 antigen; (97) a sta061 antigen; (98) a
	sta062 antigen; (99) a sta063 antigen; (100) a sta064 antigen; (101) a sta065 antigen; (102) a sta066 antigen; (103)

a sta067 antigen; (104) a sta068 antigen; (105) a sta069 antigen; (106) a sta070 antigen; (107) a sta071 antigen; (108) a sta072 antigen; (109) a sta073 antigen; (110) a sta074 antigen; (111) a sta075 antigen; (112) a sta076 antigen; (113) a sta077 antigen; (114) a sta078 antigen; (115) a sta079 antigen; (116) a sta080 antigen; (117) a sta082 antigen; (118) a sta083 antigen; (119) a sta084 antigen; (120) a sta085 antigen; (121) a sta086 antigen; (122) a sta087 antigen; (123) a sta088 antigen; (124) a sta089 antigen; (125) a sta090 antigen; (126) a sta091 antigen; (127) a sta092 antigen; (128) a sta093 antigen; (129) a sta094 antigen; (130) a sta095 antigen; (131) a sta096 antigen; (132) a sta097 antigen; (133) a sta098 antigen; (134) a sta099 antigen; (135) a sta100 antigen; (136) a sta101 antigen; (137) a sta102 antigen; (138) a sta103 antigen; (139) a sta104 antigen; (140) a sta105 antigen; (141) a sta106 antigen; (142) a sta107 antigen; (143) a sta108 antigen; (144) a sta109 antigen; (145) a sta110 antigen; (150) a sta111 antigen; (147) a sta112 antigen; (148) a sta113 antigen; (149) a sta114 antigen; (150) a sta115 antigen; (151) a sta116 antigen; (152) a sta117 antigen; (153) a sta118 antigen; (154) a sta119 antigen; (155) a sta120 antigen; (156) a NW\_6 antigen; (157) a NW\_9 antigen; (158) a NW\_10 antigen; (159) a NW\_7 antigen; (160) a NW\_8 antigen; (161) a NW\_2 antigen; (162) a NW\_1 antigen; (163) a sta081 antigen; and (164) a NW\_5 antigen.

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2. The composition of embodiment 1, comprising at least one antigen selected from numbers (3) to (38) and at least one antigen selected from numbers (1), (2) and (37) to (149).

3. The composition of embodiment 2, comprising:

at least one antigen selected from numbers (37), (38), (8), (9), (3), (4), (5), (17), (18), (19), (31), (32), (33), (34), (35) and (36);

and at least one antigen selected from (40), (1), (43), (2), (64), (96), (133) and (147).

4. The composition of embodiment 1, comprising two or more antigens selected from the group consisting of: (1) a clfA antigen; (2) a clfB antigen; (3) a sdrE2 antigen; (4) a sdrC antigen; (5) a SasF antigen; (6) a emp antigen; (7) a sdrD antigen; (8) a spa antigen; (9) a esaC antigen; (10) a esxA antigen; (11) a esxB antigen; (12) a sta006 antigen; (13) a isdC antigen; (14) a hla antigen; (15) a sta011 antigen; (16) isdA antigen; (17) a isdB antigen; (18) a sasF antigen.

5. The composition of embodiment 1, two or more antigens selected from the group consisting of: (1) a esxA antigen; (2) a esxB antigen; (3) a sta006 antigen; (4) a hla antigen; (5) a sta011 antigen.

6. The composition of any preceding embodiment, wherein one or more of said antigens is adsorbed to an aluminium hydroxide adjuvant, and optionally wherein the composition includes a histidine buffer.

7. The composition of any preceding embodiment, further comprising: one or more conjugates of (i) a *S. aureus* exopolysaccharide and (ii) a carrier protein.

- 40 8. The composition of any preceding embodiment, further comprising: one or more conjugates of (i) a *S. aureus* capsular polysaccharide and (ii) a carrier protein.
  - 9. A polypeptide of formula  $NH_2$ -A-{-X-L-}<sub>n</sub>-B-COOH, wherein:
- 45 X is an amino acid sequence of a staphylococcal antigen, selected from the group consisting of S.aureus antigens sta006, sta011, esxA, esxB, hla, clfA, clfB, coA, eap, ebhA, ebpS, efb, emp, esaC, FnBA, FnBB, hlgB, hlgC, isdA, isdB, isdC, isdG, isdH, isdI, lukD, lukE, lukF, lukS, nuc, sasA, sasB, sasC, sasD, sasF, sdrC, sdrD, sdrE2, spa, sta001, sta002, sta003, sta004, sta005, sta007, sta008, sta009, sta010, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta021, sta022, sta023, sta024, sta025, sta026, sta027, sta028, 50 sta029, sta030, sta031, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, 55 sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, NW\_6, NW\_9, NW\_10, NW\_7, NW\_8, NW\_2, NW\_1, and NW\_ 5;

L is an optional linker amino acid sequence;

A is an optional N-terminal amino acid sequence; B is an optional C-terminal amino acid sequence; and n is an integer of 2 or more.

- <sup>5</sup> 10. An immunogenic composition comprising the polypeptide of embodiment 9 and further comprising: (A) one or more conjugates of (i) a *S.aureus* exopolysaccharide and (ii) a carrier protein; and/or (B) one or more conjugates of (i) a *S.aureus* capsular polysaccharide and (ii) a carrier protein.
- 11. The composition or polypeptide of any preceding embodiment, wherein the clfA antigen can elicit an antibody
   which recognises SEQ ID NO: 1 and comprises an amino acid sequence: (a) having 80% or more identity to SEQ ID NO: 1; and/or (b) comprising a fragment of at least 7 consecutive amino acids of SEQ ID NO: 1, wherein the fragment comprises an epitope from SEQ ID NO: 1.
- 12. A polypeptide comprising amino acid sequence (a) having 80% or more identity to SEQ ID NO: 151; and/or (b) comprising a fragment of at least 7 consecutive amino acids from amino acids 1-97 of SEQ ID NO: 151 and at least 7 consecutive amino acids 104-207 of SEQ ID NO: 151, wherein the polypeptide can elicit antibodies which recognise both the wild-type staphylococcal protein comprising SEQ ID NO: 10 and the wild-type staphylococcal protein comprising SEQ ID NO: 10 and the wild-type staphylococcal protein comprising SEQ ID NO: 11.
- <sup>20</sup> 13. An immunogenic composition comprising the polypeptide of embodiment 12 and one or more of (i) a sta006 antigen; (ii) a hla antigen; and/or (iii) a sta011 antigen.
  - 14. The composition of embodiment 13, including an adjuvant.
- 25 15. A polypeptide comprising amino acid sequence having 80% or more identity to an amino acid sequence selected from SEQ ID NOs: 151, 152, 168, 202, 203, 204, 205. 206, 207, 208, 209 210,211,212,220,221,222,223,224,237,238,241.
- 16. A polypeptide comprising an amino acid sequence selected from SEQ ID NOs: 151, 152, 168, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 220, 221, 222, 223, 224, 237, 238, 241, 242,243,244,245.

17. A polypeptide comprising: (a) a first sequence having 90% or more identity to SEQ ID NO: 218; and (b) a second sequence having 90% or more identity to SEQ ID NO: 219, wherein the first and second sequences are either directly joined or are joined by an intervening amino acid sequence having fewer than 10 amino acids.

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18. A pharmaceutical composition comprising the polypeptide of any one of embodiments 12, 15, 16 or 17.

19. A method for raising an immune response in a mammal comprising the step of administering to the mammal an effective amount of the polypeptide or composition of any preceding embodiment.

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- 20. Nucleic acid encoding the polypeptide of embodiment 9, 12, 15, 16 or 17.

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	Thr	Thr	Thr	Ala	Glu 805	Gln	Leu	Arg	Gly	Thr 810	Ala	Leu	Gln	Lys	Val 815	Pro
5	Val	Asn	Ile	Ser 820	Gly	Ile	Pro	Leu	Asp 825	Pro	Ser	Ala	Leu	Va1 830	Tyr	Leu
	Val	Ala	Pro 835	⊤hr	Asn	Gln	Thr	⊤hr 840	Asn	Gly	Gly	Ser	Glu 845	Ala	Asp	Gln
10	I]e	Pro 850	Ser	G∖J	Туr	Thr	I]e 855	Leu	Ala	Thr	Gly	Thr 860	Pro	Asp	Gly	Val
	ніs 865	Asn	Thr	Ile	Thr	Ile 870	Arg	Pro	Gln	Asp	Туг 875	Val	Val	Phe	Ile	Pro 880
15	Pro	Val	Gly	Lys	Gln 885	Ile	Arg	Ala	Val	Val 890	Туr	Тyr	Asn	Lys	Va1 895	Val
	Ala	Ser	Asn	Met 900	Ser	Asn	Ala	Val	тhr 905	Ile	Leu	Pro	Asp	Asp 910	Ile	Pro
20	Pro	Thr	I]e 915	Asn	Asn	Pro	Val	Gly 920	Ile	Asn	Ala	Lys	Туг 925	туr	Arg	Gly
	Asp	Glu 930	Val	Asn	Phe	Thr	Met 935	Gly	Val	Ser	Asp	Arg 940	His	Ser	Gly	Ile
25	Lys 945	Asn	Thr	⊤hr	Ile	тhr 950	Thr	Leu	Pro	Asn	Gly 955	тгр	Thr	Ser	Asn	Leu 960
	Thr	Lys	Ala	Asp	Lys 965	Asn	Asn	Gly	Ser	Leu 970	Ser	Ile	Thr	Gly	Arg 975	Val
30	Ser	Met	Asn	G]n 980	Ala	Phe	Asn	Ser	Asp 985	Ile	Thr	Phe	Lys	Va1 990	Ser	Ala
	Thr	Asp	Asn 995	Val	Asn	Asn	Thr	Thr 1000	Asn )	Asp	Ser	Gln	Ser 1005	Lys	His	Val
35	Ser	I]e 1010	His )	Val	Gly	Lys	I]e 1015	Ser	Glu	Asp	Ala	His 1020	Pro )	Ile	Val	Leu
	Gly 1025	Asn	Thr	Glu	Lys	val 1030	val )	Val	Val	Asn	Pro 1035	Thr 5	Ala	Val	Ser	Asn 1040
40	Asp	Glu	Lys	Gln	Ser 1045	I]e	Ile	Thr	Ala	Phe 1050	Met )	Asn	Lys	Asn	Gln 1055	Asn
-0	Ile	Arg	Gly	⊤yr 1060	Leu )	Ala	Ser	Thr	Asp 1065	Pro 5	Val	Тhr	Val	Asp 1070	Asn )	Asn
45	Gly	Asn	Val 1075	⊤hr 5	Leu	His	туг	Arg 108(	Asp )	Gly	Ser	Ser	тhr 1085	Thr	Leu	Asp
	Ala	Thr 1090	Asn )	Val	Met	Thr	Туг 1095	Glu 5	Pro	Val	Val	Lys 1100	Pro )	Glu	Туr	Gln
50	Thr 1109	Val 5	Asn	Ala	Ala	Lys 1110	Thr )	Ala	Тhr	Val	Thr 1119	Ile 5	Ala	Lys	Gly	G]n 1120
50	Ser	Phe	Ser	Ile	Gly 1125	Asp	Ile	Lys	Gln	Туг 1130	Phe )	Thr	Leu	Ser	Asn 1135	Gly
	Gln	Pro	Ile	Pro 1140	Ser )	Gly	Thr	Phe	Thr 1145	Asn 5	Ile	Thr	Ser	Asp 1150	Arg )	Thr
00	I]e	Pro	Thr 1155	Ala 5	Gln	Glu	Val	Ser 1160	Gln )	Met	Asn	Ala	Gly 1165	Thr	Gln	Leu
5

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Tyr His Ile Thr Ala Thr Asn Ala Tyr His Lys Asp Ser Glu Asp Phe 1170 1175 1180 Tyr Ile Ser Leu Lys Ile Ile Asp Val Lys Gln Pro Glu Gly Asp Gln 1185 1190 1195 120 1200 Arg Val Tyr Arg Thr Ser Thr Tyr Asp Leu Thr Thr Asp Glu Ile Ser 1205 1210 Lys Val Lys Gln Ala Phe Ile Asn Ala Asn Arg Asp Val Ile Thr Leu 1220 1225 1230 Ala Glu Gly Asp Ile Ser Val Thr Asn Thr Pro Asn Gly Ala Asn Val 1235 1240 1245 Ser Thr Ile Thr Val Asn Ile Asn Lys Gly Arg Leu Thr Lys Ser Phe 1250 1255 1260 Ala Ser Asn Leu Ala Asn Met Asn Phe Leu Arg Trp Val Asn Phe Pro 1265 1270 1275 1280 1280 Gln Asp Tyr Thr Val Thr Trp Thr Asn Ala Lys Ile Ala Asn Arg Pro 1285 1290 1295 Thr Asp Gly Gly Leu Ser Trp Ser Asp Asp His Lys Ser Leu Ile Tyr 1300 1305 1310 Arg Tyr Asp Ala Thr Leu Gly Thr Gln Ile Thr Thr Asn Asp Ile Leu131513201325 Thr Met Leu Lys Ala Thr Thr Thr Val Pro Gly Leu Arg Asn Asn Ile 1330 1335 1340 Thr Gly Asn Glu Lys Ser Gln Ala Glu Ala Gly Gly Arg Pro Asn Phe 1345 1350 1355 1360 1360 Arg Thr Thr Gly Tyr Ser Gln Ser Asn Ala Thr Thr Asp Gly Gln Arg136513701375 Gln Phe Thr Leu Asn Gly Gln Val Ile Gln Val Leu Asp Ile Ile Asn 1380 1385 1390 Pro Ser Asn Gly Tyr Gly Gly Gln Pro Val Thr Asn Ser Asn Thr Arg 1395 1400 1405 Ala Asn His Ser Asn Ser Thr Val Val Asn Val Asn Glu Pro Ala Ala 1410 1415 1420 1420 Asn Gly Ala Gly Ala Phe Thr Ile Asp His Val Val Lys Ser Asn Ser 1425 1430 1435 1440 Thr His Asn Ala Ser Asp Ala Val Tyr Lys Ala Gln Leu Tyr Leu Thr 1445 1450 1450 1455 Pro Tyr Gly Pro Lys Gln Tyr Val Glu His Leu Asn Gln Asn Thr Gly 1460 1465 1470 Asn Thr Thr Asp Ala Ile Asn Ile Tyr Phe Val Pro Ser Asp Leu Val 1475 1480 1485 Asn Pro Thr Ile Ser Val Gly Asn Tyr Thr Asn His Gln Val Phe Ser 1490 1495 1500 1490 Gly Glu Thr Phe Thr Asn Thr Ile Thr Ala Asn Asp Asn Phe Gly Val 1505 1510 1515 152 1520 Gln Ser Val Thr Val Pro Asn Thr Ser Gln Ile Thr Gly Thr Val Asp 1525 1530 1535 Asn Asn His Gln His Val Ser Ala Thr Ala Pro Asn Val Thr Ser Ala

		1540		1545	155	50
	Thr Asn Lys 155	Thr Ile 5	Asn Leu Le 15	eu Ala Thr Asp 560	Thr Ser Gly 1565	Asn Thr
5	Ala Thr Thr 1570	Ser Phe	Asn Val Th 1575	nr Val Lys Pro	Leu Arg Asp 1580	) Lys Tyr
	Arg Val Gly 1585	Thr Ser	Ser Thr Al 1590	la Ala Asn Pro 1595	Val Arg Ile	e Ala Asn 1600
10	Ile Ser Asn	Asn Ala 1605	Thr Val Se	er Gln Ala Asp 1610	Gln Thr Thr	Ile Ile 1615
	Asn Ser Leu	Thr Phe 1620	Thr Glu Th	ır Val Pro Asn 1625	Arg Ser Tyr 163	r Ala Arg 80
15	Ala Ser Ala 163	Asn Glu 5	Ile ⊤hr Se 16	er Lys Thr Val 540	Ser Asn Val 1645	Ser Arg
	Thr Gly Asn 1650	Asn Ala	Asn Val Th 1655	ır Val Thr Val	Thr Tyr Glr 1660	ı Asp Gly
20	Thr Thr Ser 1665	Thr Val	Thr Val Pr 1670	ro Val Lys His 1675	Val Ile Pro 5	o Glu Ile 1680
	Val Ala His	Ser His 1685	Tyr Thr Va	al Gln Gly Gln 1690	Asp Phe Pro	o Ala Gly 1695
25	Asn Gly Ser	Ser Ala 1700	Ser Asp Ty	r Phe Lys Leu 1705	Ser Asn Gly 171	Ser Asp 0
	Ile Ala Asp 171	Ala Thr 5	Ile ⊤hr ⊤r 17	rp Val Ser Gly 720	Gln Ala Pro 1725	) Asn Lys
30	Asp Asn Thr 1730	Arg Ile	Gly Glu As 1735	sp Ile Thr Val	Thr Ala His 1740	s Ile Leu
	Ile Asp Gly 1745	Glu Thr	Thr Pro Il 1750	le ⊤hr Lys ⊤hr 1755	Ala Thr Tyr 5	' Lys Val 1760
35	Val Arg Thr	Val Pro 1765	Lys His Va	al Phe Glu ⊤hr 1770	Ala Arg Gly	/ Val Leu 1775
	Tyr Pro Gly	Val Ser 1780	Asp Met Ty	r Asp Ala Lys 1785	Gln Tyr Val 179	Lys Pro 00
40	Val Asn Asn 179	Ser Trp 5	Ser ⊤hr As 18	sn Ala Gln His 300	Met Asn Phe 1805	e Gln Phe
	Val Gly Thr 1810	Tyr Gly	Pro Asn Ly 1815	/s Asp Val Val	Gly Ile Ser 1820	Thr Arg
45	Leu Ile Arg 1825	Val Thr	Tyr Asp As 1830	sn Arg Gln ⊤hr 1835	Glu Asp Leu	ı Thr Ile 1840
	Leu Ser Lys	Val Lys 1845	Pro Asp Pr	ro Pro Arg Ile 1850	Asp Ala Asr	1855 Ser Val
50	Thr Tyr Lys	Ala Gly 1860	Leu Thr As	sn Gln Glu Ile 1865	Lys Val Asr 187	a Asn Val '0
	Leu Asn Asn 187	Ser Ser 5	Val Lys Le 18	eu Phe Lys Ala 380	Asp Asn Thr 1885	Pro Leu
55	Asn Val Thr 1890	Asn Ile	Thr His Gl 1895	ly Ser Gly Phe	Ser Ser Val 1900	Val Thr
00	Val Ser Asp 1905	Ala Leu	Pro Asn Gl 1910	ly Gly Ile Lys 1915	Ala Lys Ser	Ser Ile 1920

	Ser	Met	Asn	Asn	Val 1925	Thr	Туr	Thr	Thr	Gln 1930	Asp )	Glu	His	Gly	Gln 1935	Val ;
5	Val	Thr	Val	⊤hr 1940	Arg )	Asn	Glu	Ser	Val 1945	Asp	Ser	Asn	Asp	Ser 1950	Ala	Thr
	Val	Thr	Val 1955	⊤hr	Pro	Gln	Leu	Gln 1960	Ala )	Thr	Thr	Glu	Gly 1965	Ala	Val	Phe
10	Ile	Lys 1970	G]y	Gly	Asp	Gly	Phe 1975	Asp	Phe	Gly	His	Val 1980	Glu )	Arg	Phe	Ile
10	Gln 1985	Asn	Pro	Pro	His	Gly 1990	Ala )	Thr	Val	Ala	Trp 1995	His 5	Asp	Ser	Pro	Asp 2000
15	Thr	тгр	Lys	Asn	Thr 2005	Val ;	Gly	Asn	Thr	His 2010	Lys )	Thr	Ala	Val	Va] 2015	Thr
15	Leu	Pro	Asn	G]y 2020	Gln )	Gly	Thr	Arg	Asn 2025	Val 5	Glu	Val	Pro	va] 2030	Lys	Val
20	Туr	Pro	Va] 2035	Ala	Asn	Ala	Lys	Ala 2040	Pro )	Ser	Arg	Asp	Val 2045	Lys	Gly	Gln
20	Asn	Leu 2050	Thr	Asn	Gly	Thr	Asp 2055	Ala	Met	Asn	туr	Ile 2060	Thr )	Phe	Asp	Pro
25	Asn 2065	Thr	Asn	⊤hr	Asn	Gly 2070	ıle )	Thr	Ala	Ala	тгр 2075	Ala 5	Asn	Arg	Gln	G]n 2080
20	Pro	Asn	Asn	Gln	Gln 2085	Ala	Gly	Val	Gln	His 2090	Leu )	Asn	Val	Asp	Va] 2095	Thr
20	Туr	Pro	Gly	I]e 2100	Ser )	Ala	Ala	Lys	Arg 2105	Val 5	Pro	Val	Thr	Va] 2110	Asn	Val
30	Tyr	Gln	Phe 2115	Glu	Phe	Pro	Gln	Thr 2120	Thr )	Туr	Thr	Thr	Thr 2125	Val 5	Gly	Gly
95	Thr	Leu 2130	Ala	Ser	Gly	Thr	Gln 2135	Ala	Ser	Gly	Tyr	Ala 2140	His )	Met	Gln	Asn
35	Ala 2145	Thr 5	Gly	Leu	Pro	⊤hr 2150	Asp )	Gly	Phe	⊤hr	Туг 2155	Lys	тгр	Asn	Arg	Asp 2160
	Thr	Thr	Gly	⊤hr	Asn 2165	Asp	Ala	Asn	Тгр	Ser 2170	Ala )	Met	Asn	Lys	Pro 2175	Asn
40	Val	Ala	Lys	Val 2180	Val )	Asn	Ala	Lys	Туг 2185	Asp 5	Val	Ile	туr	Asn 2190	Gly	His
	Thr	Phe	Ala 2195	⊤hr	Ser	Leu	Pro	Ala 2200	Lys )	Phe	Val	Val	Lys 2205	Asp	Val	Gln
45	Pro	Ala 2210	Lys )	Pro	Thr	Val	Thr 2215	Glu	Thr	Ala	Ala	G]y 2220	Ala )	Ile	Thr	Ile
	Ala 2225	Pro 5	Gly	Ala	Asn	G]n 2230	Thr )	Val	Asn	Thr	His 2235	Ala 5	Gly	Asn	Val	Thr 2240
50	Thr	Tyr	Ala	Asp	Lys 2245	Leu	Val	Ile	Lys	Arg 2250	Asn )	Gly	Asn	Val	Va] 2255	Thr
	Thr	Phe	Thr	Arg 2260	Arg )	Asn	Asn	Thr	Ser 2265	Pro 5	тгр	Val	Lys	Glu 2270	Ala	Ser
55	Ala	Ala	Thr 2275	Val 5	Ala	Gly	Ile	Ala 2280	Gly )	Тhr	Asn	Asn	G]y 2285	I]e	Thr	Val

	Ala	Ala 2290	Gly )	Thr	Phe	Asn	Pro 2295	Ala	Asp	Thr	Ile	G]n 2300	Val )	Val	Ala	⊤hr
5	Gln 2305	g]y	Ser	Gly	Glu	тhr 2310	val )	ser	Asp	Glu	G]n 2315	Arg	Ser	Asp	Asp	Phe 2320
0	⊤hr	Val	Val	Ala	Pro 2325	Gln	Pro	Asn	Gln	Ala 2330	Thr )	Тhr	Lys	I]e	тгр 2335	Gln
	Asn	Gly	His	Ile 2340	Asp )	Ile	Thr	Pro	Asn 2345	Asn	Pro	Ser	Gly	His 2350	Leu	Ile
10	Asn	Pro	Thr 2355	Gln	Ala	Met	Asp	I]e 2360	Ala )	туr	Thr	Glu	Lys 2365	Val 5	Gly	Asn
	Gly	Ala 2370	Glu	His	Ser	Lys	тhr 2375	Ile	Asn	Val	Val	Arg 2380	Gly	Gln	Asn	Asn
15	Gln 2385	тгр	Thr	Ile	Ala	Asn 2390	Lys )	Pro	Asp	Туr	Va] 2395	Thr 5	Leu	Asp	Ala	Gln 2400
	⊤hr	Gly	Lys	Val	Thr 2405	Phe	Asn	Ala	Asn	Thr 2410	Ile )	Lys	Pro	Asn	Ser 2415	Ser
20	Ile	Thr	Ile	Thr 2420	Pro )	Lys	Ala	Gly	Thr 2425	Gly	His	Ser	Val	Ser 2430	Ser	Asn
	Pro	Ser	Thr 2435	Leu	⊤hr	Ala	Pro	A]a 244(	Ala )	His	Thr	Val	Asn 2445	Thr	Thr	Glu
25	Ile	Va] 2450	Lys )	Asp	Tyr	Gly	Ser 2455	Asn	Val	Thr	Ala	A]a 2460	Glu )	Ile	Asn	Asn
	Ala 2465	Val	Gln	Val	Ala	Asn 2470	Lys )	Arg	Thr	Ala	Thr 2475	Ile	Lys	Asn	Gly	⊤hr 2480
30	Ala	Met	Pro	Thr	Asn 2485	Leu	Ala	Gly	Gly	Ser 249(	Thr	Thr	Thr	Ile	Pro 2495	Val
	⊤hr	Val	Thr	туr 2500	Asn	Asp	Gly	Ser	Thr 2505	Glu	Glu	Val	Gln	Glu 251(	Ser	Ile
35	Phe	Thr	Lys 251ª	Ala	Asp	Lys	Arg	Glu 2520	Leu	Ile	Тhr	Ala	Lys 252ª	Asn	His	Leu
	Asp	Asp 2530	Pro	Val	Ser	Thr	Glu 2535	Gly	Lys	Lys	Pro	G]y 2540	Thr	Ile	Thr	Gln
40	Tyr 2545	Asn	Asn	Ala	Met	His 2550	Asn	Ala	Gln	Gln	G]n 2559	Ile	Asn	Thr	Ala	Lys 2560
	⊤hr	Glu	Ala	Gln	G]n 2565	val	Ile	Asn	Asn	Glu 2570	Arg	Ala	Thr	Pro	G]n 2575	Gln
45	Val	Ser	Asp	A]a 2580	Leu	, Thr	Lys	Val	Arg	Ala	Ala	G]n	Thr	Lys 2590	Ile	Asp
	Gln	Ala	Lys	Ala	Leu	Leu	Gln	Asn 2600	Lys	, Glu	Asp	Asn	Ser	Gln	Leu	Val
50	⊤hr	Ser	Lys	, Asn	Asn	Leu	Gln 2615	Ser	, Ser	Val	Asn	G]n	Val	, Pro	Ser	⊤hr
50	Ala	Gly	, Met	тhr	Gln	Gln	Ser	, Ile	Asp	Asn	Tyr	Asn	, Ala	Lys	Lys	Arg 2640
	Glu	Ala	Glu	Thr	Glu 2645	ile	, Thr	Ala	Ala	Gln	Arg	, Val	Ile	Asp	Asn 2655	Gly
55	Asp	Ala	Thr	Ala	Gln	, Gln	Ile	Ser	Asp	Glu	Lys	His	Arg	Val	Asp	Asn

				2660	)				2665	5				2670	)	
	Ala	Leu	Thr 2675	Ala	Leu	Asn	Gln	Ala 2680	Lys )	His	Asp	Leu	Thr 2685	Ala	Asp	Thr
5	His	Ala 2690	Leu )	Glu	Gln	Ala	Va] 2695	Gln 5	Gln	Leu	Asn	Arg 2700	Thr	Gly	Thr	Thr
	Thr 2705	Gly	Lys	Lys	Pro	Ala 2710	Ser )	Ile	⊤hr	Ala	⊤yr 2715	Asn	Asn	Ser	Ile	Arg 2720
10	Ala	Leu	Gln	Ser	Asp 2725	Leu	Thr	Ser	Ala	Lys 2730	Asn )	Ser	Ala	Asn	Ala 2735	Ile
	Ile	Gln	Lys	Pro 2740	Ile )	Arg	Thr	Val	Gln 2745	Glu 5	Val	Gln	Ser	Ala 2750	Leu )	Thr
15	Asn	Val	Asn 2755	Arg 5	Val	Asn	Glu	Arg 2760	Leu )	Thr	Gln	Ala	Ile 2765	Asn	Gln	Leu
	Val	Pro 2770	Leu )	Ala	Asp	Asn	Ser 2775	Ala 5	Leu	Lys	⊤hr	Ala 2780	Lys	Thr	Lys	Leu
20	Asp 2785	Glu	Glu	Ile	Asn	Lys 2790	Ser )	Val	⊤hr	Thr	Asp 2795	Gly	Met	Thr	Gln	Ser 2800
	Ser	Ile	Gln	Ala	туг 2805	Glu 5	Asn	Ala	Lys	Arg 2810	Ala	Gly	Gln	Thr	Glu 2815	Ser
25	Thr	Asn	Ala	Gln 2820	Asn )	Val	Ile	Asn	Asn 2825	Gly 5	Asp	Ala	Thr	Asp 2830	Gln )	Gln
	Ile	Ala	Ala 2835	Glu 5	Lys	Thr	Lys	Va] 2840	Glu )	Glu	Lys	Tyr	Asn 2845	Ser	Leu	Lys
30	Gln	Ala 2850	ıle	Ala	Gly	Leu	⊤hr 2855	Pro 5	Asp	Leu	Ala	Pro 2860	Leu	Gln	Thr	Ala
	Lys 2865	Thr	Gln	Leu	Gln	Asn 2870	Asp )	Ile	Asp	Gln	Pro 2875	Thr	Ser	Thr	Thr	G]y 2880
35	Met	Thr	Ser	Ala	Ser 2885	Ile 5	Ala	Ala	Phe	Asn 2890	Glu )	Lys	Leu	Ser	Ala 2895	Ala
	Arg	Thr	Lys	Ile 2900	Gln )	Glu	Ile	Asp	Arg 2905	Val 5	Leu	Ala	Ser	ніs 2910	Pro )	Asp
40	Val	Ala	Thr 2915	ile	Arg	Gln	Asn	Val 2920	⊤hr )	Ala	Ala	Asn	Ala 2925	Ala	Lys	Ser
	Ala	Leu 2930	Asp )	Gln	АТа	Arg	Asn 2935	Gly 5	Leu	Thr	Val	Asp 2940	Lys	Ala	Pro	Leu
45	Glu 2945	Asn	Ala	Lys	Asn	Gln 2950	Leu )	Gln	His	Ser	Ile 2955	Asp	Thr	Gln	Thr	Ser 2960
	Thr	Thr	Gly	Met	Thr 2965	Gln 5	Asp	Ser	Ile	Asn 2970	Ala	туr	Asn	Ala	Lys 2975	Leu
50	Thr	Ala	Ala	Arg 2980	Asn )	Lys	Ile	Gln	Gln 2985	Ile 5	Asn	Gln	Val	Leu 2990	Ala )	Gly
	Ser	Pro	Thr 2995	Val 5	Glu	Gln	Ile	Asn 3000	⊤hr )	Asn	⊤hr	Ser	Thr 3005	Ala 5	Asn	Gln
	Ala	Lys 3010	Ser	Asp	Leu	Asp	His 3015	Ala 5	Arg	Gln	Ala	Leu 3020	Thr	Pro	Asp	Lys
55	Ala 3025	Pro	Leu	Gln	Thr	Ala 3030	Lys )	Thr	Gln	Leu	Glu 3035	Gln	Ser	Ile	Asn	G]n 3040

	Pro	Thr	Asp	⊤hr	Thr 3045	Gly 5	Met	Thr	Thr	Ala 3050	Ser )	Leu	Asn	Ala	Tyr 3055	Asn 5
5	Gln	Lys	Leu	Gln 3060	Ala )	Ala	Arg	Gln	Lys 3065	Leu	Thr	Glu	Ile	Asn 3070	Gln )	Val
	Leu	Asn	Gly 3075	Asn	Pro	Thr	Val	G]n 3080	Asn )	Ile	Asn	Asp	Lys 3085	Val 5	Thr	Glu
10	Ala	Asn 3090	Gln )	Ala	Lys	Asp	Gln 3095	Leu	Asn	Тhr	Ala	Arg 3100	Gln )	Gly	Leu	Thr
	Leu 3105	Asp	Arg	Gln	Pro	Ala 3110	Leu )	Thr	Thr	Leu	His 3115	Gly	Ala	Ser	Asn	Leu 3120
15	Asn	Gln	Ala	Gln	G]n 3125	Asn	Asn	Phe	Thr	G]n 3130	Gln )	Ile	Asn	Ala	Ala 3135	Gln
15	Asn	His	Ala	Ala 3140	Leu )	Glu	Thr	Ile	Lys 3145	Ser	Asn	Ile	Тhr	Ala 3150	Leu )	Asn
20	Thr	Ala	Met 3155	⊤hr	Lys	Leu	Lys	Asp 3160	Ser )	Val	Ala	Asp	Asn 3165	Asn	Thr	Ile
20	Lys	Ser 3170	Asp )	Gln	Asn	Туr	Thr 3175	Asp	Ala	Тhr	Pro	Ala 3180	Asn )	Lys	Gln	Ala
25	туг 3185	Asp	Asn	Ala	Val	Asn 3190	Ala )	Ala	Lys	Gly	Val 3195	] j	Gly	Glu	Thr	Thr 3200
20	Asn	Pro	Thr	Met	Asp 3205	Val 5	Asn	Thr	Val	Asn 3210	Gln )	Lys	Ala	Ala	Ser 3215	Val 5
22	Lys	Ser	Thr	Lys 3220	Asp )	Ala	Leu	Asp	G]y 3225	G]n	Gln	Asn	Leu	Gln 3230	Arg	Ala
30	Lys	Thr	Glu 3235	Ala 5	Thr	Asn	Ala	Ile 3240	Thr )	His	Ala	Ser	Asp 3245	Leu	Asn	Gln
~~	Ala	Gln 3250	Lys )	Asn	Ala	Leu	Thr 3255	Gln	Gln	Val	Asn	Ser 3260	Ala )	Gln	Asn	Val
35	G]n 3265	Ala 5	Val	Asn	Asp	Ile 3270	Lys )	Gln	Thr	тhr	Gln 3275	Ser	Leu	Asn	Thr	Ala 3280
	Met	Thr	Gly	Leu	Lys 3285	Arg	Gly	Val	Ala	Asn 3290	His )	Asn	Gln	Val	Va] 3295	Gln
40	Ser	Asp	Asn	⊤yr 3300	Val )	Asn	Ala	Asp	Thr 3305	Asn 5	Lys	Lys	Asn	Asp 3310	Tyr )	Asn
	Asn	Ala	туг 3315	Asn	His	Ala	Asn	Asp 3320	Ile )	Ile	Asn	Gly	Asn 3325	Ala	Gln	His
45	Pro	Va] 3330	Ile )	⊤hr	Pro	Ser	Asp 3335	Val	Asn	Asn	Ala	Leu 3340	Ser )	Asn	Val	Thr
	Ser 3345	Lys	Glu	His	Ala	Leu 3350	Asn )	Gly	Glu	Ala	Lys 3355	Leu	Asn	Ala	Ala	Lys 3360
50	Gln	Glu	Ala	Asn	Thr 3365	Ala	Leu	Gly	His	Leu 3370	Asn )	Asn	Leu	Asn	Asn 3375	Ala 5
	Gln	Arg	Gln	Asn 3380	Leu )	Gln	Ser	Gln	Ile 3385	Asn 5	Gly	Ala	His	Gln 3390	Ile )	Asp
55	Ala	Val	Asn 3395	⊤hr 5	Ile	Lys	Gln	Asn 3400	Ala )	Тhr	Asn	Leu	Asn 3403	Ser	Ala	Met

Gly Asn Leu Arg Gln Ala Val Ala Asp Lys Asp Gln Val Lys Arg Thr 3410 3415 3420 Glu Asp Tyr Ala Asp Ala Asp Thr Ala Lys Gln Asn Ala Tyr Asn Ser 3430 3425 3435 3440 5 Ala Val Ser Ser Ala Glu Thr Ile Ile Asn Gln Thr Thr Asn Pro Thr 3445 3450 Met Ser Val Asp Asp Val Asn Arg Ala Thr Ser Ala Val Thr Ser Asn 3460 3465 3470 10 Asn Ala Leu Asn Gly Tyr Glu Lys Leu Ala Gln Ser Lys Thr Asp 3475 3480 3485 Lys Ala Ala Arg Ala Ile Asp Ala Leu Pro His Leu Asn Asn Ala Gln Lys 3490 3495 3500 15 Ala Asp Val Lys Ser Lys Ile Asn Ala Ala Ser Asn Ile Ala Gly Val 3505 3510 3515 3520 Asn Thr Val Lys Gln Gln Gly Thr Asp Leu Asn Thr Ala Met Gly Asn 3525 3530 3535 20 Leu Gln Gly Ala Ile Asn Asp Glu Gln Thr Thr Leu Asn Ser Gln Asn 3540 3545 3550 Tyr Gln Asp Ala Thr Pro Ser Lys Lys Thr Ala Tyr Thr Asn Ala Val 3555 3560 3565 25 Gln Ala Ala Lys Asp Ile Leu Asn Lys Ser Asn Gly Gln Asn Lys Thr 3570 3575 3580 Lys Asp Gln Val Thr Glu Ala Met Asn Gln Val Asn Ser Ala Lys Asn 3585 3590 3595 3600 3600 Asn Leu Asp Gly Thr Arg Leu Leu Asp Gln Ala Lys Gln Thr Ala Lys 3605 3610 3615 30 Gln Gln Leu Asn Asn Met Thr His Leu Thr Thr Ala Gln Lys Thr Asn 3620 3625 3630 Leu Thr Asn Gln Ile Asn Ser Gly Thr Thr Val Ala Gly Val Gln Thr 3635 3640 3645 35 Val Gln Ser Asn Ala Asn Thr Leu Asp Gln Ala Met Asn Thr Leu Arg 3650 3655 3660 3660 Gln Ser Ile Ala Asn Lys Asp Ala Thr Lys Ala Ser Glu Asp Tyr Val 3665 3670 3675 3680 40 Asp Ala Asn Asn Asp Lys Gln Thr Ala Tyr Asn Asn Ala Val Ala Ala 3685 3690 3695 Ala Glu Thr Ile Ile Asn Ala Asn Ser Asn Pro Glu Met Asn Pro Ser 3700 3705 3710 45 Thr Ile Thr Gln Lys Ala Glu Gln Val Asn Ser Ser Lys Thr Ala Leu 3715 3720 3725 Gly Asp Glu Asn Leu Ala Ala Ala Lys Gln Asn Ala Lys Thr Tyr 3730 3735 3740 Asn 50 Leu Asn Thr Leu Thr Ser Ile Thr Asp Ala Gln Lys Asn Asn Leu Ile 3745 3750 3755 3760 3760 Ser Gln Ile Thr Ser Ala Thr Arg Val Ser Gly Val Asp Thr Val Lys 3765 3770 3775 55 Gln Asn Ala Gln His Leu Asp Gln Ala Met Ala Ser Leu Gln Asn Gly

				3780	)				3785	,				3790	)	
	Ile	Asn	Asn 3795	Glu	Ser	Gln	Val	Lys 3800	Ser	Ser	Glu	Lys	Туг 3805	Arg	Asp	Ala
5	Asp	Thr 3810	Asn	Lys	Gln	Gln	Glu 3815	Tyr 5	Asp	Asn	Ala	Ile 3820	Thr	Ala	Ala	Lys
	Ala 3825	Ile	Leu	Asn	Lys	Ser 3830	Thr )	Gly	Pro	Asn	⊤hr 3835	Ala	Gln	Asn	Ala	Va] 3840
10	Glu	Ala	Ala	Leu	Gln 3845	Arg	Val	Asn	Asn	Ala 3850	Lys	Asp	Ala	Leu	Asn 3855	Gly
	Asp	Ala	Lys	Leu 3860	Ile	Ala	Ala	Gln	Asn 3865	Ala	Ala	Lys	G]n	His 3870	Leu	Gly
15	Thr	Leu	Thr 3875	His	Ile	Thr	⊤hr	Ala 3880	Gln )	Arg	Asn	Asp	Leu 3885	Thr	Asn	Gln
	Ile	Ser 3890	Gln	Ala	Thr	Asn	Leu 3895	Ala 5	Gly	Val	Glu	Ser 3900	Val	Lys	Gln	Asn
20	Ala 3905	Asn	Ser	Leu	Asp	Gly 3910	Ala )	Met	Gly	Asn	Leu 3915	Gln	Thr	Ala	Ile	Asn 3920
	Asp	Lys	Ser	Gly	тhr 3925	Leu	Ala	Ser	Gln	Asn 3930	Phe	Leu	Asp	Ala	Asp 3935	Glu
25	Gln	Lys	Arg	Asn 3940	Ala	Tyr	Asn	Gln	Ala 3945	Val	Ser	Ala	Ala	Glu 3950	Thr	Ile
	Leu	Asn	Lys 3955	Gln	Тhr	Gly	Pro	Asn 3960	⊤hr )	Ala	Lys	Thr	Ala 3965	Val	Glu	Gln
30	Ala	Leu 3970	Asn	Asn	Val	Asn	Asn 3975	Ala 5	Lys	His	Ala	Leu 3980	Asn	Gly	Thr	Gln
	Asn 3985	Leu	Asn	Asn	Ala	Lys 3990	Gln )	Ala	Ala	Ile	⊤hr 3995	Ala	I]e	Asn	Gly	Ala 4000
35	Ser	Asp	Leu	Asn	G]n 4005	Lys	Gln	Lys	Asp	Ala 4010	Leu	Lys	Ala	Gln	Ala 4015	Asn
	Gly	Ala	Gln	Arg 4020	Val	Ser	Asn	Ala	Gln 4025	Asp	Val	Gln	His	Asn 4030	Ala	Thr
40	Glu	Leu	Asn 4035	Thr	АТа	Met	Gly	⊤hr 4040	Leu )	Lys	His	Ala	Ile 4045	Ala	Asp	Lys
	Thr	Asn 4050	Thr	Leu	Ala	Ser	Ser 4055	Lys	⊤yr	Val	Asn	а]а 4060	Asp	Ser	Thr	Lys
45	Gln 4065	Asn	Ala	Tyr	Thr	Thr 4070	Lys )	Val	⊤hr	Asn	Ala 4075	Glu	His	Ile	Ile	Ser 4080
	Gly	Thr	Pro	Thr	Val 4085	Val	⊤hr	Thr	Pro	Ser 4090	Glu	Val	Thr	Ala	Ala 4095	Ala
50	Asn	Gln	Val	Asn 4100	Ser	Ala	Lys	Gln	Glu 4105	Leu	Asn	Gly	Asp	Glu 4110	Arg	Leu
	Arg	Glu	Ala 4115	Lys	Gln	Asn	Ala	Asn 4120	⊤hr )	Ala	Ile	Asp	Ala 4125	Leu	Thr	Gln
55	Leu	Asn 4130	Thr	Pro	Gln	Lys	Ala 4135	Lys	Leu	Lys	Glu	Gln 4140	Val	Gly	Gln	Ala
	Asn 4145	Arg	Leu	Glu	Asp	Val 4150	Gln )	Thr	Val	Gln	⊤hr 4155	Asn	Gly	Gln	Ala	Leu 4160

	Asn	Asn	Ala	Met	Lys 4165	Gly 5	Leu	Arg	Asp	Ser 4170	Ile )	Ala	Asn	Glu	Thr 4175	Thr 5
5	Val	Lys	Thr	Ser 4180	Gln )	Asn	Tyr	Thr	Asp 4185	Ala 5	Ser	Pro	Asn	Asn 4190	Gln )	Ser
	Thr	Туr	Asn 4195	Ser	Ala	Val	Ser	Asn 4200	Ala )	Lys	Gly	Ile	I]e 4203	Asn 5	Gln	Thr
10	Asn	Asn 4210	Pro )	⊤hr	Met	Asp	Thr 4215	Ser	Ala	Ile	Thr	G]n 4220	Ala )	Thr	Thr	Gln
	Val 4225	Asn	Asn	Ala	Lys	Asn 4230	Gly )	Leu	Asn	Gly	Ala 4235	Glu 5	Asn	Leu	Arg	Asn 4240
15	Ala	Gln	Asn	⊤hr	Ala 4245	Lys	Gln	Asn	Leu	Asn 4250	Thr )	Leu	Ser	His	Leu 4255	Thr
	Asn	Asn	Gln	Lys 4260	Ser )	Ala	Ile	Ser	Ser 4265	Gln 5	Ile	Asp	Arg	Ala 4270	Gly	His
20	Val	Ser	Glu 4275	Val	Thr	Ala	Thr	Lys 4280	Asn )	Ala	Ala	Thr	Glu 4285	Leu	Asn	Thr
20	Gln	Met 4290	Gly )	Asn	Leu	Glu	Gln 4295	Ala	Ile	His	Asp	G]n 4300	Asn )	Thr	Val	Lys
25	Gln 4305	Ser	Val	Lys	Phe	Thr 4310	Asp )	Ala	Asp	Lys	Ala 4315	Lys	Arg	Asp	Ala	туг 4320
	Thr	Asn	Ala	Val	Ser 4325	Arg	Ala	Glu	Ala	Ile 4330	Leu )	Asn	Lys	Thr	G]n 4335	Gly
30	Ala	Asn	Thr	Ser 4340	Lys )	Gln	Asp	Val	Glu 4345	Ala 5	Ala	Ile	Gln	Asn 4350	Val )	Ser
	Ser	Ala	Lys 4355	Asn	Ala	Leu	Asn	Gly 4360	Asp )	Gln	Asn	Val	тhr 4365	Asn	Ala	Lys
25	Asn	Ala 4370	Ala )	Lys	Asn	Ala	Leu 4375	Asn	Asn	Leu	Thr	Ser 4380	ıle )	Asn	Asn	Ala
55	G]n 4385	Lys	Arg	Asp	Leu	⊤hr 4390	Thr )	Lys	Ile	Asp	Gln 4395	Ala 5	⊤hr	Thr	Val	Ala 4400
40	Gly	Val	Glu	Ala	Va] 4405	Ser	Asn	Thr	Ser	⊤hr 4410	Gln )	Leu	Asn	Thr	Ala 4415	Met
40	Ala	Asn	Leu	G]n 4420	Asn )	Gly	Ile	Asn	Asp 4425	Lys 5	Thr	Asn	Thr	Leu 4430	Ala )	Ser
45	Glu	Asn	туг 4435	His	Asp	Ala	Asp	Ser 444(	Asp )	Lys	Lys	Thr	Ala 4445	Tyr 5	Thr	Gln
40	Ala	Val 4450	Thr )	Asn	Ala	Glu	Asn 4455	Ile	Leu	Asn	Lys	Asn 4460	Ser )	Gly	Ser	Asn
50	Leu 4465	Asp	Lys	⊤hr	Ala	Val 4470	Glu )	Asn	Ala	Leu	Ser 4475	Gln	Val	Ala	Asn	Ala 4480
50	Lys	Gly	Ala	Leu	Asn 4485	Gly G	Asn	His	Asn	Leu 4490	Glu )	Gln	Ala	Lys	Ser 4495	Asn
	Ala	Asn	Thr	⊤hr 4500	Ile )	Asn	Gly	Leu	Gln 4505	His 5	Leu	Thr	Thr	Ala 4510	Gln )	Lys
00	Asp	Lys	Leu 4515	Lys	Gln	Gln	Val	Gln 4520	Gln )	Ala	Gln	Asn	Val 4525	Ala 5	G∣y	Val

	Asp	Thr 4530	Val )	Lys	Ser	Ser	Ala 4535	Asn	Thr	Leu	Asn	Gly 4540	Ala )	Met	Gly	⊤hr
5	Leu 4545	Arg	Asn	Ser	Ile	Gln 4550	Asp )	Asn	Thr	Ala	тhr 4555	Lys	Asn	Gly	Gln	Asn 4560
5	⊤yr	Leu	Asp	Ala	Thr 4565	Glu	Arg	Asn	Lys	Thr 457(	Asn )	Тyr	Asn	Asn	A]a 4575	Val
	Asp	Ser	Ala	Asn 4580	Gly )	Val	Ile	Asn	Ala 4585	Thr	Ser	Asn	Pro	Asn 4590	Met	Asp
10	Ala	Asn	Ala 4595	Ile	Asn	Gln	Ile	Ala 4600	Thr )	Gln	Val	Thr	Ser 4605	Thr	Lys	Asn
	Ala	Leu 4610	Asp )	Gly	Thr	His	Asn 4615	Leu	Thr	Gln	Ala	Lys 4620	Gln )	Thr	Ala	Thr
15	Asn 4625	Ala	Ile	Asp	Gly	Ala 4630	Thr )	Asn	Leu	Asn	Lys 4635	Ala	Gln	Lys	Asp	A]a 4640
	Leu	Lys	Ala	Gln	Val 4645	Thr	Ser	Ala	Gln	Arg 465(	Val	Ala	Asn	Val	Thr 465'	Ser
20	Ile	Gln	Gln	Thr 4660	Ala	Asn	Glu	Leu	Asn 4665	Thr	Ala	Met	Gly	G]n 4670	Leu	Gln
	His	Gly	1]e 4679	Asp	Asp	Glu	Asn	A]a 4680	Thr	Lys	Gln	⊤hr	G]n 4685	Lys	туr	Arg
25	Asp	Ala 4690	Glu	Gln	Ser	Lys	Lys 4695	Thr	Ala	Тyr	Asp	G]n 4700	Ala	, Val	Ala	Ala
	Ala 4705	Lys	Ala	Ile	Leu	Asn 4710	Lys	, G]n	Thr	Gly	Ser 471	Asn	Ser	Asp	Lys	Ala 4720
30	Ala	, Val	Asp	Arg	Ala 4725	Leu	, Gln	Gln	Val	Thr	Ser	, Thr	Lys	Asp	A]a 4735	Leu
	Asn	Gly	Asp	A]a	Lys	, Leu	Ala	Glu	Ala 4745	Lys	, Ala	Ala	Ala	Lys	Gln	, Asn
35	Leu	Gly	Thr 4755	Leu	, Asn	His	Ile	Thr	Asn	, Ala	Gln	Arg	Thr 4765	Asp	, Leu	Glu
	Gly	Gln	Ile	, Asn	Gln	Ala	Thr	Thr	, Val	Asp	Gly	Val	Asn	, Thr	Val	Lys
40	Thr	Asn	, Ala	Asn	Thr	Leu	Asp	, Gly	Ala	Met	Asn	Ser	, Leu	Gln	Gly	Ser
	Ile	, Asn	Asp	Lys	Asp	Ala	, Thr	Leu	Arg	Asn	Gln	, Asn	Тyr	Leu	Asp	4800 Ala
45	Asp	Glu	Ser	Lys	Arg	, Asn	Ala	Тyr	Thr	Gln	, Ala	Val	Thr	Ala	Ala	, Glu
	Gly	Ile	Leu	Asn	, Lys	Gln	Thr	Gly	4823 Gly	Asn	Thr	Ser	Lys	4850 Ala	, Asp	Val
	Asp	Asn	4653 Ala	, Leu	Asn	Ala	Val	4840 	, Arg	Ala	Lys	Ala	4843 Ala	, Leu	Asn	Gly
50	Ala	Asp	Asn	Leu	Arg	Asn	4855 Ala	Lys	Thr	Ser	Ala	4800 	Asn	Тhr	Ile	Asp
	4865 Gly	Leu	Pro	Asn	Leu	4870 Thr	, Gln	Leu	Gln	Lys	4873 Asp	Asn	Leu	Lys	His	4880 Gln
55	Val	Glu	Gln	Ala	4885 Gln	Asn	Val	Ala	Gly	4890 Val	, Asn	Gly	Val	Lys	4895 Asp	b Lys

				4900	)				4905	5				4910	)	
	Gly	Asn	Thr 4915	Leu	Asn	Thr	Ala	Met 4920	Gly )	Ala	Leu	Arg	Thr 4925	Ser	Ile	Gln
5	Asn	Asp 4930	Asn	Thr	Thr	Lys	⊤hr 4935	Ser	Gln	Asn	Туr	Leu 4940	Asp	Ala	Ser	Asp
	Ser 4945	Asn	Lys	Asn	Asn	Tyr 4950	Asn )	Thr	Ala	Val	Asn 4955	Asn	Ala	Asn	Gly	Val 4960
10	Ile	Asn	Ala	Thr	Asn 4965	Asn	Pro	Asn	Met	Asp 4970	Ala	Asn	Ala	Ile	Asn 4975	Gly
	Met	Ala	Asn	Gln 4980	Val )	Asn	Thr	Thr	Lys 4985	Ala	Ala	Leu	Asn	Gly 4990	Ala	Gln
15	Asn	Leu	Ala 4995	Gln	Ala	Lys	⊤hr	Asn 5000	Ala )	Thr	Asn	Thr	Ile 5005	Asn	Asn	Ala
	His	Asp 5010	Leu	Asn	Gln	Lys	Gln 5015	Lys	Asp	Ala	Leu	Lys 5020	Thr	Gln	Val	Asn
20	Asn 5025	Ala	Gln	Arg	Val	Ser 5030	Asp )	Ala	Asn	Asn	Va] 5035	Gln	His	Thr	Ala	Thr 5040
	Glu	Leu	Asn	Ser	А]а 5045	Met	⊤hr	Ala	Leu	Lys 5050	Ala	Ala	I]e	Ala	Asp 5055	Lys
25	Glu	Arg	Thr	Lys 5060	Ala )	Ser	Gly	Asn	⊤yr 5065	Val 5	Asn	Ala	Asp	G]n 5070	Glu	Lys
	Arg	Gln	Ala 5075	Tyr	Asp	Ser	Lys	Va] 5080	⊤hr )	Asn	Ala	Glu	Asn 5085	I]e	Ile	Ser
30	Gly	Thr 5090	Pro	Asn	Ala	Тhr	Leu 5095	Thr 5	Val	Asn	Asp	Val 5100	Asn	Ser	Ala	Ala
	Ser 5105	Gln	Val	Asn	Ala	Ala 5110	Lys )	Thr	Ala	Leu	Asn 5115	Gly	Asp	Asn	Asn	Leu 5120
35	Arg	Val	Ala	Lys	Glu 5125	His	Ala	Asn	Asn	Thr 5130	I]e	Asp	Gly	Leu	Ala 5135	Gln
	Leu	Asn	Asn	Ala 5140	Gln )	Lys	Ala	Lys	Leu 5145	Lys	Glu	Gln	Val	Gln 5150	Ser	Ala
40	Thr	Thr	Leu 5155	Asp	Gly	Val	Gln	⊤hr 5160	val )	Lys	Asn	Ser	Ser 5165	Gln	Thr	Leu
	Asn	Thr 5170	Ala	Met	Lys	Gly	Leu 5175	Arg 5	Asp	Ser	Ile	Ala 5180	Asn	Glu	Ala	Thr
45	Ile 5185	Lys	Ala	Gly	Gln	Asn 5190	⊤yr )	Thr	Asp	Ala	Ser 5195	Pro	Asn	Asn	Arg	Asn 5200
	Glu	туг	Asp	Ser	Ala 5205	Val ;	⊤hr	Ala	Ala	Lys 5210	Ala	Ile	I]e	Asn	Gln 5215	Thr
50	Ser	Asn	Pro	Thr 5220	Met )	Glu	Pro	Asn	⊤hr 5225	Ile 5	⊤hr	Gln	Val	Thr 5230	Ser	Gln
	Val	Thr	Thr 5235	Lys	Glu	Gln	Ala	Leu 5240	Asn )	Gly	Ala	Arg	Asn 5245	Leu	Ala	Gln
55	Ala	Lys 5250	Thr	Thr	АТа	Lys	Asn 5255	Asn 5	Leu	Asn	Asn	Leu 5260	Thr	Ser	Ile	Asn
	Asn 5265	Ala	Gln	Lys	Asp	Ala 5270	Leu )	Thr	Arg	Ser	Ile 5275	Asp	Gly	Ala	Thr	Thr 5280

	Val	Ala	Gly	Val	Asn 5285	Gln	Glu	Thr	Ala	Lys 5290	Ala )	Thr	Glu	Leu	Asn 5295	Asn
5	Ala	Met	His	Ser 5300	Leu	Gln	Asn	Gly	Ile 5305	Asn	Asp	Glu	Thr	Gln 5310	Thr	Lys
	Gln	Thr	Gln 5315	Lys	Tyr	Leu	Asp	Ala 5320	Glu )	Pro	Ser	Lys	Lys 5325	Ser	Ala	Туr
10	Asp	G]n 5330	Ala )	Val	Asn	Ala	Ala 5335	Lys	Ala	Ile	Leu	Thr 5340	Lys )	Ala	Ser	Gly
	Gln 5345	Asn	Val	Asp	Lys	Ala 5350	Ala )	Val	Glu	Gln	Ala 5355	Leu	Gln	Asn	Val	Asn 5360
15	Ser	Thr	Lys	⊤hr	Ala 5365	Leu	Asn	Gly	Asp	Ala 5370	Lys )	Leu	Asn	Glu	Ala 5375	Lys
	Ala	Ala	Ala	Lys 5380	Gln	Thr	Leu	Gly	Thr 5385	Leu	Thr	His	Ile	Asn 5390	Asn	Ala
20	Gln	Arg	Thr 5395	Ala	Leu	Asp	Asn	Glu 5400	Ile	Thr	Gln	Ala	Thr 5405	Asn	Val	Glu
20	Gly	Va] 5410	Asn )	⊤hr	Val	Lys	Ala 5415	Lys	Ala	Gln	Gln	Leu 5420	Asp )	Gly	Ala	Met
25	Gly 5425	Gln	Leu	Glu	Thr	Ser 5430	ıle )	Arg	Asp	Lys	Asp 5435	Thr	Thr	Leu	Gln	Ser 5440
20	Gln	Asn	Tyr	Gln	Asp 5445	Ala	Asp	Asp	Ala	Lys 5450	Arg	Thr	Ala	Tyr	Ser 5455	Gln
20	Ala	Val	Asn	Ala 5460	Ala	Ala	Thr	Ile	Leu 5465	Asn	Lys	Thr	Ala	Gly 5470	Gly	Asn
30	Thr	Pro	Lys 5475	Ala	Asp	Val	Glu	Arg 5480	Ala )	Met	Gln	Ala	Va] 5485	Thr	Gln	Ala
05	Asn	Thr 5490	Ala )	Leu	Asn	Gly	Ile 5495	Gln	Asn	Leu	Asp	Arg 5500	Ala )	Lys	Gln	Ala
35	Ala 5505	Asn	Thr	Ala	Ile	⊤hr 5510	Asn )	Ala	Ser	Asp	Leu 5515	Asn	Thr	Lys	Gln	Lys 5520
	Glu	Ala	Leu	Lys	Ala 5525	Gln	Val	Thr	Ser	Ala 5530	Gly	Arg	Val	Ser	Ala 5535	Ala
40	Asn	Gly	Val	Glu 5540	His	Thr	Ala	Thr	Glu 5545	Leu	Asn	Thr	Ala	Met 5550	Thr	Ala
	Leu	Lys	Arg 5555	Ala	Ile	Ala	Asp	Lys 5560	Ala )	Glu	Thr	Lys	Ala 5565	Ser	Gly	Asn
45	Туr	Val 5570	Asn )	Ala	Asp	Ala	Asn 5575	Lys	Arg	Gln	Ala	туг 5580	Asp )	Glu	Lys	Val
	Thr 5585	Ala	Ala	Glu	Asn	Ile 5590	Val )	Ser	Gly	Thr	Pro 5595	Thr	Pro	Thr	Leu	Thr 5600
50	Pro	Ala	Asp	Val	Thr 5605	Asn	Ala	Ala	Thr	Gln 5610	Val )	Thr	Asn	Ala	Lys 5615	Thr
	Gln	Leu	Asn	G]y 5620	Asn	His	Asn	Leu	Glu 5625	Val 5	Ala	Lys	Gln	Asn 5630	Ala	Asn
55	Thr	Ala	Ile 5635	Asp	Gly	Leu	Thr	Ser 5640	Leu )	Asn	Gly	Pro	G]n 5645	Lys	Ala	Lys

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Leu Lys Glu Gln Val Gly Gln Ala Thr Thr Leu Pro Asn Val Gln Thr 5650 5655 5660 Val Arg Asp Asn Ala Gln Thr Leu Asn Thr Ala Met Lys Gly Leu Arg 5665 5670 5675 568 5680 Asp Ser Ile Ala Asn Glu Ala Thr Ile Lys Ala Gly Gln Asn Tyr Thr 5685 5690 5695 Asp Ala Ser Gln Asn Lys Gln Thr Asp Tyr Asn Ser Ala Val Thr Ala 5700 5705 5710 10 Ala Lys Ala Ile Ile Gly Gln Thr Thr Ser Pro Ser Met Asn Ala Gln 5715 5720 5725 Glu Ile Asn Gln Ala Lys Asp Gln Val Thr Ala Lys Gln Gln Ala Leu 5730 5735 5740 15 Asn Gly Gln Glu Asn Leu Arg Thr Ala Gln Thr Asn Ala Lys Gln His 5745 5750 5755 576 5760 Leu Asn Gly Leu Ser Asp Leu Thr Asp Ala Gln Lys Asp Ala Val Lys 5765 5770 5775 20 Arg Gln Ile Glu Gly Ala Thr His Val Asn Glu Val Thr Gln Ala Gln 5780 5785 5790 Asn Asn Ala Asp Ala Leu Asn Thr Ala Met Thr Asn Leu Lys Asn Gly 5795 5800 5805 25 Ile Gln Asp Gln Asn Thr Ile Lys Gln Gly Val Asn Phe Thr Asp Ala 5810 5815 5820 5820 Asp Glu Ala Lys Arg Asn Ala Tyr Thr Asn Ala Val Thr Gln Ala Glu 5825 5830 5835 5840 5840 Gln Ile Leu Asn Lys Ala Gln Gly Pro Asn Thr Ser Lys Asp Gly Val 5845 5850 5855 30 Glu Thr Ala Leu Glu Asn Val Gln Arg Ala Lys Asn Glu Leu Asn Gly 5860 5865 5870 Asn Gln Asn Val Ala Asn Ala Lys Thr Thr Ala Lys Asn Ala Leu Asn 5875 5880 5885 35 Asn Leu Thr Ser Ile Asn Asn Ala Gln Lys Glu Ala Leu Lys Ser Gln 5890 5895 5900 5890 Ile Glu Gly Ala Thr Thr Val Ala Gly Val Asn Gln Val Ser Thr Thr 5905 5910 5915 5920 40 5920 Ala Ser Glu Leu Asn Thr Ala Met Ser Asn Leu Gln Asn Gly Ile Asn 5925 5930 5935 Asp Glu Ala Ala Thr Lys Ala Ala Leu Asn Gly Thr Gln Asn Leu Glu 5940 5945 5950 45 Ala Lys Gln His Ala Asn Thr Ala Ile Asp Gly Leu Ser His Leu 5955 5960 5965 Asn Ala Gln Lys Glu Ala Leu Lys Gln Leu Val Gln Gln Ser Thr 5970 5975 5980 Thr 50 Thr Val Ala Glu Ala Gln Gly Asn Glu Gln Lys Ala Asn Asn Val Asp 5985 5990 5995 600 6000 Ala Ala Met Asp Lys Leu Arg Gln Ser Ile Ala Asp Asn Ala Thr Thr 6005 6010 6015 55 Lys Gln Asn Gln Asn Tyr Thr Asp Ala Ser Gln Asn Lys Lys Asp Ala

				6020	)				6025	5				6030	)	
	Туr	Asn	Asn 6035	Ala	Val	Thr	Thr	Ala 6040	Gln )	Gly	Ile	Ile	Asp 6045	Gln	Thr	Thr
5	Ser	Pro 6050	Thr )	Leu	Asp	Pro	⊤hr 6055	Val 5	Ile	Asn	Gln	Ala 6060	Ala	Gly	Gln	Val
	Ser 6065	Thr	Thr	Lys	Asn	Ala 6070	Leu )	Asn	Gly	Asn	Glu 6075	Asn	Leu	Glu	Ala	Ala 6080
10	Lys	Gln	Gln	Ala	Ser 6085	Gln	Ser	Leu	Gly	Ser 6090	Leu )	Asp	Asn	Leu	Asn 6095	Asn
	Ala	Gln	Lys	Gln 6100	Thr )	Val	⊤hr	Asp	Gln 6105	Ile 5	Asn	Gly	Ala	Ніs 6110	Thr )	Val
15	Asp	Glu	Ala 6115	Asn	Gln	Ile	Lys	Gln 6120	Asn )	Ala	Gln	Asn	Leu 6125	Asn	Thr	Ala
	Met	G]y 6130	Asn )	Leu	Lys	Gln	Ala 6135	Ile 5	Ala	Asp	Lys	Asp 6140	Ala	Thr	Lys	Ala
20	тhr 6145	Val ;	Asn	Phe	Thr	Asp 6150	Ala )	Asp	Gln	Ala	Lys 6155	Gln	G]n	Ala	Туr	Asn 6160
	Тhr	Ala	Val	Thr	Asn 6165	Ala	Glu	Asn	Ile	I]e 6170	Ser	Lys	Ala	Asn	G]y 6175	Gly Б
25	Asn	Ala	Тhr	Gln 6180	Ala	Glu	Val	Glu	G]n 6185	Ala	Ile	Lys	G]n	Val 6190	Asn )	Ala
	Ala	Lys	G]n 6195	Ala	Leu	Asn	Gly	Asn 6200	Ala )	Asn	Val	Gln	His 6205	Ala 5	Lys	Asp
30	Glu	Ala 6210	Thr )	Ala	Leu	Ile	Asn 6215	Ser	Ser	Asn	Asp	Leu 6220	Asn	Gln	Ala	Gln
	Lys 6225	Asp	Ala	Leu	Lys	G]n 6230	Gln )	Val	Gln	Asn	Ala 6235	Thr	Thr	Val	Ala	G]y 6240
35	Val	Asn	Asn	Val	Lys 6245	Gln	⊤hr	Ala	Gln	Glu 6250	Leu )	Asn	Asn	Ala	Met 6255	Thr
	Gln	Leu	Lys	Gln 6260	Gly )	Ile	Ala	Asp	Lys 6265	Glu 5	Gln	Thr	Lys	Ala 6270	Asp )	Gly
40	Asn	Phe	Va1 6275	Asn	Аlа	Asp	Pro	Asp 6280	Lys )	Gln	Asn	Ala	туг 6285	Asn	Gln	Ala
	Val	Ala 6290	Lys )	Ala	Glu	Ala	Leu 6295	ıle 5	Ser	Ala	⊤hr	Pro 6300	Asp	Val	Val	Val
45	Thr 6305	Pro	Ser	Glu	Ile	Thr 6310	Ala )	Ala	Leu	Asn	Lys 6315	Val	Thr	Gln	Ala	Lys 6320
	Asn	Asp	Leu	Asn	Gly 6325	Asn	⊤hr	Asn	Leu	Ala 6330	⊤hr )	Ala	Lys	Gln	Asn 6335	val
50	Gln	His	Ala	Ile 6340	Asp	Gln	Leu	Pro	Asn 6345	Leu	Asn	Gln	Ala	Gln 6350	Arg )	Asp
	Glu	Tyr	Ser 6355	Lys	Gln	Ile	Thr	Gln 6360	Ala )	Thr	Leu	Val	Pro 6365	Asn	Val	Asn
55	Ala	Ile 6370	Gln )	Gln	Ala	Ala	⊤hr 6375	Thr 5	Leu	Asn	Asp	Ala 6380	Met	Thr	Gln	Leu
	Lys 6385	Gln	Gly	Ile	Ala	Asn 6390	Lys )	Ala	Gln	Ile	Lys 6395	Gly	Ser	Glu	Asn	туг 6400

	His	Asp	Ala	Asp	Thr 6405	Asp 5	Lys	Gln	Thr	A]a 6410	Tyr )	Asp	Asn	Ala	Va] 6415	Thr 5
5	Lys	Ala	Glu	Glu 6420	Leu )	Leu	Lys	Gln	Thr 6425	Thr 5	Asn	Pro	Thr	Met 6430	Asp )	Pro
	Asn	Thr	Ile 6435	Gln 5	Gln	Ala	Leu	тhr 6440	Lys )	Val	Asn	Asp	тhr 6445	Asn	Gln	Ala
10	Leu	Asn 6450	Gly )	Asn	Gln	Lys	Leu 6455	Ala 5	Asp	Ala	Lys	G]n 6460	Asp )	Ala	Lys	Thr
	тhr 6465	Leu	Gly	⊤hr	Leu	Asp 6470	His )	Leu	Asn	Asp	Ala 6475	Gln	Lys	Gln	Ala	Leu 6480
15	Thr	Thr	Gln	Val	Glu 6485	Gln 5	Ala	Pro	Asp	Ile 6490	Ala )	Thr	Val	Asn	Asn 6495	Val
	Lys	Gln	Asn	Ala 6500	Gln )	Asn	Leu	Asn	Asn 6505	Ala 5	Met	Thr	Asn	Leu 6510	Asn )	Asn
20	Ala	Leu	Gln 6515	Asp	Lys	Thr	Glu	тhr 6520	Leu )	Asn	Ser	Ile	Asn 6525	Phe	Thr	Asp
20	Ala	Asp 6530	Gln )	Ala	Lys	Lys	Asp 6535	Ala	Туr	Тhr	Asn	Ala 6540	Val )	Ser	His	Ala
25	Glu 6545	Gly 5	Ile	Leu	Ser	Lys 6550	Ala )	Asn	Gly	Ser	Asn 6555	Ala	Ser	Gln	Thr	G]u 6560
20	Val	Glu	Gln	Ala	Met 6565	Gln 5	Arg	Val	Asn	Glu 6570	Ala )	Lys	Gln	Ala	Leu 6575	Asn
30	Gly	Asn	Asp	Asn 6580	Val )	Gln	Arg	Ala	Lys 6585	Asp 5	Ala	Ala	Lys	Gln 6590	Val )	Ile
	Thr	Asn	Ala 6595	Asn	Asp	Leu	Asn	Gln 6600	Ala )	Met	Thr	Gln	Leu 6605	Lys	Gln	Gly
25	Ile	Ala 6610	Asp )	Lys	Asp	Gln	Thr 6615	Lys	Ala	Asn	Gly	Asn 6620	Phe	Val	Asn	Ala
30	Asp 6625	Thr 5	Asp	Lys	Gln	Asn 6630	Ala )	туr	Asn	Asn	Ala 6635	val 5	Ala	His	Ala	Glu 6640
10	Gln	Ile	Ile	Ser	Gly 6645	Thr	Pro	Asn	Ala	Asn 6650	Val )	Asp	Pro	Gln	Gln 6655	Val 5
40	Ala	Gln	Ala	Leu 6660	Gln )	Gln	Val	Asn	Gln 6665	Ala 5	Lys	Gly	Asp	Leu 6670	Asn )	Gly
45	Asn	His	Asn 6675	Leu	Gln	Val	Ala	Lys 6680	Asp )	Asn	Ala	Asn	Thr 6685	Ala 5	Ile	Asp
40	Gln	Leu 6690	Pro )	Asn	Leu	Asn	Gln 6695	Pro 5	Gln	Lys	Thr	Ala 6700	Leu )	Lys	Asp	Gln
	Val 6705	Ser 5	His	Ala	Glu	Leu 6710	Val )	Thr	Gly	Val	Asn 6715	Ala 5	Ile	Lys	Gln	Asn 6720
50	Ala	Asp	Ala	Leu	Asn 6725	Asn 5	Ala	Met	Gly	тhr 6730	Leu )	Lys	Gln	Gln	Ile 6735	Gln
	Ala	Asn	Ser	G]n 6740	Val )	Pro	Gln	Ser	Va] 6745	Asp 5	Phe	Thr	Gln	Ala 6750	Asp )	Gln
22	Asp	Lys	G]n 6755	Gln 5	Ala	Туr	Asn	Asn 6760	Ala )	Ala	Asn	Gln	Ala 6765	Gln 5	Gln	Ile

Ala Asn Gly Ile Pro Thr Pro Val Leu Thr Pro Asp Thr Val Thr Gln 6770 6775 6780 Ala Val Thr Thr Met Asn Gln Ala Lys Asp Ala Leu Asn Gly Asp Glu 6785 6790 6795 680 6785 6800 5 Lys Leu Ala Gln Ala Lys Gln Glu Ala Leu Ala Asn Leu Asp Thr Leu 6805 6810 6815 Arg Asp Leu Asn Gln Pro Gln Arg Asp Ala Leu Arg Asn Gln Ile Asn682068256830 10 Gln Ala Gln Ala Leu Ala Thr Val Glu Gln Thr Lys Gln Asn Ala Gln 6835 6840 6845 Asn Val Asn Thr Ala Met Ser Asn Leu Lys Gln Gly Ile Ala Asn Lys 6850 6855 6860 15 Asp Thr Val Lys Ala Ser Glu Asn Tyr His Asp Ala Asp Ala Asp Lys 6865 6870 6875 6886 6880 Gln Thr Ala Tyr Thr Asn Ala Val Ser Gln Ala Glu Gly Ile Ile Asn 6885 6890 6895 20 Gln Thr Thr Asn Pro Thr Leu Asn Pro Asp Glu Ile Thr Arg Ala Leu 6900 6905 6910 Thr Gln Val Thr Asp Ala Lys Asn Gly Leu Asn Gly Glu Ala Lys Leu 6915 6920 6925 25 Ala Thr Glu Lys Gln Asn Ala Lys Asp Ala Val Ser Gly Met Thr His 6930 6935 6940 Leu Asn Asp Ala Gln Lys Gln Ala Leu Lys Gly Gln Ile Asp Gln Ser 6945 6950 6955 6960 6960 Pro Glu Ile Ala Thr Val Asn Gln Val Lys Gln Thr Ala Thr Ser Leu 6965 6970 6975 30 Asp Gln Ala Met Asp Gln Leu Ser Gln Ala Ile Asn Asp Lys Ala Gln 6980 6985 6990 Thr Leu Ala Asp Gly Asn Tyr Leu Asn Ala Asp Pro Asp Lys Gln Asn 6995 7000 7005 35 Ala Tyr Lys Gln Ala Val Ala Lys Ala Glu Ala Leu Leu Asn Lys Gln 7010 7015 7020 Ser Gly Thr Asn Glu Val Gln Ala Gln Val Glu Ser Ile Thr Asn Glu 7025 7030 7035 7040 40 7040 Val Asn Ala Ala Lys Gln Ala Leu Asn Gly Asn Asp Asn Leu Ala Asn 7045 7050 7055 Ala Lys Gln Gln Ala Lys Gln Gln Leu Ala Asn Leu Thr His Leu Asn 7060 7065 7070 45 Asp Ala Gln Lys Gln Ser Phe Glu Ser Gln Ile Thr Gln Ala Pro Leu 7075 7080 7085 Val Thr Asp Val Thr Thr Ile Asn Gln Lys Ala Gln Thr Leu Asp His 7090 7095 7100 50 Ala Met Glu Leu Leu Arg Asn Ser Val Ala Asp Asn Gln Thr Thr Leu 7105 7110 7115 7120 7120 Ala Ser Glu Asp Tyr His Asp Ala Thr Ala Gln Arg Gln Asn Asp Tyr 7125 7130 7135 55 Asn Gln Ala Val Thr Ala Ala Asn Asn Ile Ile Asn Gln Thr Thr Ser

		7140		7145	7150
	Pro Thr Met 715	Asn Pro A	sp Asp Val 7160	Asn Gly Ala T )	nr Thr Gln Val Asn 7165
5	Asn Thr Lys 7170	Val Ala L	eu Asp Gly. 7175	Asp Glu Asn L 7	eu Ala Ala Ala Lys 180
	Gln Gln Ala 7185	Asn Asn A 7	rg Leu Asp 190	Gln Leu Asp H 7195	is Leu Asn Asn Ala 7200
10	Gln Lys Gln	Gln Leu G 7205	Gln Ser Gln	Ile Thr Gln S 7210	er Ser Asp Ile Ala 7215
	Ala Val Asn	Gly His L 7220	ys Gln Thr	Ala Glu Ser L 7225	eu Asn Thr Ala Met 7230
15	Gly Asn Leu 723	Ile Asn A	ala Ile Ala 7240	Asp His Gln A	la Val Glu Gln Arg 7245
	Gly Asn Phe 7250	Ile Asn A	ala Asp Thr 7255	Asp Lys Gln T 7	nr Ala Tyr Asn Thr 260
20	Ala Val Asn 7265	Glu Ala A 7	ala Ala Met 270	Ile Asn Lys G 7275	ln Thr Gly Gln Asn 7280
	Ala Asn Gln	Thr Glu V 7285	/al Glu Gln	Ala Ile Thr L 7290	ys Val Gln Thr Thr 7295
25	Leu Gln Ala	Leu Asn G 7300	ily Asp His	Asn Leu Gln V 7305	al Ala Lys Thr Asn 7310
	Ala Thr Gln 731	Ala Ile A	sp Ala Leu 7320	⊤hr Ser Leu A	sn Asp Pro Gln Lys 7325
30	Thr Ala Leu 7330	Lys Asp G	iln Val Thr 7335	Ala Ala Thr L 7	eu Val Thr Ala Val 340
	His Gln Ile 7345	Glu Gln A 7	Asn Ala Asn '350	⊤hr Leu Asn G 7355	ln Ala Met His Gly 7360
35	Leu Arg Gln	Ser Ile G 7365	iln Asp Asn	Ala Ala Thr L 7370	ys Ala Asn Ser Lys 7375
	Tyr Ile Asn	Glu Asp G 7380	iln Pro Glu	Gln Gln Asn T 7385	yr Asp Gln Ala Val 7390
40	Gln Ala Ala 739	Asn Asn I	le Ile Asn 7400	Glu Gln Thr A	la Thr Leu Asp Asn 7405
	Asn Ala Ile 7410	Asn Gln A	la Ala Thr 7415	⊤hr Val Asn T 7	nr Thr Lys Ala Ala 420
45	Leu His Gly 7425	Asp Val L 7	ys Leu Gln 430	Asn Asp Lys A 7435	sp His Ala ∟ys Gln 7440
	Thr Val Ser	Gln Leu A 7445	ala His Leu	Asn Asn Ala G 7450	ln Lys His Met Glu 7455
50	Asp Thr Leu	Ile Asp S 7460	Ser Glu Thr	Thr Arg Thr A 7465	la Val Lys Gln Asp 7470
	Leu Thr Glu 747	Ala Gln A 5	ala Leu Asp 7480	Gln Leu Met A	sp Ala Leu Gln Gln 7485
	Ser Ile Ala 7490	Asp Lys A	sp Ala Thr 7495	Arg Ala Ser S 7	er Ala Tyr Val Asn 500
55	Ala Glu Pro 7505	Asn Lys L 7	ys Gln Ser '510	Tyr Asp Glu A 7515	la Val Gln Asn Ala 7520

val Ser Ser Ala Thr Gln Ala Val The Ser Ser Lys Asn Ala Leu Asp 7550Gly Val Glu Arg Leu Ala Gln Asp Lys Gln Thr Ala Gly Asn Ser Leu Asn His Leu Asp Gln Leu Thr Pro Ala Gln Gln Gln Ala Leu Glu Asn 757070Gln Ala Gln Asn Ala Thr Thr Arg Asp Lys Val Ala Glu Ile Ile Ala 7585710Gln Ala Gln Ala Leu Asn Glu Ala Met Lys Ala Leu Lys Glu Ser Ile 7680715Gln Ala Gln Ala Leu Asn Glu Ala Met Lys Ala Leu Lys Glu Ser Ile 7663716Gln Ala Gln Ala Leu Asn Glu Ala Ser Ser Lys Phe Ile Asn Glu Asp 7663717Gln Ala Gln Lys Asp Ala Tyr Thr Gln Ala val Gln His Ala Lys Asp 7665718Leu Ile Asn Lys Thr Thr Asp Pro Thr Leu Ala Lys Ser Ile Ile Asp 7665720Gln Ala Gln Ala Gln Asp Lys Gln Arg Asn Asn Asn Asn Asp 7655721Leu Ile Asn Lys Thr Thr Asp Ala Lys Asn Asn Lu His Gly Asp 7665725Gln Lys Leu Ala Gln Asp Lys Gln Arg Ala Thr Glu Thr Leu Asp 7665726Gln Lys Leu Ala Gln Asp Lys Gln Arg Ala Thr Glu Thr Leu Asp 76780726Gln Lys Leu Ala Gln Asp Lys Gln Arg Ala Thr Glu Thr Leu Asp 7770726Gln Ala thr Gln Ala Val Thr Asp Ala Lys Asp Ash Ser Ile Gln Asp 7770726Gln Lys Leu Asn Gln Ala Met Glu Ala Leu Arg Asn Ser Ile Gln Asp 77730726Gln Ala Leu Asn Gln Ala Met Glu Ala Leu Arg Ash Ser Ile Gln Asp 77730736Gln Ala Leu Asn Gln Ala Asp Asp Lys Asp Ash Leu His Gly Asp Int 77730737Gln Ala Leu Asn Gln Ala Asp Asp Lys Asp Ash Leu His Gly Asp Gln Leu 77730737Gln Ala Asp Asp Lys Gln Ala Leu Arg Ash Ash Lys Asp Lys Pro 77730746Asn Gln Thr Glu Ala Gln Ala Leu Arg Ash Ash Lys Asp Int<		Glu	Ser	Ile	Ile	Ala 7525	Gly 5	Leu	Asn	Asn	Pro 7530	Thr )	Ile	Asn	Lys	Gly 7535	Asn 5
Gly Val Glu Arg Leu Ala Gln Asp Lys Gln Thr Ala Gly Asn Ser LeuAsn His Leu Asp Gln Leu Thr Pro Ala Gln Gln Gln Ala Leu Glu AsnGln Tle Asn Asn Ala Thr Thr Arg Asp Lys Yala Ala Glu Ile Ile Ala7585Gln Ala Gln Ala Leu Asn Glu Ala Met Lys Ala Leu Lys Glu Ser Tle101112131415151516161717171819191910191019101010101010111212131414151515161616171718 <t< td=""><td>5</td><td>Val</td><td>Ser</td><td>Ser</td><td>Ala 7540</td><td>Thr )</td><td>Gln</td><td>Ala</td><td>Val</td><td>Ile 7545</td><td>Ser</td><td>Ser</td><td>Lys</td><td>Asn</td><td>Ala 7550</td><td>Leu )</td><td>Asp</td></t<>	5	Val	Ser	Ser	Ala 7540	Thr )	Gln	Ala	Val	Ile 7545	Ser	Ser	Lys	Asn	Ala 7550	Leu )	Asp
Asn His Leu Asp Gln Leu Thr Pro Ala Gln Gln Gln Ala Leu Glu Asn 7580Gln Tle Asn Asn Ala Thr Thr Arg Asp Lys Val Ala Glu Ile Ile Ala 7585Gln Ala Gln Ala Leu Asn Glu Ala Met Lys Ala Leu Lys Glu Ser Ile 7620Lys Asp Gln Pro Gln Thr Glu Ala Ser Ser Lys Phe Ile Asn Glu Asp 7620Gln Ala Gln Lys Asp Ala Tyr Thr Gln Ala Val Gln His Ala Lys Asp 7625Leu Ile Asn Lys Thr Thr Asp Pro Thr Leu Ala Lys Ser Ile Ile Asp 7665Gln Ala Thr Gln Ala Val Thr Gln Ala Lys Asp Ala Tyr 7640Leu Ile Asn Lys Thr Thr Asp Pro Thr Leu Ala Lys Asn Leu His Gly Asp 7665Gln Ala Thr Gln Ala Val Thr Asp Ala Lys Asn Asn Leu His Gly Asp 7670Jan Asn Ala Ala Thr Gln Ala Val Thr Asp Ala Lys Asn Asn Leu Glu Asn Gln Ile 7700Asn Asn Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Thr Glu Ala 7775Gln Ala Leu Asn Gln Ala Met Glu Ala Leu Arg Asn Ser Ile Gln Asp 7775Gln Lys Leu Asn Gln Ala Met Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro 7765Gln Lys Asp Ala Tyr Gln Ala Ala Val Gln Asp Lys Asp Asn Leu Fig Glu Ala 7770Gln Lys Asp Ala Tyr Gln Ala Ala Val Gln Asp Asp Ser Ile Gln Asp 7775Gln Lys Asp Ala Tyr Gln Ala Ala Val Gln Asn Glu Asp Lys Pro 7785Gln Lys Asp Ala Tyr Gln Ala Ala Val Gln Asn Ala Lys Asp Lys Pro 7785Asn Gln Thr Asn Asn Pro Thr Leu Asp Lys Asp Ash Leu His Gly Asp Gln Lys 7780Asn Gln Thr Asn Asn Pro Thr Leu Asp Lys Asp Ash Leu Asp Gln Ala Lys Asp Asp Cur 7780Asn Ash Ala Asp Asp Lys Gln Ala Ala Val Gln Val Gln Val Glu Gln Leu 7780An Ash Asp Asp Lys Gln Ala Lys Asp Asp Leu Asn Gln Leu Asn 7880As Ash Asp Asp Lys Gln Ala Lys Asp Asp Leu Asp Gln Lys 7880As Ash Ash Asn Pro Gln Ala L		Gly	Val	Glu 7555	Arg	Leu	Ala	Gln	Asp 7560	Lys )	Gln	Thr	Ala	Gly 7565	Asn	Ser	Leu
Gin Ile Asn Asn Ala Thr Thr Arg Asp Lys Val Ala Glu Ile Ile Ala 7585Gin Ile Asn Asn Ala Thr Thr Arg Asp Lys Val Ala Glu Ile Ile Ala 7585Gin Ala Gin Ala Leu Asn Glu Ala Met Lys Ala Leu Lys Glu Ser Ile 7620Lys Asp Gin Pro Gin Thr Glu Ala Ser Ser Lys Phe Ile Asn Glu Asp 7635Gin Ala Gin Lys Asp Ala Tyr Thr Gin Ala Val Gin His Ala Lys Asp 7665Leu Ile Asn Lys Thr Thr Asp Pro Thr Leu Ala Lys Ser Ile Ile Asp 7665Gin Ala Thr Gin Ala Val Thr Asp Ala Ly Asn Asn Asn Leu His Gly Asp 7665Gin Lys Leu Ala Gin Asp Tro Gin Arg Ala Thr Glu Thr Leu Asn Asn 7680Gin Lys Leu Ala Gin Asp Lys Glu Arg Gin Ala Leu Glu Asn Gin Ile 7700Asn Asn Ala Ala Thr Arg Gly Glu Val Ala Gin Lys Leu Ala 7715Gin Ala Chi Thr Glu Ala Met Gin Ala Leu Arg Asn Ser Ile Gln Asp 77730Gin Ala Chi Thr Glu Ala Met Gin Ala Leu Arg Asn Ser Ile Gin Asp 77735Gin Ala Chi Thr Glu Ala Met Gin Ala Val Gin Lys Asp Leu 	10	Asn	His 7570	Leu )	Asp	Gln	Leu	Thr 7575	Pro	Ala	Gln	Gln	Gln 7580	Ala )	Leu	Glu	Asn
Gln Ala Gln Ala Leu Asn Glu Ala Met Lys Ala Leu Lys Glu Ser Ile 761015Lys Asp Gln Pro Gln Thr Glu Ala Ser Ser Lys Phe Ile Asn Glu Asp 762320Gln Ala Gln Lys Asp Ala Tyr Thr Gln Ala Val Gln His Ala Lys Asp 765520Leu Ile Asn Lys Thr Thr Asp Pro Thr Leu Ala Lys Ser Ile Ile Asp 765521Gln Ala Thr Gln Ala Val Thr Asp Ala Lys Asp Af65525Gln Lys Leu Ala Gln Asp Lys Gln Arg Ala Thr Glu Thr Leu Asn Asn 766530Asn Asn Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Glu Asn Gln Ala 771530Gln Ala Chin Thr Glu Ala Mag Gly Ser Lys Phe Ile Asn Glu Asp 777031Gln Ala Chin Thr Glu Ala Mag Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro 774535Gln Gln Thr Glu Ala Glin Ala Ala Val Glin Asn Ala Lys Asp Lys Pro 774546Asn Glin Thr Glu Ala Gli Ser Lys Phe Ile Asn Glu Asp Lys Pro 7775547Asn Glin Thr Asn Asn Pro Thr Leu Asp Lys Ala Glin Val Glin Ceu 7770548Glin Ala Lya Asp Asp Lys Glin Ala Leu Glu Ser Jie Glin Leu 7770549Asn Glin Thr Glu Ala Gli Ser Lys Phe Ile Asn Glu Asp Lys Pro 7775540Asn Glin Thr Asp Asp Crys Asp Asp Lys Ala Glin Val Glin Leu 7770541Asn Glin Ala Val Glin Ala Ala Val Thr Asp Leu Asp Glin Leu Asp 788042Ala Ala Thr Arg Glin Ala Cal Thr Asp Leu Ala Glin Leu Asp 	10	Gln 7585	Ile 5	Asn	Asn	Ala	Thr 7590	Thr )	Arg	Asp	Lys	Val 7595	Ala	Glu	Ile	Ile	Ala 7600
LysAspGlnProGlnThrGluAlaSerSerLysPheIleAsnGluAsp20GlnAlaGlnAlaGlnAlaGlnAlaLysAspAsp20LeuIleAsnLysAsnLysAsnFrFrGlnAlaLysAsnGlnAlaLysAsnLeuIleAsnAsp20GlnAlaThrGlnAlaValThrAsnAsnAsnAsnAsp20GlnAlaThrGlnAlaValAsnAsnAsnAsnAsp766525GlnAlaThrGlnAlaValAsn <td< td=""><td>15</td><td>Gln</td><td>Ala</td><td>Gln</td><td>Ala</td><td>Leu 7605</td><td>Asn</td><td>Glu</td><td>Ala</td><td>Met</td><td>Lys 7610</td><td>Ala )</td><td>Leu</td><td>Lys</td><td>Glu</td><td>Ser 7615</td><td>Ile</td></td<>	15	Gln	Ala	Gln	Ala	Leu 7605	Asn	Glu	Ala	Met	Lys 7610	Ala )	Leu	Lys	Glu	Ser 7615	Ile
20Gln Ala Gln Lys Asp Ala Tyr Thr Gln Ala Val Gln His Ala Lys Asp 763520Leu Ile Asn Lys Thr Thr Asp Pro Thr Leu Ala Lys Ser Ile Ile Asp 766025Gln Ala Thr Gln Ala Val Thr Asp Ala Lys Asn Asn Leu His Gly Asp 766526Gln Lys Leu Ala Gln Asp Lys Gln Arg Ala Thr Glu Thr Leu Asn Asn 766530Gln Lys Leu Ala Gln Asp Lys Gln Arg Gln Ala Leu Glu Asn Gln Ile 770030Asn Asn Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Thr Glu Ala 771531Gln Ala Leu Asn Gln Ala Met Glu Ala Leu Arg Asn Ser Ile Gln Asp 773535Gln Gln Gln Thr Glu Ala Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro 774540Gln Lys Asp Ala Tyr Gln Ala Ala Val Gln Ala Leu His Gly Asp Crift 776540Asn Gln Thr Asn Gln Ala Ala Val Gln Ala Lys Asp Lys Pro 777540Asn Gln Thr Glu Ala Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro 777541Asn Gln Thr Asn Gln Ala Lys Asp Asn Leu His Gly Asp Gln Leu 778042Thr Gln Ala Val Asn Gln Ala Lys Asp Asn Leu His Gly Asp Gln Lys 778043Thr Gln Ala Sp Sp Lys Gln His Ala Val Thr Asp Leu Asn Gln Lys 780044Ala Asp Asp Lys Gln Ala Lys Asp Asn Leu His Gly Asp Gln Lys 780045Leu Asn Asn Pro 781046Ala Asp Asp Lys Gln Arg Gln Ala Leu Glu Ser Gln Ile Asn Asn 782546Asn Gln Asn Pro 783047Gln Ala Cu Asn Asn Pro 783048Gln Ala Leu Asn Asn Pro 783049Ala Ala Thr Arg Gly Glu Val Ala Gln Leu Glu Asn Gln Leu Asn 782046Ala Ala Thr Arg Gly Ser Lys Phe Ile Asn Ser Ile Gln Asp Gln Gln 785047Ala Ala Thr Arg Gl	15	Lys	Asp	Gln	Pro 7620	Gln )	Thr	Glu	Ala	Ser 7625	Ser	Lys	Phe	Ile	Asn 7630	Glu )	Asp
Leu Ile Asn Lys Thr Thr Asp Pro Thr Leu Ala Lys Ser Ile Ile Asp25Gln Ala Thr Gln Ala Val Thr Asp Ala Lys Asn Asn Leu His Gly Asp26Gln Lys Leu Ala Gln Asp Lys Gln Arg Ala Thr Glu Thr Leu Asn Asn30Gln Asn Asn Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Thr Glu Ala30Asn Asn Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Thr Glu Ala30Gln Ala Leu Asn Gln Ala Met Glu Ala Leu Arg Asn Ser Ile Gln Asp31Gln Ala Leu Asn Gln Ala Met Glu Ala Leu Arg Asn Ser Ile Gln Asp32Gln Gln Gln Thr Glu Ala Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro35Gln Lys Asp Ala Tyr Gln Ala Ala Val Gln Asn Asn Gln Lys Asp Leu36Gln Lys Asp Ala Tyr Gln Ala Ala Val Gln Val Glu Gln Lys Asp Leu37Fredo36Gln Lys Asp Ala Tyr Gln Ala Ala Val Gln Val Glu Gln Lus36Gln Lys Asp Ala Tyr Gln Ala Ala Val Gln Val Glu Gln Leu37778036Gln Lys Asp Asp Asp Clys Gln His Ala Val Gln Val Glu Gln Leu37778036Gln Ala Ser Asp Asp Clys Gln His Ala Val Thr Asp Leu Asn Gln Leu Asn 781037Asn Asn Asn Pro Gln Arg Gln Ala Leu Glu Ser Gln Ile Asn 784036Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Ala Glu Ala Lys Asp37Gln Ja Ser Gln Ala Met Gln Ala Leu Arg Asn Ser Ile Gln Asp 784538Gln Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Ala Glu Ala Lys Asp39Gln Thr Glu Ser Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro Gln Lys 7845	20	Gln	Ala	Gln 7635	Lys	Asp	Ala	Tyr	Thr 7640	Gln )	Ala	Val	Gln	His 7645	Ala	Lys	Asp
25Gln Ala Thr Gln Ala Val Thr Asp Ala Lys Asn Asn Leu His Gly Asp 766526Gln Lys Leu Ala Gln Asp Lys Gln Arg Ala Thr Glu Thr Leu Asn Asn 768530Leu Ser Asn Leu Asn Thr Pro Gln Arg Gln Ala Leu Glu Asn Gln Ile 770030Asn Asn Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Thr Glu Ala 771531Gln Ala Leu Asn Gln Ala Met Gly Asg Glu Ala Leu Arg Asn Gln Asp 773035Gln Gln Gln Thr Glu Ala Met Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro 774540Gln Lys Asp Ala Tyr Gln Ala Ala Val Gln Asn Ala Lys Asp Leu 778040Asn Gln Thr Asn Asn Pro Thr Leu Asp Lys Ash Ala Lys Asp Leu 778040Asn Gln Thr Asn Asn Pro Thr Leu Asp Lys Ash Ala Lys Asp Leu 778040Asn Gln Thr Asn Asn Pro Thr Leu Asp Lys Ash Ala Lys Asp Clu Gln Lys 778040Asn Gln Thr Asn Asn Pro Thr Leu Asp Lys Ash Ala Lys Asp Gln Lys 778041Ash Ash Ash Ash Pro Thr Leu Asp Lys Ash Ala Lys Asp Gln Lys 780042Ash Gln Ala Val Ash Gln Ala Lys Asp Ash Leu His Gly Asp Gln Lys 780043Ala Ala Thr Arg Gly Glu Val Ala Gln Leu Glu Ser Gln Ile Ash 7840 782544Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Ala Glu Ala Lys Ala 782545Leu Ash Ash Pro Gln Ala Leu Arg Ash Ser Ile Gln Asp Cla Lys 782546Gln Thr Glu Ser Gly Ser Lys Phe Ile Ash Glu Asp Lys Pro Gln Lys47Ala Ala Thr Arg Cly Glu Val Ala Gln Lys Leu Ala Glu Ala Lys Ala 786048Ala Ala Thr Arg Phy Cly Clu Val Ala Gln Lys Pro Cln Lys 786045Gln Thr Glu Ser Gly Ser Lys Phe Ile Ash Glu Asp Lys Pro Gln Lys	20	Leu	Ile 7650	Asn )	Lys	Thr	Thr	Asp 7655	Pro	Thr	Leu	Ala	Lys 7660	Ser )	Ile	Ile	Asp
Gln Lys Leu Ala Gln Asp Lys Gln Arg Ala Thr Glu Thr Leu Asn Asn Gln Lys Leu Ala Gln Asp Lys Gln Arg Gln Ala Leu Glu Asn Gln Ile Leu Ser Asn Leu Asn Thr Pro Gln Arg Gln Ala Leu Glu Asn Gln Ile Asn Asn Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Thr Glu Ala Gln Ala Leu Asn Gln Ala Met Glu Ala Leu Arg Asn Ser Ile Gln Asp Gln Gln Gln Thr Glu Ala Gly Ser Lys Phe Tle Asn Glu Asp Lys Pro 7745 Gln Lys Asp Ala Tyr Gln Ala Ala Val Gln Asn Ala Lys Asp Leu Ile Asn Gln Thr Asn Asn Pro Thr Leu Asp Lys Ala Gln Val Glu Gln Leu Thr Gln Ala Sp Asp Lys Gln Ala Lys Asp Asn Leu His Gly Asp Gln Leu Thr Gln Ala Sp Asp Lys Gln His Ala Val Thr Asp Leu Asn Gln Leu Asn Gly Leu Asn Asn Pro Gln Arg Gln Ala Leu Glu Ser Gln Ile Asn Asn 7825 Gly Leu Asn Asn Pro Gln Arg Gln Ala Leu Glu Ser Gln Ile Asn Asn 7840 Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Ala Glu Ala Lys Asp Leu Asp Gln Asn Asn Pro Gln Arg Gln Ala Leu Glu Ser Gln Ile Asn 7840 Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Ala Glu Ala Lys Asn 60 Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Ala Glu Ala Lys Asn 7840 Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Ala Glu Asp Gln Gln T 7850 Gln Thr Glu Ser Gly Ser Lys Phe Tle Asn Glu Asp Lys Pro Gln Lys 7860 Gln Thr Glu Ser Gly Ser Lys Phe Tle Asn Glu Asp Lys Pro Gln Lys 7880	05	Gln 7665	Ala	Thr	Gln	Ala	Val 7670	Thr )	Asp	Ala	Lys	Asn 7675	Asn	Leu	His	Gly	Asp 7680
Leu Ser Asn Leu Asn Thr Pro Gln Arg Gln Ala Leu Glu Asn Gln Ile Asn Asn Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Thr Glu Ala Gln Ala Leu Asn Gln Ala Met Glu Ala Leu Arg Asn Ser Ile Gln Asp 7730 Gln Gln Gln Thr Glu Ala Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro 7745 Gln Lys Asp Ala Tyr Gln Ala Ala Val Gln Asn Ala Lys Asp Leu Ile Asn Gln Thr Asn Asn Pro Thr Leu Asp Lys Ala Gln Val Glu Gln Leu 7785 Leu Ala Asp Asp Lys Gln Ala Lys Asp Asn Leu His Gly Asp Gln Lys 6 Gly Leu Asn Asn Pro Gln Ala Lys Asp Asn Leu His Gly Asp Gln Lys 7810 Gly Leu Asn Asn Pro Gln Ala Lys Asp Asn Leu His Gly Asp Gln Lys 7825 Leu Ala Asp Asp Lys Gln His Ala Val Thr Asp Leu Asn Gln Leu Asn 7825 Gly Leu Asn Asn Pro Gln Ala Cln Leu Glu Ser Gln Ile Asn Asn 7825 Gln Thr Asn Asn Pro Gln Ala Cln Leu Glu Ser Gln Ala Lys Asp Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Ala Glu Ala Lys Asp Leu Asp Gln Ala Met Gln Ala Leu Arg Asn Ser Ile Gln Asp Cln Thr Glu Ser Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro Gln Cln 7865 Gln Thr Glu Ser Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro Gln Lys 7800 Gln Thr Glu Ser Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro Gln Lys 7800 Gln Thr Glu Ser Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro Gln Lys	25	Gln	Lys	Leu	Ala	Gln 7685	Asp	Lys	Gln	Arg	Ala 7690	Thr )	Glu	Thr	Leu	Asn 7695	Asn
Asn Asn Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Thr Glu Ala Gln Ala Leu Asn Gln Ala Met Glu Ala Leu Arg Asn Ser Ile Gln Asp 7730 Gln Gln Gln Thr Glu Ala Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro 7745 Gln Lys Asp Ala Tyr Gln Ala Ala Val Gln Asn Ala Lys Asp Leu Ile Asn Gln Thr Asn Asn Pro Thr Leu Asp Lys Ala Gln Val Glu Gln Leu Thr Gln Ala Val Asn Gln Ala Lys Asp Asn Leu His Gly Asp Gln Lys Leu Ala Asp Asp Lys Gln His Ala Val Thr Asp Leu Asn Gln Leu Asn 7810 Gly Leu Asn Asn Pro Gln Arg Gln Ala Leu Glu Ser Gln Ile Asn Asn 7840 Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Ala Glu Ala Lys Ala Leu Asp Gln Ala Met Gln Ala Leu Arg Asn Ser Ile Gln Asp Gln Thr Glu Ser Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro 7880 Gln Thr Gln Ala Thr Arg Cly Ser Lys Phe Ile Asn Glu Asp Lys Pro 60 Ala Ala Thr Arg Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro 61 Gln Thr Glu Ser Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro 61 Gln Thr Glu Ser Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro 61 Gln Thr Glu Ser Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro 61 61 61 61 7875 61 7875 61 7875 61 7875 61 7875 61 7875 61 7875 7885		Leu	Ser	Asn	Leu 7700	Asn )	Thr	Pro	Gln	Arg 7705	Gln	Ala	Leu	Glu	Asn 7710	Gln )	Ile
Gln Ala Leu Asn Gln Ala Met Glu Ala Leu Arg Asn Ser Ile Gln Asp Gln Gln Gln Thr Glu Ala Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro 7745 Gln Lys Asp Ala Tyr Gln Ala Ala Val Gln Asn Ala Lys Asp Leu Ile Asn Gln Thr Asn Asn Pro Thr Leu Asp Lys Ala Gln Val Glu Gln Leu Thr Gln Ala Val Asn Gln Ala Lys Asp Asn Leu His Gly Asp Gln Lys Leu Ala Asp Asp Lys Gln His Ala Val Thr Asp Leu Asn Gln Leu Asn 619 Leu Asn Asn Pro Gln Arg Gln Ala Leu Glu Ser Gln Ile Asn Asn 620 Ala Ala Thr Arg Gly Glu Val Ala Gln Leu Grass er Gln Ile Asn Asn 630 641 642 643 644 644 654 644 645 645 646 647 647 647 647 647 647 647	30	Asn	Asn	Ala 7715	Ala	Thr	Arg	Gly	Glu 7720	Val )	Ala	Gln	Lys	Leu 7725	Thr	Glu	Ala
<ul> <li><sup>35</sup> Gln Gln Gln Thr Glu Ala Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro 7760</li> <li>Gln Lys Asp Ala Tyr Gln Ala Ala Val Gln Asn Ala Lys Asp Leu Ile 7765</li> <li>Asn Gln Thr Asn Asn Pro Thr Leu Asp Lys Ala Gln Val Glu Gln Leu 7780</li> <li><sup>40</sup> Thr Gln Ala Val Asn Gln Ala Lys Asp Asn Leu His Gly Asp Gln Leu 7780</li> <li><sup>45</sup> Leu Ala Asp Asp Lys Gln His Ala Val Thr Asp Leu Asn Gln Leu Asn 7810</li> <li><sup>50</sup> Gly Leu Asn Asn Pro Gln Arg Gln Ala Leu Glu Ser Gln Ile Asn Asn 7840</li> <li><sup>50</sup> Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Ala Glu Ala Lys Ala Glu Ala Lys Asp Gln Gln Gln Gln Ala Cheu Asn 7850</li> <li><sup>56</sup> Gln Thr Gln Ala Met Gln Ala Leu Asn 7865</li> <li><sup>56</sup> Gln Thr Glu Ser Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro Gln Lys 7860</li> </ul>		Gln	Ala 7730	Leu )	Asn	Gln	Ala	Met 7735	Glu	Ala	Leu	Arg	Asn 7740	Ser	Ile	Gln	Asp
Gln Lys Asp Ala Tyr Gln Ala Ala Val Gln Asn Ala Lys Asp Leu Ile Asn Gln Thr Asn Asn Pro Thr Leu Asp Lys Ala Gln Val Glu Gln Leu Thr Gln Ala Val Asn Gln Ala Lys Asp Asn Leu His Gly Asp Gln Lys Leu Ala Asp Asp Lys Gln His Ala Val Thr Asp Leu Asn Gln Leu Asn Gly Leu Asn Asn Pro Gln Arg Gln Ala Leu Glu Ser Gln Ile Asn Asn Gly Leu Asn Asn Pro Gly Gln Val Ala Gln Leu Glu Ser Gln Ile Asn Asn Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Ala Glu Ala Lys Ala Leu Asp Gln Ala Met Gln Ala Leu Arg Asn Ser Ile Gln Asp Gln Gln Thr Glu Ser Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro Gln Lys 7880	35	Gln 7745	G]n	Gln	⊤hr	Glu	Ala 7750	Gly	Ser	Lys	Phe	Ile 7755	Asn	Glu	Asp	Lys	Pro 7760
<ul> <li>Asn Gln Thr Asn Asn Pro Thr Leu Asp Lys Ala Gln Val Glu Gln Leu Thr Gln Ala Val Asn Gln Ala Lys Asp Asn Leu His Gly Asp Gln Lys 7795 Ala Asn Gln Ala Lys Asp Asn Leu His Gly Asp Gln Lys Leu Ala Asp Asp Lys Gln His Ala Val Thr Asp Leu Asn Gln Leu Asn 7810 Gly Leu Asn Asn Pro Gln Arg Gln Ala Leu Glu Ser Gln Ile Asn Asn 7825 Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Ala Glu Ala Lys Ala Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Ala Glu Ala Lys Ala Leu Asp Gln Ala Met Gln Ala Leu Arg Asn Ser Ile Gln Asp Gln Gln 7875 Gln Thr Glu Ser Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro Gln Lys 7880 Asp Cln Asp Pro Gln Lys</li> </ul>		Gln	Lys	Asp	Ala	Туг 7765	Gln	Ala	Ala	Val	Gln 7770	Asn )	Ala	Lys	Asp	Leu 7775	Ile 5
<ul> <li>Thr Gln Ala Val Asn Gln Ala Lys Asp Asn Leu His Gly Asp Gln Lys</li> <li>Leu Ala Asp Asp Lys Gln His Ala Val Thr Asp Leu Asn Gln Leu Asn 7810</li> <li>Gly Leu Asn Asn Pro Gln Arg Gln Ala Leu Glu Ser Gln Ile Asn Asn 7840</li> <li>Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Ala Glu Ala Lys Ala 7855</li> <li>Leu Asp Gln Ala Met Gln Ala Leu Arg Asn Ser Ile Gln Asp Gln Gln Gln 7865</li> <li>Gln Thr Glu Ser Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro Gln Lys 7885</li> </ul>	40	Asn	Gln	Thr	Asn 7780	Asn )	Pro	Thr	Leu	Asp 7785	Lys	Ala	Gln	Val	Glu 7790	Gln )	Leu
<ul> <li>Leu Ala Asp Asp Lys Gln His Ala Val Thr Asp Leu Asn Gln Leu Asn 7810</li> <li>Gly Leu Asn Asn Pro Gln Arg Gln Ala Leu Glu Ser Gln Ile Asn Asn 7825</li> <li>Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Ala Glu Ala Lys Ala 7855</li> <li>Leu Asp Gln Ala Met Gln Ala Leu Arg Asn Ser Ile Gln Asp Gln Gln 7860</li> <li>Gln Thr Glu Ser Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro Gln Lys 7880</li> </ul>		Thr	Gln	Ala 7795	Val 5	Asn	Gln	Ala	Lys 7800	Asp )	Asn	Leu	His	Gly 7805	Asp 5	Gln	Lys
Gly Leu Asn Asn Pro Gln Arg Gln Ala Leu Glu Ser Gln Ile Asn Asn 7825 Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Ala Glu Ala Lys Ala 7855 Leu Asp Gln Ala Met Gln Ala Leu Arg Asn Ser Ile Gln Asp Gln Gln 7860 Gln Thr Glu Ser Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro Gln Lys 7880	45	Leu	Ala 7810	Asp )	Asp	Lys	Gln	His 7815	Ala	Val	Thr	Asp	Leu 7820	Asn )	Gln	Leu	Asn
Ala Ala Thr Arg Gly Glu Val Ala Gln Lys Leu Ala Glu Ala Lys Ala 7855 Leu Asp Gln Ala Met Gln Ala Leu Arg Asn Ser Ile Gln Asp Gln Gln 7860 55 Gln Thr Glu Ser Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro Gln Lys 7880		Gly 7825	Leu	Asn	Asn	Pro	Gln 7830	Arg )	Gln	Ala	Leu	Glu 7835	Ser	Gln	Ile	Asn	Asn 7840
Leu Asp Gln Ala Met Gln Ala Leu Arg Asn Ser Ile Gln Asp Gln Gln 7860 55 Gln Thr Glu Ser Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro Gln Lys 7875 7880 7885	50	Ala	Ala	Thr	Arg	Gly 7845	Glu	Val	Ala	Gln	Lys 7850	Leu )	Ala	Glu	Ala	Lys 7855	Ala
<sup>55</sup> Gln Thr Glu Ser Gly Ser Lys Phe Ile Asn Glu Asp Lys Pro Gln Lys 7875 7880 7885		Leu	Asp	Gln	Ala 7860	Met	Gln	Ala	Leu	Arg 7865	Asn 5	Ser	Ile	Gln	Asp 7870	Gln )	Gln
	55	Gln	Thr	Glu 7875	Ser	Gly	Ser	Lys	Phe 7880	Ile )	Asn	Glu	Asp	Lys 7885	Pro	Gln	Lys

Ala Tyr Gln Ala Ala Val Gln Asn Ala Lys Asp Leu Ile Asn Gln 7890 7895 7900 Thr Gly Asn Pro Thr Leu Asp Lys Ser Gln Val Glu Gln Leu Thr Gln Ala Val Thr Thr Ala Lys Asp Asn Leu His Gly Asp Gln Lys Leu Ala 7925 7930 7935 Arg Asp Gln Gln Gln Ala Val Thr Thr Val Asn Ala Leu Pro Asn Leu 7940 7945 7950 Asn His Ala Gln Gln Gln Ala Leu Thr Asp Ala Ile Asn Ala Ala Pro Thr Arg Thr Glu Val Ala Gln His Val Gln Thr Ala Thr Glu Leu Asp 7970 7975 7980 His Ala Met Glu Thr Leu Lys Asn Lys Val Asp Gln Val Asn Thr Asp 7985 7990 7995 800 Lys Ala Gln Pro Asn Tyr Thr Glu Ala Ser Thr Asp Lys Lys Glu Ala 8005 8010 8015 Val Asp Gln Ala Leu Gln Ala Ala Glu Ser Ile Thr Asp Pro Thr Asn 8020 8025 8030 Gly Ser Asn\_Ala Asn Lys Asp Ala Val Asp Gln Val Leu Thr Lys Leu Gln Glu Lys Glu Asn Glu Leu Asn Gly Asn Glu Arg Val Ala Glu Ala 8050 8055 8060 Lys Thr Gln Ala Lys Gln Thr Ile Asp Gln Leu Thr His Leu Asn Ala 8065 8070 8075 8080 Asp Gln Ile Ala Thr Ala Lys Gln Asn Ile Asp Gln Ala Thr Lys Leu 8085 8090 8095 Gln Pro Ile Ala Glu Leu Val Asp Gln Ala Thr Gln Leu Asn Gln Ser Met Asp Gln Leu Gln Gln Ala Val Asn Glu His Ala Asn Val Glu Gln 8115 8120 8125 Thr Val Asp Tyr Thr Gln Ala Asp Ser Asp Lys Gln Asn Ala Tyr Lys 8130 8135 8140 Gln Ala Ile Ala Asp Ala Glu Asn Val Leu Lys Gln Asn Ala Asn Lys 8145 8150 8155 8160 Gln Gln Val Asp Gln Ala Leu Gln Asn Ile Leu Asn Ala Lys Gln Ala Leu Asn Gly Asp Glu Arg Val Ala Leu Ala Lys Thr Asn Gly Lys His 8180 8185 8190 Asp Ile Asp Gln Leu Asn Ala Leu Asn Asn Ala Gln Gln Asp Gly Phe 8195 8200 Gly Arg Ile Asp Gln Ser Asn Asp Leu Asn Gln Ile Gln Gln Ile Lys Val Asp Glu Ala Lys Ala Leu Asn Arg Ala Met Asp Gln Leu Ser Gln Glu Ile Thr Asp Asn Glu Gly Arg Thr Lys Gly Ser Thr Asn Tyr Val 8245 8250 8255 Asn Ala Asp Thr Gln Val Lys Gln Val Tyr Asp Glu Thr Val Asp Lys

				8260	)				8265	5				8270	)	
	Ala	Lys	Gln 8275	Ala	Leu	Asp	Lys	Ser 8280	⊤hr )	Gly	Gln	Asn	Leu 8285	Thr	Ala	Lys
5	Gln	Va] 8290	Ile	Lys	Leu	Asn	Asp 8295	Ala 5	Val	Thr	Ala	Ala 8300	Lys	Lys	Ala	Leu
	Asn 8305	Gly	Glu	Glu	Arg	Leu 8310	Asn )	Asn	Arg	Lys	Ala 8315	Glu	Ala	Leu	Gln	Arg 8320
10	Leu	Asp	Gln	Leu	Thr 8325	His	Leu	Asn	Asn	Ala 8330	Gln )	Arg	Gln	Leu	Ala 8335	Ile
	Gln	Gln	Ile	Asn 8340	Asn	Ala	Glu	Thr	Leu 8345	Asn	Lys	Ala	Ser	Arg 8350	Ala )	Ile
15	Asn	Arg	Ala 8355	Thr	Lys	Leu	Asp	Asn 8360	Ala )	Met	Gly	Ser	Va] 8365	Gln 5	Gln	Tyr
	Ile	Asp 8370	Glu	Gln	His	Leu	Gly 8375	Val 5	Ile	Ser	Ser	Thr 8380	Asn	Tyr	Ile	Asn
20	Ala 8385	Asp	Asp	Asn	Leu	Lys 8390	Ala )	Asn	Tyr	Asp	Asn 8395	Ala	Ile	Ala	Asn	Ala 8400
	Ala	His	Glu	Leu	Asp 8405	Lys	Val	Gln	Gly	Asn 8410	Ala	Ile	Ala	Lys	Ala 8415	Glu
25	Ala	Glu	Gln	Leu 8420	Lys )	Gln	Asn	Ile	Ile 8425	Asp	Ala	Gln	Asn	Ala 8430	Leu )	Asn
	Gly	Asp	Gln 8435	Asn	Leu	Ala	Asn	Ala 8440	Lys )	Asp	Lys	Ala	Asn 8445	Ala	Phe	Val
30	Asn	ser 8450	Leu	Asn	Gly	Leu	Asn 8455	Gln 5	Gln	Gln	Gln	Asp 8460	Leu	Ala	His	Lys
	Ala 8465	Ile	Asn	Asn	Ala	Asp 8470	⊤hr )	Val	Ser	Asp	Val 8475	Thr	Asp	Ile	Val	Asn 8480
35	Asn	Gln	Ile	Asp	Leu 8485	Asn	Asp	Ala	Met	Glu 8490	⊤hr )	Leu	Lys	His	Leu 8495	Val
	Asp	Asn	Glu	Ile 8500	Pro )	Asn	Ala	Glu	Gln 8505	Thr	Val	Asn	Туr	Gln 8510	Asn )	Ala
40	Asp	Asp	Asn 8515	Ala	Lys	Thr	Asn	Phe 8520	Asp )	Asp	Ala	Lys	Arg 8525	Leu	Ala	Asn
	Thr	Leu 8530	Leu	Asn	Ser	Asp	Asn 8535	Thr 5	Asn	Val	Asn	Asp 8540	Ile	Asn	Gly	Ala
45	Ile 8545	Gln	Ala	Val	Asn	Asp 8550	Ala )	Ile	His	Asn	Leu 8555	Asn	Gly	Asp	Gln	Arg 8560
	Leu	Gln	Asp	Ala	Lys 8565	Asp	Lys	Ala	Ile	Gln 8570	Ser )	Ile	Asn	Gln	Ala 8575	Leu
50	Ala	Asn	Lys	Leu 8580	Lys	Glu	Ile	Glu	Ala 8585	Ser	Asn	Ala	Thr	Asp 8590	Gln )	Asp
	Lys	Leu	Ile 8595	Ala	Lys	Asn	Lys	Ala 8600	Glu )	Glu	Leu	Ala	Asn 8605	Ser	Ile	Ile
55	Asn	Asn 8610	Ile	Asn	Lys	Ala	⊤hr 8615	Ser	Asn	Gln	Ala	Va] 8620	Ser	Gln	Val	Gln
	Thr 8625	Ala	Gly	Asn	His	Ala 8630	Ile )	Glu	Gln	Val	His 8635	Ala	Asn	Glu	Ile	Pro 8640

	Lys	Ala	Lys	Ile	Asp 8645	Ala 5	Asn	Lys	Asp	Val 8650	Asp )	Lys	Gln	Val	Gln 8655	Ala 5
5	Leu	Ile	Asp	Glu 8660	ıle )	Asp	Arg	Asn	Pro 8665	Asn 5	Leu	Thr	Asp	Lys 8670	Glu )	Lys
	Gln	Ala	Leu 8675	Lys	Asp	Arg	Ile	Asn 8680	Gln )	Ile	Leu	Gln	Gln 8685	Gly 5	His	Asn
10	Gly	Ile 8690	Asn )	Asn	Ala	Met	Thr 8695	Lys	Glu	Glu	I]e	Glu 8700	Gln )	Ala	Lys	Ala
	Gln 8705	Leu	Ala	Gln	Ala	Leu 8710	Gln )	Asp	Ile	Lys	Asp 8715	Leu	Val	Lys	Ala	Lys 8720
15	Glu	Asp	Ala	Lys	Gln 8725	Asp	Val	Asp	Lys	G]n 8730	Val )	Gln	Ala	Leu	Ile 8735	Asp
15	Glu	Ile	Asp	Gln 8740	Asn )	Pro	Asn	Leu	Thr 8745	Asp 5	Lys	Glu	Lys	Gln 8750	Ala )	Leu
20	Lys	Asp	Arg 8755	Ile	Asn	Gln	Ile	Leu 8760	Gln )	Gln	Gly	His	Asn 8765	Asp	Ile	Asn
20	Asn	Ala 8770	Met )	⊤hr	Lys	Glu	Ala 8775	Ile 5	Glu	Gln	Ala	Lys 8780	Glu )	Arg	Leu	Ala
05	Gln 8785	Ala	Leu	Gln	Asp	Ile 8790	Lys )	Asp	Leu	Val	Lys 8795	Ala	Lys	Glu	Asp	Ala 8800
25	Lys	Asn	Asp	Ile	Asp 8805	Lys	Arg	Val	Gln	A]a 8810	Leu )	Ile	Asp	Glu	Ile 8815	Asp
	Gln	Asn	Pro	Asn 8820	Leu )	Тhr	Asp	Lys	Glu 8825	Lys	Gln	Ala	Leu	Lys 8830	Asp )	Arg
30	Ile	Asn	Gln 8835	Ile 5	Leu	Gln	Gln	Gly 8840	His )	Asn	Asp	Ile	Asn 8845	Asn	Ala	Leu
	Thr	Lys 8850	Glu )	Glu	Ile	Glu	Gln 8855	Ala	Lys	Ala	Gln	Leu 8860	Ala )	Gln	Ala	Leu
35	Gln 8865	Asp	Ile	Lys	Asp	Leu 8870	val )	Lys	Ala	Lys	Glu 8875	Asp	Ala	Lys	Asn	Ala 8880
	Ile	Lys	Ala	Leu	Ala 8885	Asn	Ala	Lys	Arg	Asp 8890	Gln )	Ile	Asn	Ser	Asn 8895	Pro
40	Asp	Leu	Thr	Pro 8900	Glu )	Gln	Lys	Ala	Lys 8905	Ala 5	Leu	Lys	Glu	I]e 8910	Asp )	Glu
	Ala	Glu	Lys 8915	Arg	Ala	Leu	Gln	Asn 8920	Val )	Glu	Asn	Ala	Gln 8925	Thr	Ile	Asp
45	Gln	Leu 8930	Asn )	Arg	Gly	Leu	Asn 8935	Leu	Gly	Leu	Asp	Asp 8940	Ile )	Arg	Asn	Thr
	His 8945	Val 5	тгр	Glu	Val	Asp 8950	Glu )	Gln	Pro	Ala	Val 8955	Asn	Glu	Ile	Phe	Glu 8960
50	Ala	Thr	Pro	Glu	Gln 8965	Ile 5	Leu	Val	Asn	Gly 8970	Glu )	Leu	Ile	Val	His 8975	Arg
	Asp	Asp	Ile	Ile 8980	Thr )	Glu	Gln	Asp	Ile 8985	Leu	Ala	His	Ile	Asn 8990	Leu )	Ile
55	Asp	Gln	Leu 8995	Ser	Ala	Glu	Val	Ile 9000	Asp )	Тhr	Pro	Ser	Thr 9003	Ala 5	Thr	Ile

	Ser	Asp 9010	Ser )	Leu	⊤hr	Ala	Lys 9015	Val 5	Glu	Val	Thr	Leu 9020	Leu )	Asp	Gly	Ser
5	Lys 9025	val 5	Ile	Val	Asn	val 9030	Pro )	Val	Lys	Val	va1 9035	G]u	Lys	Glu	Leu	ser 9040
	Val	Val	Lys	Gln	Gln 9045	Ala	Ile	G]u	Ser	Ile 9050	Glu )	Asn	Ala	Ala	Gln 9055	Gln
	Lys	Ile	Asn	Glu 9060	Ile )	Asn	Asn	Ser	Val 9065	Thr	Leu	Thr	Leu	Glu 9070	Gln	Lys
10	Glu	Ala	Ala 9075	Ile	Ala	Glu	Val	Asn 9080	Lys )	Leu	Lys	Gln	Gln 9085	Ala	Ile	Asp
	His	Val 9090	Asn )	Asn	Ala	Pro	Asp 9095	Val	His	Ser	Val	G]u 9100	Glu )	Ile	Gln	Gln
15	Gln 9105	Glu	Gln	Ala	His	Ile 9110	Glu )	G]n	Phe	Asn	Pro 9115	Glu	Gln	Phe	Thr	I]e 9120
	Glu	Gln	Ala	Lys	Ser 9125	Asn	Ala	I]e	Lys	Ser 9130	I]e	Glu	Asp	Ala	I]e 9135	Gln
20	His	Met	Ile	Asp 9140	Glu	Ile	Lys	Ala	Arg 9145	Thr	Asp	Leu	Thr	Asp 9150	Lys	Glu
	Lys	Gln	Glu 9154	Ala	Ile	Ala	Lys	Leu 9160	Asn	Gln	Leu	Lys	Glu 9165	Gln	Ala	Ile
25	Gln	A]a 9170	Ile	Gln	Arg	Ala	G]n 9175	Ser	Ile	Asp	Glu	I]e 9180	Ser	Glu	Gln	Leu
	Glu 9185	Gln	Phe	Lys	Ala	G]n 9190	Met	Lys	Ala	Ala	Asn 9195	Pro	Thr	Ala	Lys	Glu 9200
30	Leu	, Ala	Lys	Arg	Lys 9205	Gln	Glu	Ala	Ile	Ser	Arg	Ile	Lys	Asp	Phe 9215	Ser
	Asn	Glu	Lys	Ile	Asn	, Ser	Ile	Arg	Asn	Ser	, Glu	I]e	Gly	Thr	Ala	Asp
35	Glu	Lys	Gln 9235	Ala	, Ala	Met	Asn	G]n 9240	Ile	, Asn	Glu	I]e	Val 9245	Leu	, Glu	⊤hr
	Ile	Arg	Asp	, Ile	Asn	Asn	Ala	His	, Thr	Leu	Gln	Gln	Val	, Glu	Ala	Ala
40	Leu	Asn	Asn	Gly	Ile	Ala	Arg	, Ile	Ser	Ala	Val	G]n	, Ile	Val	Thr	Ser
	Asp	, Arg	Ala	Lys	Gln	Ser	, Ser	Ser	Thr	Gly	Asn	, Glu	Ser	Asn	Ser	His
45	Leu	Thr	Ile	Gly	Tyr	, Gly	Thr	Ala	Asn	His	, Pro	Phe	Asn	Ser	Ser	, ⊤hr
	Ile	Gly	His	Lys	, Lys	Lys	Leu	Asp	Glu	Asp	Asp	Asp	Ile	Asp	, Pro	Leu
	His	Met	931: Arg	, His	Phe	Ser	Asn	9320 _Asn	) Phe	Gly	Asn	Val	9325 Ile	b Lys	Asn	Ala
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	Gly Asp 50	) Leu	Val	Thr	Тyr	Asp 55	Lys	Glu	Asn	Gly	Met 60	His	Lys	Lys	Val
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	Thr Asi 290	ı⊤rp )	Lys	Gly	Thr	Asn 295	Thr	Lys	Asp	Lys	Тгр 300	Ile	Asp	Arg	Ser
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	Ala	Thr	Gly	Asn	Ile 85	Asn	Ser	Gly	Phe	Val 90	Lys	Pro	Asn	Pro	Asn 95	Asp
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EP 2 510 947 A1

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	Ala	Asp 530	Pro	Phe	Ser	Val	Ala 535	Val	Glu	Met	Asn	Lys 540	Asp	Ala	Leu	Gln
55	G]n 545	Gln	Val	Asn	Ser	G1n 550	Val	Asp	Asn	Ser	His 555	туr	Thr	Тhr	Ala	Ser 560

Ile Ala Glu Tyr Asn Lys Leu Lys Gln Gln Ala Asp Thr Ile Leu Asn 565 570 575 Glu Asp Ala Asn His Val Lys Thr Ala Asn Arg Ala Ser Gln Ala Asp 580 585 590 5 Ile Asp Gly Leu Val Thr Lys Leu Gln Ala Ala Leu Ile Asp Asn Gln 595 600 605 Ala Ala Ile Ala Glu Leu Asp Thr Lys Ala Gln Glu Lys Val Thr Ala 610 615 620 10 Ala Gln Gln Ser Lys Lys Val Thr Gln Asp Glu Val Ala Ala Leu Val 625 630 635 640 Thr Lys Ile Asn Asn Asp Lys Asn Asn Ala Ile Ala Glu Ile Asn Lys 645 650 655 15 Gln Thr Thr Ala Gln Gly Val Thr Thr Glu Lys Asp Asn Gly Ile Ala 660 665 670 Val Leu Glu Gln Asp Val Ile Thr Pro Thr Val Lys Pro Gln Ala Lys 675 680 685 20 Gln Asp Ile Ile Gln Ala Val Thr Thr Arg Lys Gln Gln Ile Lys Lys 690 695 700 Ser Asn Ala Ser Leu Gln Asp Glu Lys Asp Val Ala Asn Asp Lys Ile 705 710 715 720 25 Gly Lys Ile Glu Thr Lys Ala Ile Lys Asp Ile Asp Ala Ala Thr Thr 725 730 735 Asn Ala Gln Val Glu Ala Ile Lys Thr Lys Ala Ile Asn Asp Ile Asn 740 745 750 Gln Thr Thr Pro Ala Thr Thr Ala Lys Ala Ala Ala Leu Glu Glu Phe 755 760 765 30 Asp Glu Val Val Gln Ala Gln Ile Asp Gln Ala Pro Leu Asn Pro Asp 770 775 780 Thr Thr Asn Glu Glu Val Ala Glu Ala Ile Glu Arg Ile Asn Ala Ala 785 790 795 800 35 Lys Val Ser Gly Val Lys Ala Ile Glu Ala Thr Thr Ala Gln Asp 805 810 815 Leu Glu Arg Val Lys Asn Glu Glu Ile Ser Lys Ile Glu Asn Ile Thr 820 825 830 40 Asp Ser Thr Gln Thr Lys Met Asp Ala Tyr Asn Glu Val Lys Gln Ala 835 840 845 Ala Thr Ala Arg Lys Ala Gln Asn Ala Thr Val Ser Asn Ala Thr Asn 850 855 860 45 Glu Glu Val Ala Glu Ala Asp Ala Ala Val Asp Ala Ala Gln Lys Gln 865 870 875 880 865 Gly Leu His Asp Ile Gln Val Val Lys Ser Lys Gln Glu Val Ala Asp 885 890 895 50 Thr Lys Ser Lys Val Leu Asp Lys Ile Asn Ala Ile Gln Thr Gln Ala 900 905 910 Lys Val Lys Pro Ala Ala Asp Thr Glu Val Glu Asn Ala Tyr Asn Thr 915 920 925 55 Arg Lys Gln Glu Ile Gln Asn Ser Asn Ala Ser Thr Thr Glu Glu Lys

	93	0				935					940				
	Gln Al 945	a Ala	Tyr	Тhr	Glu 950	Leu	Asp	⊤hr	Lys	Lys 955	Gln	Glu	Ala	Arg	Thr 960
5	Asn Le	u Asp	Ala	Ala 965	Asn	⊤hr	Asn	Ser	Asp 970	Val	тhr	Тhr	Ala	Lys 975	Asp
	Asn Se	r Ile	Ala 980	Ala	Ile	Asn	Gln	Va] 985	Gln	Ala	Ala	Thr	тhr 990	Lys	Lys
10	Ser As	р Аla 995	Lys	Ala	Glu	Ile	Ala 1000	Gln )	Lys	Ala	Ser	Glu 1005	Arg 5	Lys	Thr
	Ala Il 10	e Glu 10	Ala	Met	Asn	Asp 1015	Ser	⊤hr	Тhr	Glu	Glu 1020	G]n )	Gln	Ala	Ala
15	Lys As 1025	p Lys	Val	Asp	Gln 1030	Ala )	Val	Val	Тhr	Ala 1035	Asn 5	Ala	Asp	Ile	Asp 1040
	Asn Al	a Ala	Ala	Asn 104:	Asn 5	Asp	Val	Asp	Asn 105(	Ala )	Lys	Тhr	Тhr	Asn 1055	Glu 5
20	Ala Th	r Ile	Ala 1060	Ala )	Ile	⊤hr	Pro	Asp 1065	Ala 5	Asn	Val	Lys	Pro 107(	Ala )	Ala
	Lys Gl	n Ala 107	ıle 5	Ala	Asp	Lys	Va] 1080	Gln )	Ala	Gln	Glu	Thr 1085	Ala 5	Ile	Asp
25	Gly As 10	n Asn 90	Gly	Ser	Тhr	⊤hr 1095	Glu 5	Glu	Lys	Ala	A]a 1100	Ala )	Lys	Gln	Gln
	Val Gl 1105	n Thr	Glu	Lys	Thr 111(	⊤hr )	Ala	Asp	Ala	A]a 1115	I]e	Asp	Ala	Ala	ніs 1120
30	Thr As	n Ala	Glu	Val 112	Glu 5	Ala	Ala	Lys	Lys 113(	Ala )	Ala	Ile	Ala	Lys 1135	ile
	Glu Al	a Ile	Gln 1140	Pro )	Ala	⊤hr	Thr	⊤hr 1145	Lys 5	Asp	Asn	Ala	Lys 115(	Glu )	Ala
35	Ile Al	a Thr 115	Lys 5	Ala	Asn	Glu	Arg 116(	Lys )	Тhr	Ala	Ile	A]a 1165	Gln	⊤hr	Gln
	Asp Il 11	е Thr 70	Ala	Glu	Glu	I]e 1175	Ala 5	Ala	Ala	Asn	Ala 1180	Asp )	Val	Asp	Asn
40	Ala Va 1185	l Thr	Gln	Ala	Asn 119(	Ser )	Asn	Ile	Glu	Ala 1195	Ala 5	Asn	Ser	Gln	Asn 1200
	Asp Va	l Asp	Gln	Ala 1205	Lys 5	⊤hr	Тhr	Gly	Glu 121(	Asn )	Ser	I]e	Asp	Gln 1215	val
45	Thr Pr	o Thr	Val 1220	Asn )	Lys	Lys	Ala	⊤hr 1225	Ala 5	Arg	Asn	Glu	I]e 1230	Thr )	Ala
	Ile Le	u Asn 123	Asn 5	Lys	Leu	Gln	Glu 124(	ıle )	Gln	Ala	тhr	Pro 1245	Asp	Ala	⊤hr
50	Asp Gl 12	u Glu 50	Lys	Gln	Ala	Ala 1255	Asp 5	Ala	Glu	Ala	Asn 1260	Thr )	Glu	Asn	Gly
	Lys Al 1265	a Asn	Gln	Ala	I]e 127(	Ser )	Ala	Ala	Thr	⊤hr 1275	Asn 5	Ala	Gln	Val	Asp 1280
	Glu Al	a Lys	Ala	Asn 1285	Ala 5	Glu	Ala	Ala	I]e 129(	Asn )	Ala	Val	Thr	Pro 1295	Lys
55	Val Va	l Lys	Lys 1300	Gln )	Ala	Ala	Lys	Asp 1305	Glu 5	Ile	Asp	Gln	Leu 1310	Gln )	Ala

	Thr Gln Thr Asn Val Ile Asn Asn Asp Gln Asn Ala Thr Thr Glu 1315 1320 1325	Glu
5	Lys Glu Ala Ala Ile Gln Gln Leu Ala Thr Ala Val Thr Asp Ala 1330 1335 1340	Lys
	Asn Asn Ile Thr Ala Ala Thr Asp Asp Asn Gly Val Asp Gln Ala 1345 1350 1355	Lys 1360
10	Asp Ala Gly Lys Asn Ser Ile Gln Ser Thr Gln Pro Ala Thr Ala 1365 1370 1375	Val
	Lys Ser Asn Ala Lys Asn Asp Val Asp Gln Ala Val Thr Thr Gln 1380 1385 1390	Asn
15	Gln Ala Ile Asp Asn Thr Thr Gly Ala Thr Thr Glu Glu Lys Asn 1395 1400 1405	Ala
15	Ala Lys Asp Leu Val Leu Lys Ala Lys Glu Lys Ala Tyr Gln Asp 1410 1415 1420	Ile
20	Leu Asn Ala Gln Thr Thr Asn Asp Val Thr Gln Ile Lys Asp Gln 1425 1430 1435	Ala 1440
20	Val Ala Asp Ile Gln Gly Ile Thr Ala Asp Thr Thr Ile Lys Asp 1445 1450 1450	val ;
25	Ala Lys Asp Glu Leu Ala Thr Lys Ala Asn Glu Gln Lys Ala Leu 1460 1465 1470	Ile
20	Ala Gln Thr Ala Asp Ala Thr Thr Glu Glu Lys Glu Gln Ala Asn 1475 1480 1485	Gln
30	Gln Val Asp Ala Gln Leu Thr Gln Gly Asn Gln Asn Ile Glu Asn 1490 1495 1500	Ala
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25	Ile Asp Pro Ile Gln Ala Ser Thr Asp Val Lys Thr Asn Ala Arg 1525 1530 1535	Ala ;
35	Glu Leu Leu Thr Glu Met Gln Asn Lys Ile Thr Glu Ile Leu Asn 1540 1545 1550	Asn
10	Asn Glu Thr Thr Asn Glu Glu Lys Gly Asn Asp Ile Gly Pro Val 1555 1560 1565	Arg
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	Gln Ala Ala Asp Lys Lys Thr Gln Ile Glu Gln Thr Pro Asn 1620 1625 1630	Ala
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	Asn Gln Ala Lys Thr Asn Val Asp Gln Ser Ser Thr Asn Glu Tyr 1650 1655 1660	Val
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	Phe	Ser	Glu	Туr	Lys 1685	Lys	Asp	Ala	Leu	Ala 1690	Lys )	Ile	Glu	Asp	Ala 1695	Tyr
5	Asn	Ala	Lys	Val 1700	Asn )	Glu	Ala	Asp	Asn 1705	Ser	Asn	Ala	Ser	Thr 171(	Ser )	Ser
0	Glu	Ile	Ala 1715	Glu	Ala	Lys	Gln	Lys 1720	Leu )	Ala	Glu	Leu	Lys 1725	Gln	Thr	Ala
	Asp	Gln 1730	Asn )	Val	Asn	Gln	Ala 1735	Thr 5	Ser	Lys	Asp	Asp 1740	I]e )	Glu	Val	Gln
10	I]e 1745	His 5	Asn	Asp	Leu	Asp 1750	Asn )	Ile	Asn	Asp	Туг 1755	Thr	I]e	Pro	⊤hr	Gly 1760
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15	Lys	Asn	Asn	Ile 1780	Ser )	Ala	Asp	Thr	Asn 1785	Ala	⊤hr	Gln	Asp	Glu 1790	Lys )	Gln
	Gln	Ala	I]e 1795	Lys	Gln	Val	Asp	Gln 1800	Asn )	Val	Gln	Thr	A]a 1805	Leu	Glu	Ser
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	Gly 1825	Lys	Ala	Ala	Ile	Asp 1830	Ala )	Ile	Gln	Val	Asp 1835	Ala	Thr	Val	Lys	Pro 1840
25	Lys	Ala	Asn	Gln	Ala 1845	Ile	Glu	Val	Lys	Ala 1850	Glu )	Asp	Thr	Lys	Glu 1855	Ser
	Ile	Asp	Gln	Ser 1860	Asp )	Gln	Leu	Thr	Ala 1865	Glu	Glu	Lys	Thr	Glu 1870	Ala )	Leu
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	Ala	Thr 1890	Thr )	Thr	Ala	Glu	Va] 1895	Glu	Lys	Ala	Lys	Ala 1900	G]n )	Gly	Leu	Glu
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	Glu	Glu	Leu	Glu	Thr 1925	Ala	Leu	Asp	Gln	Ile 1930	Glu )	Ala	G∣y	val	Asn 1935	val
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	Glu	Asp	I]e 1955	Leu	Ser	Lys	Ala	Thr 1960	G]u )	Asp	I]e	Ser	Asp 1965	Gln	Thr	Thr
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	Ala 1985	Gln	Arg	Ile	Asn	Pro 1990	Glu	Val	Lys	Lys	Asn 1995	Ala	Leu	Glu	Ala	I]e 2000
50	Arg	Glu	Val	Val	Asn 2005	Lys	Gln	Ile	Glu	I]e 2010	I]e	Lys	Asn	Ala	Asp 2015	Ala
	Asp	Ala	Ser	Ala 2020	Lys )	Glu	Ile	Ala	Arg 2025	Thr	Asp	Leu	G∣y	Arg 2030	Туr )	Phe
55	Asp	Arg	Phe 2035	Ala	Asp	Lys	Leu	Asp 2040	Lys	Thr	Gln	Thr	Asn 2045	Ala	Glu	Val
	Ala	Glu	Leu	Gln	Asn	Val	⊤hr	Ile	Pro	Ala	Ile	Glu	Ala	Ile	Val	Pro

		2050	)				2055	5				2060	)			
	G]n 2065	Asn	Asp	Pro	Asp	Ala 2070	Asn )	Asp	⊤hr	Asn	Asn 2075	Gly	I]e	Asp	Asn	Asn 2080
5	Asp	Ala	Thr	Ala	Asn 2085	Ser	Asn	Ala	Asn	Ala 2090	⊤hr )	Pro	Glu	Asn	Thr 2095	Gly Б
	Gln	Pro	Asn	Val 2100	Ser	Glu	Thr	Thr	Ala 2105	Asn 5	Gly	Lys	Ala	Asp 2110	Ala )	Ser
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	Thr	Ser 2130	Ala	Thr	Asp	Asp	Ala 2135	Asn	Asp	Lys	Pro	Gln 2140	Ala )	Asn	Asn	Asn
15	Ser 2145	Ser	Val	Asp	Ala	Ser 2150	⊤hr )	Asn	Ser	Pro	⊤hr 2155	Met	Asp	Asn	Asp	Va] 2160
	Thr	Ser	Lys	Pro	Glu 2165	Val 5	Glu	Ser	⊤hr	Asn 2170	Asn )	Gly	Thr	Thr	Asp 2175	Lys
20	Pro	Val	Thr	Glu 2180	Thr )	Asp	Asn	Ala	⊤hr 2185	Pro 5	Ala	Glu	Ser	Thr 2190	Thr )	Asn
	Asn	Asn	Ser 2195	Thr	Тhr	Тhr	АТа	Thr 2200	Asn )	Glu	Asn	Ala	Pro 2205	Thr	Gly	Ser
25	Thr	Ala 2210	Thr	Ala	Pro	Thr	⊤hr 2215	Ala 5	Ser	Thr	Glu	Ala 2220	Ala )	Ser	Ser	Ala
	Asp 2225	ser	Lys	Asp	Asn	Ala 2230	Ser )	Val	Asn	Asp	Ser 2235	Lys	G]n	Asn	Ala	GTU 2240
30	Val	Asn	Asn	Ser	Ala 2245	Glu 5	Ser	Gln	Ser	Thr 2250	Asn )	Asp	Lys	Val	Ala 2255	Gln
	Pro	Lys	Ser	Glu 2260	Asn	Lys	АТа	Lys	Ala 2265	Glu 5	Lys	Asp	Gly	Ser 2270	Asp )	Ser
35	Thr	Asn	G]n 2275	Ser	Met	Val	Glu	Ser 2280	⊤hr )	Thr	Glu	Thr	Leu 2285	Pro	Ser	Ala
	Asp	Ile 2290	Thr	Glu	Pro	Asn	Va] 2295	Pro 5	Ser	Asn	⊤hr	Ser 2300	Lys )	Asp	Lys	Glu
40	Glu 2305	Ser	Thr	Thr	Asn	Gln 2310	⊤hr )	Asp	Ala	Gly	Gln 2315	Leu	Lys	Ser	Glu	Thr 2320
	Asn	Val	Ala	Ser	Asn 2325	Glu 5	ΑΊа	Asp	Lys	Ser 2330	Pro )	Ser	Lys	Ala	Asp 2335	Thr 5
45	Glu	Val	Ser	Asn 2340	Lys	Pro	Ser	Thr	Ser 2345	Ala 5	Ser	Ser	Glu	Ala 2350	Lys )	Glu
	Lys	Met	Thr 2355	Ser	Thr	Asn	Val	Ser 2360	Gln )	Lys	Asp	Asp	⊤hr 2365	Ala	Thr	Ala
50	Asp	Thr 2370	Asn	Asp	Thr	Gln	Lys 2375	Ser	Val	Gly	Ser	Ala 2380	Ala )	Asn	Asn	Lys
	Ala 2385	Thr	Gln	Asn	Asp	Gly 2390	Ala )	Asn	Ala	Ser	Pro 2395	Ala	Thr	Val	Ser	Asn 2400
	Gly	Ser	Asn	Ser	Ala 2405	Asn 5	Gln	Asp	Met	Leu 2410	Asn )	Val	Thr	Asn	Thr 2415	Asp
00	Asp	His	Gln	Ala 2420	Lys )	Thr	Lys	Ser	Ala 2425	Gln 5	Gln	Gly	Lys	Va] 2430	Asn )	Lys

	Ala	Lys	Gln 2435	Gln	Ala	Lys	Thr	Leu 2440	Pro )	Asp	Thr	Gly	Met 2445	Ser	His	Asn
5	Asp	Asp 2450	Leu )	Pro	Туr	Ala	Glu 2455	Leu	Ala	Leu	Gly	Ala 2460	Gly )	Met	Ala	Phe
	Leu 2465	Ile	Arg	Arg	Phe	Thr 2470	Lys )	Lys	Asp	Gln	Gln 2475	Thr	Glu	Glu		
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	Gly	Ile	Phe	Ser 20	Thr	Leu	Ile	Gly	Thr 25	Val	Leu	Leu	Leu	Ser 30	Asn	Pro
20	Asn	Gly	Ala 35	Gln	Ala	Leu	Thr	Thr 40	Asp	Asn	Asn	Val	G]n 45	Ser	Asp	Thr
	Asn	G]n 50	Ala	Thr	Pro	Val	Asn 55	Ser	Gln	Asp	Lys	Asp 60	Val	Ala	Asn	Asn
25	Arg 65	Gly	Leu	Ala	Asn	Ser 70	Ala	Gln	Asn	Thr	Pro 75	Asn	Gln	Ser	Ala	тhr 80
	Thr	Asn	Gln	Ala	Thr 85	Asn	Gln	Ala	Leu	Va] 90	Asn	His	Asn	Asn	Gly 95	Ser
30	Ile	Val	Asn	Gln 100	Ala	Thr	Pro	Thr	Ser 105	Val	Gln	Ser	Ser	Thr 110	Pro	Ser
	Ala	Gln	Asn 115	Asn	Asn	His	Thr	Asp 120	Gly	Asn	Thr	Thr	Ala 125	Thr	Glu	Thr
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	Asn 145	Val	Pro	Thr	Lys	⊤hr 150	Asn	Glu	Asn	Gly	Ser 155	Gly	Gly	His	Leu	тhr 160
40	Leu	Lys	Glu	Ile	Gln 165	Glu	Asp	Val	Arg	His 170	Ser	Ser	Asn	Lys	Pro 175	Glu
+0	Leu	Val	Ala	Ile 180	Ala	Glu	Pro	Ala	Ser 185	Asn	Arg	Pro	Lys	Lys 190	Arg	Ser
45	Arg	Arg	Ala 195	Ala	Pro	Ala	Asp	Pro 200	Asn	Ala	Thr	Pro	Ala 205	Asp	Pro	Ala
+0	Ala	Ala 210	Ala	Val	Gly	Asn	Gly 215	Gly	Ala	Pro	Val	Ala 220	Ile	Thr	Ala	Pro
50	Tyr 225	Thr	Pro	Thr	Thr	Asp 230	Pro	Asn	Ala	Asn	Asn 235	Ala	Gly	Gln	Asn	Ala 240
20	Pro	Asn	Glu	Val	Leu 245	Ser	Phe	Asp	Asp	Asn 250	Gly	Ile	Arg	Pro	Ser 255	Thr
	Asn	Arg	Ser	Va1 260	Pro	Thr	Val	Asn	Va1 265	Val	Asn	Asn	Leu	Pro 270	Gly	Phe
55	Thr	Leu	11e 275	Asn	Gly	Gly	Lys	Va1 280	Gly	Val	Phe	Ser	His 285	Ala	Met	Val

Arg Thr Ser Met Phe Asp Ser Gly Asp Asn Lys Asn Tyr Gln Ala Gln 290 295 300 Gly Asn Val Ile Ala ∟eu Gly Arg Ile His Gly Thr Asp Thr Asn Asp 305 310 315 320 5 His Gly Asp Phe Asn Gly Ile Glu Lys Ala Leu Thr Val Asn Pro Asn 325 330 335 Ser Glu Leu Ile Phe Glu Phe Asn Thr Met Thr Thr Lys Asn Gly Gln 340 345 350 10 Gly Ala Thr Asn Val Ile Ile Lys Asn Ala Asp Thr Asn Asp Thr Ile 355 360 365 Ala Glu Lys Thr Val Glu Gly Gly Pro Thr Leu Arg Leu Phe Lys Val 370 375 380 15 Pro Asp Asn Val Arg Asn Leu Lys Ile Gln Phe Val Pro Lys Asn Asp 385 390 395 400 Ala Ile Thr Asp Ala Arg Gly Ile Tyr Gln Leu Lys Asp Gly Tyr Lys 405 410 415 20 Tyr Tyr Ser Phe Val Asp Ser Ile Gly Leu His Ser Gly Ser His Val 420 425 430 Phe Val Glu Arg Arg Thr Met Asp Pro Thr Ala Thr Asn Asn Lys Glu 435 440 445 25 Phe Thr Val Thr Thr Ser Leu Lys Asn Asn Gly Asn Ser Gly Ala Ser 450 455 460 Leu Asp Thr Asn Asp Phe Val Tyr Gln Val Gln Leu Pro Glu Gly Val 465 470 475 480 465 Glu Tyr Val Asn Asn Ser Leu Thr Lys Asp Phe Pro Ser Asn Asn Ser 485 490 495 30 Gly Val Asp Val Asn Asp Met Asn Val Thr Tyr Asp Ala Ala Asn Arg 500 505 510 Val Ile Thr Ile Lys Ser Thr Gly Gly Gly Thr Ala Asn Ser Pro Ala 515 520 525 35 Arg Leu Met Pro Asp Lys Ile Leu Asp Leu Arg Tyr Lys Leu Arg Val 530 535 540 Asn Asn Val Pro Thr Pro Arg Thr Val Thr Phe Asn Glu Thr Leu Thr 545 550 555 560 40 Tyr Lys Thr Tyr Thr Gln Asp Phe Ile Asn Ser Ala Ala Glu Ser His 565 570 575 Thr Val Ser Thr Asn Pro Tyr Thr Ile Asp Ile Ile Met Asn Lys Asp 580 585 590 45 Ala Leu Gln Ala Glu Val Asp Arg Arg Ile Gln Gln Ala Asp Tyr Thr 595 600 605 Phe Ala Ser Leu Asp Ile Phe Asn Gly Leu Lys Arg Arg Ala Gln Thr 610 615 620 50 Ile Leu Asp Glu Asn Arg Asn Asn Val Pro Leu Asn Lys Arg Val Ser625630635640 625 Gln Ala Tyr Ile Asp Ser Leu Thr Asn Gln Met Gln His Thr Leu Ile 645 650 655 55 Arg Ser Val Asp Ala Glu Asn Ala Val Asn Lys Lys Val Asp Gln Met

				660					665					670		
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5	Ala	Ala 690	Ile	Gln	Val	Ile	Glu 695	Glu	His	Lys	Asn	Glu 700	I]e	Ile	Gly	Asn
	11e 705	Gly	Asp	Gln	Thr	Thr 710	Asp	Asp	G∣y	Val	⊤hr 715	Arg	I]e	Lys	Asp	G]n 720
10	Gly	Ile	Gln	Thr	Leu 725	Ser	Gly	Asp	⊤hr	Ala 730	⊤hr	Pro	Val	Val	Lys 735	Pro
	Asn	Ala	Lys	Lys 740	Ala	Ile	Arg	Asp	Lys 745	Ala	⊤hr	Lys	Gln	Arg 750	Glu	Ile
15	Ile	Asn	Ala 755	Thr	Pro	Asp	Ala	Thr 760	Glu	Asp	Glu	Ile	G]n 765	Asp	Ala	Leu
	Asn	G]n 770	Leu	Ala	Thr	Asp	Glu 775	Thr	Asp	Ala	Ile	Asp 780	Asn	Val	⊤hr	Asn
20	Ala 785	Thr	Thr	Asn	Ala	Asp 790	Val	Glu	⊤hr	Ala	Lys 795	Asn	Asn	Gly	Ile	Asn 800
	⊤hr	Ile	Gly	Ala	Va1 805	Val	Pro	Gln	Val	тhr 810	His	Lys	Lys	Ala	Ala 815	Arg
25	Asp	Ala	Ile	Asn 820	Gln	Ala	⊤hr	Ala	⊤hr 825	Lys	Arg	Gln	G]n	Ile 830	Asn	Ser
	Asn	Arg	Glu 835	Ala	Тhr	Gln	Glu	Glu 840	Lys	Asn	Ala	Ala	Leu 845	Asn	Glu	Leu
30	тhr	Gln 850	Ala	Тhr	Asn	His	Ala 855	Leu	Glu	Gln	Ile	Asn 860	G]n	Ala	Тhr	Thr
	Asn 865	Ala	Asn	Val	Asp	Asn 870	Ala	Lys	Gly	Asp	Gly 875	Leu	Asn	Ala	Ile	Asn 880
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	Ser	Ніs	Asp	Ala 900	Gln	Gln	His	Ile	Ala 905	Glu	Ile	Asn	Ala	Asn 910	Pro	Asp
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	Val	⊤hr 930	Ala	Ala	Asn	Тhr	Asn 935	Ile	Leu	Asn	Ala	Asn 940	Thr	Asn	Ala	Asp
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	Pro	Ala	Thr	Lys	Val 965	Lys	⊤hr	Asp	Ala	Lys 970	Asn	Ala	I]e	Asp	Lys 975	Ser
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	Glu	Glu	Gln 995	Gln	Ala	Ala	Gln	Gln 1000	Leu )	Leu	Asp	Gln	Ala 1005	Val 5	Ala	Thr
FF	Ala	Lys 1010	Gln )	Asn	Ile	Asn	Ala 1015	Ala 5	Asp	Thr	Asn	Gln 1020	Glu )	Val	Ala	Gln
00	Ala 1025	Lys	Asp	Gln	Gly	Thr 1030	Gln )	Asn	Ile	Val	Val 1035	Ile	Gln	Pro	Ala	Thr 1040

	Gln	Val	Lys	⊤hr	Asp 1045	Thr 5	Arg	Asn	Val	Val 1050	Asn )	Asp	Lys	Ala	Arg 1055	Glu
5	Ala	Ile	Thr	Asn 1060	ıle	Asn	Ala	Thr	Thr 1065	Gly 5	Ala	Thr	Arg	Glu 1070	Glu	Lys
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	Asn Glu 65	Thr	Ser	Lys	Va] 70	Pro	Ala	Asn	Phe	Va] 75	Lys	Leu	Asn	Asp	Ile 80
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	Ala	Тhr	⊤yr	Thr 180	Тhr	Pro	Arg	Тyr	Glu 185	Lys	Ala	Туr	Glu	Ile 190	Pro	Lys
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193

Tyr Lys Met Asp Asp Gly Lys Thr Val Asp Ile Pro Lys Asp Pro Lys

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EP 2 510 947 A1

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Ala Ser Arg Ser

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	Glu	Ser	Va] 595	Val	Arg	Ile	Ile	Phe 600	Pro	Glu	Val	Ser	Ala 605	His	Ile	Glu
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	Arg	Val	Arg 195	Asn	Leu	Glu	Ser	G]n 200	Lys	Asp	Asp	Leu	I]e 205	Thr	Asp	Val
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EP 2 510 947 A1

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535

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	Phe	Ala	His	туг	ніs 1045	Val 5	Arg	Asn	Ile	Thr 1050	Ala )	Phe	Asn	Lys	Lys 105	Ala 5
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	Ala	Asp	Leu 1075	Met	Met	Met	Ala	Pro 1080	Gln )	Glu	Val	Glu	Gln 1085	Ser	Ile	Ala
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	Gln Gln 1185	Arg Glu	Pro As 1	sp ⊤yr 190	Leu Phe	Glu Glu 1195	Lys Glu	Leu Leu Lys 120	; )0
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30	Ala Pro 50	) Tyr Ser	Gly Va	al ⊤hr 55	Trp Met	Gly Ala	Gly Thr 60	Gly Phe Val	ł
	Val Gly 65	′Asn His	Thr I 7(	le Ile O	Thr Asn	Lys His 75	Val Thr	Tyr His Met 80	-
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	Gly Gly	Gly Leu 100	Tyr Ly	ys Val	Thr Lys 105	Ile Val	Asp Tyr	Pro Gly Lys 110	;
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	Gly Arg 130	Lys Phe	Lys As	sp Phe 135	Thr Ser	Lys Phe	Asn Ile 140	Ala Ser Glu	1
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	Gly Asn	Lys Leu	Gln Me 165 -	et ⊤yr	Glu Ser	Thr Gly 170	Lys Val	Leu Ser Val 175	
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	Gly Ser	Pro Ile 195	Leu As	sn Ser	Lys His 200	Glu Ala	Ile Gly 205	Val Ile Tyr	•
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					165					170					175	
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	Ser	Тhr	Lys	Glu	Asn 245	Phe	тhr	Lys	Asp	Asn 250	тhr	Val	Asp	Asp	Va] 255	Ile
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	Val 145	Leu	Lys	Asp	Phe	туг 150	туr	Ile	Ser	Lys	Glu 155	Asp	Ile	Ser	Leu	Lys 160
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#### EP 2 510 947 A1

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5	Leu	Ala 50	Met	I]e	Asn	Ile	Thr 55	Ala	Gly	Ala	Asn	Ser 60	Ala	Thr	Thr	Gln
	Ala 65	Ala	Asn	Тhr	Arg	G]n 70	Glu	Arg	Тhr	Pro	Lys 75	Leu	Glu	Lys	Ala	Pro 80
10	Asn	Thr	Asn	Glu	Glu 85	Lys	Thr	Ser	Ala	Ser 90	Lys	Ile	Glu	Lys	Ile 95	Ser
	Gln	Pro	Lys	G]n 100	Glu	Glu	Gln	Lys	Thr 105	Leu	Asn	Ile	Ser	Ala 110	Thr	Pro
15	Ala	Pro	Lys 115	Gln	Glu	Gln	Ser	G]n 120	Thr	Thr	Thr	Glu	Ser 125	Тhr	Thr	Pro
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	⊤rp	Тhr	Thr 195	Val	Arg	Phe	Met	Asn 200	Val	Ile	Pro	Asn	Arg 205	Phe	Ile	Туr
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	Val	Asn	His	Lys 260	Val	Glu	Leu	Ser	Ile 265	Thr	Lys	Lys	Asp	Asn 270	Gln	Gly
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	Ser	Leu 290	Lys	Glu	Leu	Asp	Phe 295	Lys	Leu	Arg	Lys	G]n 300	Leu	Ile	Glu	Lys
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10	Lys	Ile 50	Glu	Ala	Pro	Gln	Ser 55	Lys	Pro	Asn	Ala	тhr 60	Thr	Pro	Pro	Ser
	Thr 65	Lys	Val	Glu	Ala	Pro 70	Gln	Gln	⊤hr	Ala	Asn 75	Ala	Thr	Thr	Pro	Pro 80
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15	Ala	Arg	Lys	Asn 100	Pro	Gly	Leu	Asp	I]e 105	Phe	Val	Val	Lys	Glu 110	Ala	Glu
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95	туr	Lys	Glu	Glu	I]e 165	Ser	Leu	Lys	Glu	Leu 170	Asp	Phe	Lys	Leu	Arg 175	Gln
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	Lys	Pro 50	Ser	Ile	Glu	Leu	Lys 55	Asn	Leu	Asp	Gly	Leu 60	туг	Arg	Gln	Lys
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	Glu 145	Lys	Ser	Lys	Asp	Ser 150	Lys	Phe	Lys	Ile	Thr 155	Lys	Glu	Glu	Ile	Ser 160
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30	Lys	Gln	Glu 35	Arg	Val	Gln	His	Leu 40	Тyr	Asp	Ile	Lys	Asp 45	Leu	His	Arg
	Tyr	туr 50	Ser	Ser	Glu	Ser	Phe 55	Glu	Phe	Ser	Asn	Ile 60	Ser	Gly	Lys	Val
35	Glu 65	Asn	туг	Asn	Gly	Ser 70	Asn	Val	Val	Arg	Phe 75	Asn	Gln	Gไน	Asn	Gln 80
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15	Lys Tyr	Glu Lys 35	Met Asn	Arg Leu 40	Tyr Asp Thr	Asn Lys Leu 45	His Gln
	Tyr Tyr 50	Ser Gly	Pro Ser	Tyr Glu 55	Leu Thr Asn	Val Ser Gly 60	Gln Ser
20	Gln Gly 65	Tyr Tyr	Asp Ser 70	Asn Val	Leu Leu Phe 75	Asn Gln Gln	Asn Gln 80
	Lys Phe	Gln Val	Phe Leu 85	Leu Gly	Lys Asp Glu 90	Asn Lys Tyr	Lys Glu 95
25	Lys Thr	ніs Gly 100	Leu Asp	Val Phe	Ala Val Pro 105	Glu Leu Val 110	Asp Leu
	Asp Gly	Arg Ile 115	Phe Ser	val ser 120	Gly Val Thr	Lys Lys Asn 125	Val Lys
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	Asp Asp 145	Lys Asp	Gly Phe 150	Ser Ile	Asp Glu Phe 155	Phe Phe Ile	Gln Lys 160
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	Ile Lys	Lys Tyr 180	Lys Leu	Tyr Glu	Gly Ser Ala 185	Asp Lys Gly 190	Arg Ile
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	туг	Tyr 50	Ser	Glu	Glu	Ser	Phe 55	Glu	Pro	Thr	Asn	Ile 60	Ser	Val	Lys	Ser
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	Ala	Phe	Lys	Val	Phe 85	Leu	Leu	Gly	Asp	Asp 90	Lys	Asn	Lys	туr	Lys 95	Glu
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299

EP 2 510 947 A1

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	Ser 145	Asn	Asp	Glu	⊤hr	Leu 150	Val	Asp	Asn	Asn	Ser 155	Asn	Ser	Asn	Asn	Glu 160
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	⊤hr	Ile	Ala 275	Тhr	Ala	Lys	His	Asp 280	Тhr	Ala	Asn	Asn	Leu 285	Ile	Тhr	Туr
55	⊤hr	Phe 290	Thr	Asp	⊤yr	Val	Asp 295	Arg	Phe	Asn	Ser	Va] 300	Gln	Met	Gly	I]e
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	Asp Val	Glu Phe A	Asn Val 325	Thr Ile Gl	y Asn Thr Thr 330	Thr Lys Thr T 335	hr
5	Ala Asn	Ile Gln T 340	Tyr Pro	Asp Tyr Va 34	l Val Asn Glu 5	Lys Asn Ser I 350	le
	Gly Ser	Ala Phe T 355	Thr Glu	Thr Val Se 360	er His Val Gly	Asn Lys Glu A 365	sn
10	Pro Gly 370	⊤yr Tyr L	Lys Gln	Thr Ile Ty 375	r Val Asn Pro 380	Ser Glu Asn S	er
	Leu Thr 385	Asn Ala L	Lys Leu 390	Lys Val Gl	n Ala Tyr His 395	Ser Ser Tyr P 4	ro 00
15	Asn Asn	Ile Gly G	Gln Ile 405	Asn Lys As	p Val Thr Asp 410	Ile Lys Ile T 415	yr
	Gln Val	Pro Lys 0 420	Gly Tyr	Thr Leu As 42	n Lys Gly Tyr 5	Asp Val Asn T 430	hr
20	Lys Glu	Leu Thr A 435	Asp Val	Thr Asn Gl 440	n Tyr Leu Gln	Lys Ile Thr T 445	yr
	Gly Asp 450	Asn Asn S	Ser Ala	val Ile As 455	p Phe Gly Asn 460	Ala Asp Ser A	la
25	туr Val 465	val Met N	val Asn 470	Thr Lys Ph	ie Gln Tyr Thr 475	Asn Ser Glu S 4	er 80
	Pro Thr	Leu Val G 4	Gln Met 485	Ala Thr Le	u Ser Ser Thr 490	Gly Asn Lys S 495	er
30	val ser	⊤hr Gly A 500	Asn Ala	Leu Gly Ph 50	ie ⊤hr Asn Asn 95	Gln Ser Gly G 510	ily
	Ala Gly	Gln Glu V 515	val Tyr	Lys Ile Gl 520	y Asn Tyr Val	Trp Glu Asp T 525	hr
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	Gln Val	Gln Lys A 35	Asp Gly	Ser Ser Gl 40	u Lys Ser His	Met Asp Asp T 45	yr
50	Met Gln 50	His Pro (	Gly Lys	Val Ile Ly 55	rs Gln Asn Asn 60	Lys Tyr Tyr P	he
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	Asn Ala	Asn Asn G 8	Gln Glu 85	Leu Ala Th	ır Thr Val Val 90	Asn Asp Asn L 95	ys
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	Ser Leu	Thr Thr 115	Lys Val	His Ile 120	val val	Pro Gln	Ile Asn 125	Tyr Asn
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	Gly Met	Leu Lys 35	Lys Val	Phe Tyr 40	Ser Phe	Ile Asp	Asp Lys 45	Asn His
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C C	Gly	Met	His 35	Lys	Lys	Val	Phe	туг 40	Ser	Phe	Ile	Asp	Asp 45	Lys	Asn	His
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	Met	Pro	Asn	Leu 20	Asn	Ala	Asp	G]n	Arg 25	Asn	Gly	Phe	Ile	G]n 30	Ser	Leu
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	Leu	Asn 50	Asp	Ser	Gln	Ala	Pro 55	Lys	Ala	Asp	Ala	G]n 60	Gln	Asn	Asn	Phe
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	Ser	Gln	Ala 115	Pro	Lys	Ala	Asp	Asn 120	Asn	Phe	Asn	Lys	Glu 125	Gln	Gln	Asn
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	Asn 145	Gly	Phe	I]e	Gln	Ser 150	Leu	Lys	Asp	Asp	Pro 155	Ser	Gln	Ser	Ala	Asn 160
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	Glu	Gln	Gln	Asn	A]a 245	Phe	туr	Glu	Ile	Leu 250	His	Leu	Pro	Asn	Leu 255	⊤hr
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Ala

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20	Thr 65	Thr	Glu	Pro	Ala	Ser 70	Thr	Asn	Glu	⊤hr	Pro 75	Gln	Pro	Thr	Ala	Ile 80
	Lys	Asn	Gln	Ala	⊤hr 85	Ala	Ala	Lys	Met	Gln 90	Asp	Gln	тhr	Val	Pro 95	Gln
25	Glu	Ala	Asn	Ser 100	Gln	Val	Asp	Asn	Lys 105	⊤hr	тhr	Asn	Asp	A]a 110	Asn	Ser
	Ile	Ala	⊤hr 115	Asn	Ser	Glu	Leu	Lys 120	Asn	Ser	Gln	тhr	Leu 125	Asp	Leu	Pro
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	Ser 145	Val	Arg	Thr	Arg	A]a 150	Val	Arg	Ser	Leu	A]a 155	Val	Ala	Glu	Pro	Va] 160
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	Ala	Ser	Asn	Phe 180	Lys	Leu	Glu	Lys	Thr 185	⊤hr	Phe	Asp	Pro	Asn 190	Gln	Ser
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	Ser	G]y 210	Asp	туг	Phe	тhr	A]a 215	Lys	Leu	Pro	Asp	Ser 220	Leu	Тhr	Gly	Asn
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EP 2 510 947 A1

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EP 2 510 947 A1

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#### Claims

1. An immunogenic composition comprising sta006 antigen for use in a method for raising an immune response in a mammal, wherein the sta006 antigen: (i) can elicit an antibody that recognises SEQ ID NO: 42; and (ii) comprises an amino acid sequence: (a) having 50% or more identity to SEQ ID NO: 42; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 42, wherein 'n' is 7 or more.

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- 2. The composition of claim 1, further comprising an adjuvant.
- 3. An immunogenic composition comprising a sta006 antigen and an adjuvant, wherein the sta006 antigen: (i) can elicit an antibody that recognises SEQ ID NO: 42; and (ii) comprises an amino acid sequence: (a) having 50% or more identity to SEQ ID NO: 42; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ

ID NO: 42, wherein 'n' is 7 or more.

- 4. The composition of claim 3 for use in a method for raising an immune response in a mammal.
- 5. The composition of any preceding claim, wherein the sta006 antigen comprises an amino acid sequence having 60%, 70%, 80%, 90% or more identity to SEQ ID NO: 42.
  - **6.** The composition of any preceding claim, wherein the sta006 antigen comprises an amino acid sequence having 90% or more identity to SEQ ID NO: 246.

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- 7. The composition of any preceding claim, wherein the sta006 antigen comprises an amino acid having 99% or more identity to SEQ ID NO: 248.
- 8. The composition of any of claims 2-7, wherein the adjuvant is aluminium hydroxide.
- 9. The composition of any preceding claim, wherein the composition includes a histidine buffer or a phosphate buffer.
- **10.** The composition of any preceding claim, further comprising one or more conjugates of a *S. aureus* exopolysaccharide and a carrier protein.

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- **11.** The composition of any of claims 1-9, further comprising one or more conjugates of a *S.aureus* capsular polysaccharide and a carrier protein.
- **12.** The composition of any preceding claim, in lyophilized form.

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- 13. The composition of any of claims 1-11, in aqueous form.
- **14.** A method for preparing the composition of claim 13, by reconstituting the composition of claim 12 with aqueous material.

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**15.** A pharmaceutical composition comprising the composition of any preceding claim, and a pharmaceutical carrier and/or an excipient.

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FIGURE 2








FIGURE 8







FIGURE 9A













# EUROPEAN SEARCH REPORT

Application Number EP 12 17 5868

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