IMMUNOGENIC COMPOSITIONS OF *STAPHYLOCOCCUS AUREUS* ANTIGENS

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the priority benefit of U.S. Provisional Patent Application No. 61/219,134, filed June 22, 2009, the entirety of which is hereby incorporated by reference herein.

FIELD OF THE INVENTION

[0002] The present invention relates to immunogenic compositions, comprising polypeptides and capsular polysaccharides isolated from *Staphylococcus aureus*. In addition, the invention relates to methods of inducing an immune response in subjects against *Staphylococcus aureus* using immunogenic compositions of the *Staphylococcus aureus* polypeptides, and capsular polysaccharides. The resulting antibodies can also be used to treat or prevent *Staphylococcus aureus* infection via passive immunotherapy.

BACKGROUND OF THE INVENTION

[0003] Humans are the natural reservoirs for *Staphylococcus aureus* (*S. aureus*). Healthy individuals can be colonized by *S. aureus* on the skin, in the nares and the throat either persistently (10-35%), intermittently (20-75%) or be in a non-carriage state (5-70%) with no associated disease. See Vandenbergh et al., *J. Clin. Micro.* 37:3133-3140 (1999). Disease subsequently occurs when individuals become immunocompromised due to breaches in immune barriers, such as during surgery,

placement of indwelling catheters or other devices, trauma, or wounds. The resulting *S. aureus* infection can cause a wide range of different diseases that range from mild skin infections to endocarditis, osteomyelitis, bacteremia, sepsis, and other forms of disease with accompanying high mortality rates. The large human reservoir enhances opportunity for evolution and spread of adapted pathogenic clonal types.

[0004] Invasive staphylococcal infections from the Gram positive cocci *S. aureus* and *S. epidermidis* are of particular concern because they are an increasing public health problem worldwide. Specifically, *S. aureus* is responsible for the majority of hospital-acquired (nosocomial) infections and its prevalence in community-onset infections is increasing. For example, the incidence of invasive methicillin-resistant *S. aureus* (MRSA) was estimated at 31.8 per 100,000 persons, including 18,650 deaths in the United States in 2005. See Klevens R.M. et al., *JAMA*, 298:1763-71 (2007).

[0005] Staphylococcal diseases have seen a dramatic increase in the last 20 years, this increase parallels the use of intravascular devices and invasive procedures. This rise in disease incidence is made more troubling because of the parallel rise of antibiotic resistance, therefore, there is an urgent need for immunogenic compositions for use in vaccines or to elicit polyclonal or monoclonal antibodies to confer passive immunity as a means to prevent or treat staphylococcal infection and associated diseases.

SUMMARY OF THE INVENTION

[0006] The present invention is directed towards a multi-antigen or multicomponent immunogenic composition comprising at least three antigens isolated from a staphylococcal bacterium. The antigens, which are polypeptides and polysaccharides, may be obtained, *inter alia*, directly from the bacterium using isolation procedures known to those skilled in the art, or they may be produced using synthetic protocols, or they may be recombinantly produced using genetic engineering procedures also known to those skilled in the art, or through a combination of any of the foregoing. In certain embodiments, an immunogenic composition of the invention comprises three or more antigens selected from an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated *S. aureus*

clumping factor B (ClfB) polypeptide, an isolated *S. aureus* capsular polysaccharide type 5 (CP5) conjugated to a carrier protein, an isolated *S. aureus* capsular polysaccharide type 8 (CP8) conjugated to a carrier protein and an isolated *S. aureus* MntC protein. In addition, the present invention provides methods for inducing an immune response against a staphylococcal bacterium, methods for preventing, reducing the severity, or delaying onset of a disease caused by a staphylococcal bacterium, and methods for preventing, reducing the severity, or delaying onset of at least one symptom of a disease caused by infection with a staphylococcal bacterium.

[0007] Accordingly, in one embodiment, the invention provides an immunogenic composition comprising: an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated *S. aureus* capsular polysaccharide type 5 (CP5) conjugated to a carrier protein, and an isolated *S. aureus* capsular polysaccharide type 8 (CP8) conjugated to a carrier protein.

[0008] In one embodiment, the invention provides an immunogenic composition comprising: an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated *S. aureus* clumping factor B (ClfB), an isolated *S. aureus* capsular polysaccharide type 5 (CP5) conjugated to a carrier protein, and an isolated *S. aureus* capsular polysaccharide type 8 (CP8) conjugated to a carrier protein.

[0009] In one embodiment, the invention provides an immunogenic composition comprising: an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated *S. aureus* clumping factor B (ClfB) polypeptide, an isolated *S. aureus* MntC protein, an isolated *S. aureus* capsular polysaccharide type 5 (CP5) conjugated to a carrier protein, and an isolated *S. aureus* capsular polysaccharide type 8 (CP8) conjugated to a carrier protein.

[0010] In one embodiment, the invention provides an immunogenic composition comprising: an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated *S. aureus* MntC protein, an isolated *S. aureus* capsular polysaccharide type 5 (CP5) conjugated to a carrier protein, and an isolated *S. aureus* capsular polysaccharide type 8 (CP8) conjugated to a carrier protein.

[0011] In one embodiment, the invention provides an immunogenic composition comprising: an isolated *S. aureus* clumping factor B (ClfB) polypeptide, an

isolated *S. aureus* capsular polysaccharide type 5 (CP5) conjugated to a carrier protein, and an isolated *S. aureus* capsular polysaccharide type 8 (CP8) conjugated to a carrier protein.

[0012] In one embodiment, the invention provides an immunogenic composition comprising: an isolated *S. aureus* clumping factor B (ClfB) polypeptide, an isolated *S. aureus* MntC protein, an isolated *S. aureus* capsular polysaccharide type 5 (CP5) conjugated to a carrier protein, and an isolated *S. aureus* capsular polysaccharide type 8 (CP8) conjugated to a carrier protein.

[0013] In one embodiment, the invention provides an immunogenic composition comprising: an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated *S. aureus* clumping factor B (ClfB) polypeptide, and an isolated *S. aureus* MntC protein.

[0014] In one embodiment, the invention provides an immunogenic composition comprising: an isolated *S. aureus* MntC protein, an isolated *S. aureus* capsular polysaccharide type 5 (CP5) conjugated to a carrier protein, and an isolated *S. aureus* capsular polysaccharide type 8 (CP8) conjugated to a carrier protein.

[0015] In one embodiment, the immunogenic composition comprises an isolated ClfA polypeptide fragment, wherein the ClfA polypeptide fragment comprises the fibrinogen binding domain of ClfA. In one embodiment, the ClfA polypeptide fragment comprises a fibrinogen binding domain comprising the N1, N2 and N3 domains of ClfA. In one embodiment, the ClfA polypeptide fragment comprises a fibrinogen binding domain comprising the N2 and N3 domains of ClfA. In one embodiment, the compositions containing the ClfA fibrinogen binding domain display reduced binding to fibrinogen. In one embodiment, the fibrinogen binding domain of ClfA binds to fibrinogen at a reduced level compared to the binding observed to fibrinogen with the native fibrinogen binding domain of ClfA. In one embodiment, the compositions containing the ClfA fibrinogen binding domain display reduced binding to fibrinogen and have an amino acid substitution at one or more of Tyr 338, Tyr 256, Pro 336, Lys 389, Ala 254 and Ile 387 of the full length protein containing the signal sequence. In one embodiment, the compositions containing the ClfA fibrinogen binding domain display an amino acid substitution at one or more of Tyr 338, Tyr 256, Pro 336, Lys 389, Ala 254 and Ile 387.

wherein the amino acid at any one or more of these positions is changed to an Ala or Ser. In one embodiment, the composition comprises a ClfA fibrinogen binding domain wherein the Tyr at position 338 is changed to an Ala.

[0016] In one embodiment, the immunogenic composition comprises an isolated ClfB polypeptide fragment, wherein the ClfB polypeptide fragment comprises the fibrinogen binding domain of ClfB. In one embodiment, the ClfB polypeptide fragment comprises a fibrinogen binding domain comprising the N1, N2 and N3 domains of ClfB. In one embodiment, the ClfB polypeptide fragment comprises a fibrinogen binding domain comprising the N2 and N3 domains of ClfB. In one embodiment, the compositions containing the ClfB fibrinogen binding domain display reduced binding to fibrinogen. In one embodiment, the fibrinogen binding domain of ClfB binds to fibrinogen at a reduced level compared to the binding observed to fibrinogen with the native fibrinogen binding domain of ClfB.

[0017] In one embodiment, the immunogenic composition comprises *S. aureus* capsular polysaccharide type 5 (CP5) which is a high molecular weight polysaccharide of between 20 and 1000 kDa. In one embodiment, the type 5 high molecular weight polysaccharide has a molecular weight of between 50 and 300 kDa. In one embodiment, the type 5 high molecular weight polysaccharide has a molecular weight of between 70 and 150 kDa.

[0018] In one embodiment, the immunogenic composition comprises an *S. aureus* capsular polysaccharide type 5, which is between 10% and 100% O-acetylated. In one embodiment, the immunogenic composition comprises an *S. aureus* capsular polysaccharide type 5, which is between 50% and 100% O-acetylated. In one embodiment, the immunogenic composition comprises an *S. aureus* capsular polysaccharide type 5, which is between 75% and 100% O-acetylated.

[0019] In one embodiment, the immunogenic composition comprises *S. aureus* capsular polysaccharide type 8 which is a high molecular weight polysaccharide of between 20 and 1000 kDa. In one embodiment, the type 8 high molecular weight polysaccharide has a molecular weight of between 50 and 300 kDa. In one embodiment, the type 8 high molecular weight polysaccharide has a molecular weight of between 70 and 150 kDa.

[0020] In one embodiment, the immunogenic composition comprises an *S. aureus* capsular polysaccharide type 8, which is between 10% and 100% O-acetylated. In one embodiment, the immunogenic composition comprises an *S. aureus* capsular polysaccharide type 8, which is between 50% and 100% O-acetylated. In one embodiment, the immunogenic composition comprises an *S. aureus* capsular polysaccharide type 8, which is between 75% and 100% O-acetylated.

[0021] In one embodiment, the capsular polysaccharide 5 and/or 8 present in an immunogenic composition is conjugated to a carrier protein. In one embodiment, the carrier protein is the *Corynebacterium diphtheriae* (*C. diphtheriae*) toxoid CRM_{197}.

[0022] In one embodiment, the immunogenic composition comprises the *S. aureus* MntC, which is a lipidated protein. In one embodiment, the immunogenic composition comprises the *S. aureus* MntC, which is not a lipidated protein.

[0023] In one embodiment, the invention provides an immunogenic composition as described herein, further comprising at least one protein from the serine-aspartate repeat (Sdr) protein family selected from the group consisting of SdrC, SdrD and SdrE.

[0024] In one embodiment, the invention provides an immunogenic composition as described herein, further comprising the iron surface determinant B (IsdB) protein.

[0025] In each of the embodiments described herein in which an immunogenic composition comprises three or more recited antigens, that composition may further comprise other immunogenic and/or non-immunogenic substances. In certain embodiments, each immunogenic composition may, alternatively, "consist essentially of" or "consist of" the three or more recited antigens and further comprise one or more non-immunogenic substances, as described in more detail herein.

[0026] In one embodiment, the invention provides an immunogenic composition as described herein, further comprising any one of the following antigens: Opp3a, DltD, HtsA, LtaS, IsdA, IsdC, SdrF, SdrG, SdrH, SrtA, SpA, Sbi FmtB, alpha-

hemolysin (hla), beta-hemolysin, fibronectin-binding protein A (fnbA), fibronectin-binding protein B (fnbB), coagulase, Fig, map, Panton-Valentine leukocidin (pvl), alpha-toxin and its variants, gamma-toxin (hlg) and variants, ica, immunodominant ABC transporter, Mg2+ transporter, Ni ABC transporter, RAP, autolysin, laminin receptors, IsaA/PisA, IsaB/PisB , SPOIIIE, SsaA, EbpS, Sas A, SasF, SasH, EFB (FIB), SBI, Npase, EBP, bone sialo binding protein II, aureolysin precursor (AUR)/SeppI, Cna, and fragments thereof such as M55, TSST-1, mecA, poly-N-acetylglucosamine (PNAG/dPNAG) exopolysaccharide, GehD, EbhA, EbhB, SSP-1, SSP-2, HBP, vitronectin binding protein, HarA, EsxA, EsxB, Enterotoxin A, Enterotoxin B, Enterotoxin C1, and novel autolysin. In certain embodiments of the invention, when the immunogenic composition comprises certain forms of CP5 and/or CP8, it may not further comprise PNAG.

[0027] In one embodiment, the immunogenic composition further comprises an adjuvant. In one embodiment, the immunogenic composition further comprises a pharmaceutically acceptable carrier.

[0028] In one embodiment, the immunogenic composition is used to formulate a vaccine. In one embodiment, the vaccine is used to induce an immune response in a subject against *S. aureus*. In one embodiment, the immunogenic composition is used to generate an antibody formulation to confer passive immunity on a subject.

[0029] In one embodiment, the invention provides a method of inducing an immune response against *S. aureus* comprising administering to a subject an immunogenic amount of any of the immunogenic compositions described herein and a pharmaceutically acceptable carrier.

[0030] In one embodiment, the invention provides a method of preventing or reducing infection with *S. aureus*, or a method of preventing or reducing the severity of at least one symptom associated with an infection caused by *S. aureus*, the methods comprising administering to a subject an immunogenic amount of any of the immunogenic compositions described herein and a pharmaceutically acceptable carrier.

[0031] In one embodiment, the methods for inducing an immune response against *S. aureus* comprise delivery of the immunogenic compositions with an adjuvant. In one embodiment, the methods for inducing an immune response

against *S. aureus* provide for delivery of the immunogenic compositions with a pharmaceutically acceptable carrier.

[0032] In one embodiment, the immune response induced by the immunogenic compositions described herein, prevents or reduces a disease or condition associated with a staphylococcal organism in a subject, or prevents or reduces one or more symptoms associated with a staphylococcal organism in a subject. In one embodiment, the disease is selected from the group consisting of invasive *S. aureus* disease, sepsis and carriage.

[0033] In one embodiment, the immune response induced comprises the generation of antibodies having opsonophagocytic activity (OPA) against *S. aureus*. In one embodiment, the immune response induced comprises the generation of higher titers of opsonophagocytic antibodies specific for *S. aureus* compared to that observed in non-immunized subjects. In one embodiment, the opsonophagocytic titer is at least 1:20.

[0034] In one embodiment, the *S. aureus* against which the immune response is induced is MRSA. In one embodiment, the *S. aureus* against which the immune response is induced is MSSA. In one embodiment, the *S. aureus* against which the immune response is induced is VRSA. In one embodiment, the *S. aureus* against which the immune response is induced is VISA.

[0035] In one embodiment, the invention provides a method of preventing a staphylococcal infection in a subject undergoing a surgical procedure, the method comprising administering an immunologically effective amount of any of the immunogenic compositions as described herein to the subject prior to the surgical procedure. The surgical procedure can be an elective surgical procedure or a non-elective surgical procedure. In one embodiment, the surgical procedure is a cardio-thoracic surgical procedure. In one embodiment, the subject is a human, veterinary animal, or a livestock animal.

[0036] In one embodiment, the invention provides a method of conferring passive immunity to a subject comprising the steps of (1) generating an antibody preparation using an immunogenic compositions of the invention; and (2) administering the antibody preparation to the subject to confer passive immunity.

BRIEF DESCRIPTION OF THE DRAWINGS

[0037] **Figure 1** depicts the various forms of recombinant ClfA and discloses SEQ ID NOs: 125 and 127-129, respectively, in order of appearance.

[0038] **Figure 2** depicts the cloning steps used for construction of pLP1179 for expressing ClfA.

[0039] **Figure 3** depicts the T7ClfA$_{(N125)}$Y338A expression Vector, pLP1179.

[0040] **Figure 4** depicts the repeating structure of the CP5 and CP8 polysaccharides.

[0041] **Figures 5A and 5B** depict molecular weight profiles of CP5 (A) and CP8 (B) produced at different broth pHs.

[0042] **Figures 6A and 6B** depict molecular weight profiles of CP5 (A) and CP8 (B) produced at different temperatures.

[0043] **Figure 7** demonstrates the correlation of the molecular weight of purified CP5 and CP8 with the treatment time for mild acid hydrolysis.

[0044] **Figure 8A-8E** depict the alignment of ClfA between various strains of *S. aureus* (SEQ ID NOs: 62, 64, 68, 84, 70, 104, 66, 78, 86, 88, 90, 72, 74, 76, 80, 94, 82, 92, 96, 98, 100, 102, 106, and 108, respectively, in order of appearance).

[0045] **Figure 9** depicts the ClfA phylogenetic tree.

[0046] **Figure 10A-10E** depict the alignment of ClfB between various strains of *S. aureus* (SEQ ID NOs: 26, 28, 32, 18, 54, 34, 36, 30, 16, 20, 22, 24, 38, 40, 42, 44, 46, 48, 50, 52, 56, 58, and 60, respectively, in order of appearance).

[0047] **Figure 11** depicts the ClfB phylogenetic tree.

[0048] **Figure 12** depicts the alignment of MntC between various strains of *S. aureus* (SEQ ID NOs: 2, 8, 10, 4, 6, 14 and 12, respectively, in order of appearance).

[0049] **Figure 13** demonstrates that polyclonal rabbit anti-ClfA antibodies reduce *S. aureus* 659-018 colony counts in a murine sepsis model.

[0050] **Figure 14** demonstrates that active immunization with ClfA reduces colonization of the heart by *S. aureus* PFESA0003 in the rabbit infective endocarditis model.

[0051] **Figures 15A and 15B** demonstrate that immunization with MntC reduces *S. aureus* in the blood. A: *S. aureus* PFESA0237 strain; B: *S. aureus* PFESA0266 strain.

[0052] **Figure 16** demonstrates that *S. aureus* CP5- CRM_{197} conjugate immunogenic formulation consistently exhibits protection in a murine pyelonephritis model.

[0053] **Figure 17** demonstrates that vaccination with CP8- CRM_{197} conjugate immunogenic formulation reduces death in a sepsis model.

[0054] **Figure 18** shows colony forming units (CFU) recovered in kidneys after challenge with *S. aureus* PFESA0266 in mice vaccinated with high molecular weight (HMW) CP5-CRM, low molecular weight (LMW) CP5-CRM or PP5-CRM control.

[0055] **Figure 19** shows a comparison of OPA titers (geomean) from serum obtained from mice vaccinated with different formulations of polysaccharide conjugate (high molecular weight (HMW) CP5-CRM, low molecular weight (LMW) CP5-CRM). Groups consisted of 5 to 9 mice.

[0056] **Figure 20** demonstrates OPA titer for non-human primate serum before (wk0, open symbols) and 2 weeks after (wk2, closed symbols) vaccination with different combinations of *S. aureus* antigens. The 3-antigen (3Ag) vaccine was composed of three antigens and the 4-antigent (4Ag) vaccine was composed of four antigens. Each formulation has two CP conjugates and either 1 or 2 peptides.

DETAILED DESCRIPTION OF THE INVENTION

[0057] Before the present methods and treatment methodology are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for purposes of describing particular embodiments only, and is not intended to be limiting.

[0058] Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated by reference in their entirety.

[0059] The terms used herein have the meanings recognized and known to those of skill in the art, however, for convenience and completeness, particular terms and their meanings are set forth below.

[0060] As used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, references to "the method" includes one or more methods, and/or steps of the type described herein and/or which will become apparent to those persons skilled in the art upon reading this disclosure and so forth.

[0061] The term "about" or "approximately" means within a statistically meaningful range of a value. Such a range can be within an order of magnitude, typically within 20%, more typically still within 10%, and even more typically within 5% of a given value or range. The allowable variation encompassed by the term "about" or "approximately" depends on the particular system under study, and can be readily appreciated by one of ordinary skill in the art. Whenever a range is recited within this application, every whole number integer within the range is also contemplated as an embodiment of the invention.

[0062] An "antibody" is an immunoglobulin molecule capable of specific binding to a target, such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. As used herein, unless otherwise indicated by context, the term is intended to encompass not only intact polyclonal or monoclonal antibodies, but also engineered antibodies (e.g., chimeric, humanized and/or derivatized to alter effector functions, stability and other biological activities) and fragments thereof (such as Fab, Fab', F(ab')2, Fv), single chain (ScFv) and domain antibodies, including shark and camelid antibodies), and fusion proteins comprising an antibody portion, multivalent antibodies, multispecific antibodies (e.g., bispecific antibodies so long as they exhibit the desired biological activity) and antibody fragments as described herein, and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site. An antibody includes an antibody of any class, such as IgG, IgA, or IgM (or sub-class thereof), and the antibody need not be of any particular class. Depending on the

antibody amino acid sequence of the constant domain of its heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2 in humans. The heavy-chain constant domains that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

[0063] "Antibody fragments" comprise only a portion of an intact antibody, wherein the portion preferably retains at least one, preferably most or all, of the functions normally associated with that portion when present in an intact antibody.

[0064] The term "antigen" generally refers to a biological molecule, usually a protein, peptide, polysaccharide, lipid or conjugate which contains at least one epitope to which a cognate antibody can selectively bind; or in some instances to an immunogenic substance that can stimulate the production of antibodies or T-cell responses, or both, in an animal, including compositions that are injected or absorbed into an animal. The immune response may be generated to the whole molecule, or to one or more various portions of the molecule (*e.g.*, an epitope or hapten). The term may be used to refer to an individual molecule or to a homogeneous or heterogeneous population of antigenic molecules. An antigen is recognized by antibodies, T-cell receptors or other elements of specific humoral and/or cellular immunity. The term "antigen" includes all related antigenic epitopes. Epitopes of a given antigen can be identified using any number of epitope mapping techniques, well known in the art. See, *e.g.*, Epitope Mapping Protocols in Methods in Molecular Biology, Vol. 66 (Glenn E. Morris, Ed., 1996) Humana Press, Totowa, N. J. For example, linear epitopes may be determined by *e.g.*, concurrently synthesizing large numbers of peptides on solid supports, the peptides corresponding to portions of the protein molecule, and reacting the peptides with antibodies while the peptides are still attached to the supports. Such techniques are known in the art and described in, *e.g.*, U.S. Pat. No. 4,708,871; Geysen et al. (1984) *Proc. Natl. Acad. Sci. USA* 81:3998-4002; Geysen et al. (1986) *Molec. Immunol.* 23:709-715, all incorporated herein by reference in their

entireties. Similarly, conformational epitopes may be identified by determining spatial conformation of amino acids such as by, *e.g.*, x-ray crystallography and 2-dimensional nuclear magnetic resonance. See, *e.g.*, Epitope Mapping Protocols, *supra*. Furthermore, for purposes of the present invention, an "antigen" may also be used to refer to a protein that includes modifications, such as deletions, additions and substitutions (generally conservative in nature, but they may be non-conservative), to the native sequence, so long as the protein maintains the ability to elicit an immunological response. These modifications may be deliberate, as through site-directed mutagenesis, or through particular synthetic procedures, or through a genetic engineering approach, or may be accidental, such as through mutations of hosts, which produce the antigens. Furthermore, the antigen can be derived, obtained, or isolated from a microbe, *e.g.* a bacterium, or can be a whole organism. Similarly, an oligonucleotide or polynucleotide, which expresses an antigen, such as in nucleic acid immunization applications, is also included in the definition. Synthetic antigens are also included, for example, polyepitopes, flanking epitopes, and other recombinant or synthetically derived antigens (Bergmann et al. (1993) *Eur. J. Immunol.* 23:2777 2781; Bergmann et al. (1996) *J. Immunol.* 157:3242 3249; Suhrbier, A. (1997) *Immunol. and Cell Biol.* 75:402 408; Gardner et al. (1998) 12th World AIDS Conference, Geneva, Switzerland, Jun. 28 - Jul. 3, 1998).

[0065] The term "adjuvant" refers to a compound or mixture that enhances the immune response to an antigen as further described and exemplified herein.

[0066] "Bacteremia" is a transient presence of bacteria in the blood. A bacteremia can progress to septicemia, or sepsis, which would be considered an infection and is the persistent presence of bacteria in the blood with associated clinical signs/symptoms. Not all bacteria are capable of surviving in the blood. Those that do have special genetic traits that provide for that ability. Also, the host factors play an important role as well.

[0067] "Capsular polysaccharide" or "capsule polysaccharide" refers to the polysaccharide capsule that is external to the cell wall of most isolates of Staphylococci. For example, *S. aureus* includes a cell wall component composed of a peptidoglycan complex, which enables the organism to survive under

unfavorable osmotic conditions and also includes a unique teichoic acid linked to the peptidoglycan. External to the cell wall a thin polysaccharide capsule coats most isolates of *S. aureus*. This serologically distinct capsule can be used to serotype various isolates of *S. aureus*. Many of the clinically significant isolates have been shown to include two capsular types: serotype 5 (CP5) and serotype 8 (CP8). The structures of CP5 and CP8 are shown schematically in Figure 4.

[0068] As used herein, "conjugates" comprise a capsule polysaccharide usually of a desired range of molecular weight and a carrier protein, wherein the capsule polysaccharide is conjugated to the carrier protein. Conjugates may or may not contain some amount of free capsule polysaccharide. As used herein, "free capsule polysaccharide" refers to capsule polysaccharide that is non-covalently associated with (i.e., non-covalently bound to, adsorbed to or entrapped in or with) the conjugated capsular polysaccharide-carrier protein. The terms "free capsule polysaccharide," "free polysaccharide" and "free saccharide" may be used interchangeably and are intended to convey the same meaning. Regardless of the nature of the carrier molecule, it can be conjugated to the capsular polysaccharide either directly or through a linker. As used herein, "to conjugate", "conjugated" and "conjugating" refers to a process whereby a bacterial capsular polysaccharide is covalently attached to the carrier molecule. Conjugation enhances the immunogenicity of the bacterial capsular polysaccharide. The conjugation can be performed according to the methods described below or by processes known in the art.

[0069] As described above, the present invention relates to conjugates comprising *S. aureus* serotype 5 capsular polysaccharides (CP5) conjugated to carrier proteins and conjugates comprising *S. aureus* serotype 8 capsular polysaccharides (CP8) conjugated to carrier proteins. One embodiment of the invention provides conjugates comprising a *S. aureus* serotype 5 capsular polysaccharide conjugated to a carrier protein and a *S. aureus* serotype 8 capsular polysaccharide conjugated to a carrier protein wherein: the type 5 capsular polysaccharide has a molecular weight of between 50 kDa and 800 kDa; the type 8 capsular polysaccharide has a molecular weight of between 50 and 700 kDa; the immunogenic conjugates have molecular weights of between about 1000 kDa and

about 5000 kDa; and the conjugates comprise less than about 30% free polysaccharide relative to total polysaccharide. In one embodiment, the conjugates comprise less than about 25%, about 20%, about 15%, about 10%, or about 5% free polysaccharide relative to total polysaccharide. In one embodiment, the type 5 or 8 polysaccharide has a molecular weight between 20 kDa and 1000 kDa.

[0070] In one embodiment, the conjugate has a molecular weight of between about 50 kDa and about 5000 kDa. In one embodiment, the conjugate has a molecular weight of between about 200 kDa and about 5000 kDa. In one embodiment, the immunogenic conjugate has a molecular weight of between about 400 kDa and about 2500 kDa. In one embodiment, the immunogenic conjugate has a molecular weight of between about 500 kDa and about 2500 kDa. In one embodiment, the immunogenic conjugate has a molecular weight of between about 600 kDa and about 2800 kDa. In one embodiment, the immunogenic conjugate has a molecular weight of between about 700 kDa and about 2700 kDa. In one embodiment, the immunogenic conjugate has a molecular weight of between about 1000 kDa and about 2000 kDa; between about 1800 kDa and about 2500 kDa; between about 1100 kDa and about 2200 kDa; between about 1900 kDa and about 2700 kDa; between about 1200 kDa and about 2400 kDa; between about 1700 kDa and about 2600 kDa; between about 1300 kDa and about 2600 kDa; between about 1600 kDa and about 3000 kDa.

[0071] Accordingly, in one embodiment, the carrier protein within the immunogenic conjugate of the invention is CRM_{197}, and the CRM_{197} is covalently linked to the capsular polysaccharide via a carbamate linkage, an amide linkage, or both. The number of lysine residues in the carrier protein that become conjugated to a capsular polysaccharide can be characterized as a range of conjugated lysines. For example, in a given immunogenic composition, the CRM_{197} may comprise 5 to 15 lysines out of 39 covalently linked to the capsular polysaccharide. Another way to express this parameter is that 12% to 40% of CRM_{197} lysines are covalently linked to the capsular polysaccharide. In some embodiments, the CRM_{197} portion of the polysaccharide covalently bound to the CRM_{197} comprises 5 to 22 lysines covalently linked to the polysaccharide. In some embodiments, the CRM_{197} portion of the polysaccharide covalently bound to the CRM_{197} comprises 5 to 23

lysines covalently linked to the polysaccharide. In some embodiments, the CRM_{197} portion of the polysaccharide covalently bound to carrier protein of comprises 8 to 15 lysines covalently linked to the polysaccharide. In some embodiments, the CRM_{197} portion of the polysaccharide covalently bound to carrier protein of comprises 8 to 12 lysines covalently linked to the polysaccharide. For example, in a given immunogenic composition, the CRM_{197} may comprise 18 to 22 lysines out of 39 covalently linked to the capsular polysaccharide. Another way to express this parameter is that 40% to 60% of CRM_{197} lysines are covalently linked to the capsular polysaccharide. In some embodiments, the CRM_{197} comprises 5 to 15 lysines out of 39 covalently linked to CP8. Another way to express this parameter is that 12% to 40% of CRM_{197} lysines are covalently linked to CP8. In some embodiments, the CRM_{197} comprises 18 to 22 lysines out of 39 covalently linked to CP5. Another way to express this parameter is that 40% to 60% of CRM_{197} lysines are covalently linked to CP5.

[0072] As discussed above, the number of lysine residues in the carrier protein conjugated to the capsular polysaccharide can be characterized as a range of conjugated lysines, which may be expressed as a molar ratio. For example, the molar ratio of conjugated lysines to CRM_{197} in the CP8 immunogenic conjugate can be between about 18:1 to about 22:1. In one embodiment, the range of molar ratio of conjugated lysines to CRM_{197} in the CP8 immunogenic conjugate can be between about 15:1 to about 25:1. In some embodiments, the range of molar ratio of conjugated lysines to CRM_{197} in the CP8 immunogenic conjugate can be between about 14:1 to about 20:1; about 12:1 to about 18:1; about 10:1 to about 16:1; about 8:1 to about 14:1; about 6:1 to about 12:1; about 4:1 to about 10:1; about 20:1 to about 26:1; about 22:1 to about 28:1; about 24:1 to about 30:1; about 26:1 to about 32:1; about 28:1 to about 34:1; about 30:1 to about 36:1; about 5:1 to about 10:1; about 5:1 to about 20:1; about 10:1 to about 20:1; or about 10:1 to about 30:1. Also, the molar ratio of conjugated lysines to CRM197 in the CP5 immunogenic conjugate can be between about 3:1 and 25:1. In one embodiment, the range of molar ratio of conjugated lysines to CRM197 in the CP5 immunogenic conjugate can be between about 5:1 to about 20:1. In one embodiment, the range of molar ratio of conjugated lysines to CRM197 in the CP5 immunogenic

conjugate can be between about 4:1 to about 20:1; about 6:1 to about 20:1; about 7:1 to about 20:1; about 8:1 to about 20:1; about 10:1 to about 20:1; about 11:1 to about 20:1; about 12:1 to about 20:1; about 13:1 to about 20:1; about 14:1 to about 20:1; about 15:1 to about 20:1; about 16:1 to about 20:1; about 17:1 to about 20:1; about 18:1 to about 20:1; about 5:1 to about 18:1; about 7:1 to about 16:1; or about 9:1 to about 14:1.

[0073] Another way to express the number of lysine residues in the carrier protein conjugated to the capsular polysaccharide can be as a range of conjugated lysines. For example, in a given CP8 immunogenic conjugate, the CRM_{197} may comprise 5 to 15 lysines out of 39 covalently linked to the capsular polysaccharide. Alternatively, this parameter can be expressed as a percentage. For example, in a given CP8 immunogenic conjugate, the percentage of conjugated lysines can be between 10% to 50%. In some embodiments, 20% to 50% of lysines can be covalently linked to CP8. Alternatively still, 30% to 50% of CRM_{197} lysines can be covalently linked to the CP8; 10% to 40% of CRM_{197} lysines; 10% to 30% of CRM_{197} lysines; 20% to 40% of CRM_{197} lysines; 25% to 40% of CRM_{197} lysines; 30% to 40% of CRM_{197} lysines; 10% to 30% of CRM_{197} lysines; 15% to 30% of CRM_{197} lysines; 20% to 30% of CRM_{197} lysines; 25% to 30% of CRM_{197} lysines; 10% to 15% of CRM_{197} lysines; or 10% to 12% of CRM_{197} lysines are covalently linked to CP8. Also, in a given CP5 immunogenic conjugate, the CRM_{197} may comprise 18 to 22 lysines out of 39 covalently linked to the capsular polysaccharide. Alternatively, this parameter can be expressed as a percentage. For example, in a given CP5 immunogenic conjugate, the percentage of conjugated lysines can be between 40% to 60%. In some embodiments, 40% to 60% of lysines can be covalently linked to CP5. Alternatively still, 30% to 50% of CRM_{197} lysines can be covalently linked to CP5; 20% to 40% of CRM_{197} lysines; 10% to 30% of CRM_{197} lysines; 50% to 70% of CRM_{197} lysines; 35% to 65% of CRM_{197} lysines; 30% to 60% of CRM_{197} lysines; 25% to 55% of CRM_{197} lysines; 20% to 50% of CRM_{197} lysines; 15% to 45% of CRM_{197} lysines; 10% to 40% of CRM_{197} lysines; 40% to 70% of CRM_{197} lysines; or 45% to 75% of CRM_{197} lysines are covalently linked to CP5.

[0074] The frequency of attachment of the capsular polysaccharide chain to a lysine on the carrier molecule is another parameter for characterizing conjugates of capsule polysaccharides. For example, in one embodiment, at least one covalent linkage between CRM_{197} and polysaccharide occurs for at least every 5 to 10 saccharide repeat units of the capsular polysaccharide. In another embodiment, there is at least one covalent linkage between CRM_{197} and capsular polysaccharide for every 5 to 10 saccharide repeat units; every 2 to 7 saccharide repeat units, every 3 to 8 saccharide repeat units; every 4 to 9 saccharide repeat units; every 6 to 11 saccharide repeat units; every 7 to 12 saccharide repeat units; every 8 to 13 saccharide repeat units; every 9 to 14 saccharide repeat units; every 10 to 15 saccharide repeat units; every 2 to 6 saccharide repeat units, every 3 to 7 saccharide repeat units; every 4 to 8 saccharide repeat units; every 6 to 10 saccharide repeat units; every 7 to 11 saccharide repeat units; every 8 to 12 saccharide repeat units; every 9 to 13 saccharide repeat units; every 10 to 14 saccharide repeat units; every 10 to 20 saccharide repeat units; every 5 to 10 saccharide repeat units of the capsular polysaccharide. In another embodiment, at least one linkage between CRM_{197} and capsular polysaccharide occurs for every 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 saccharide repeat units of the capsular polysaccharide.

[0075] The chemical activation of the polysaccharides and subsequent conjugation to the carrier protein may be achieved by conventional means. See, for example, U.S. Pat. Nos. 4,673,574 and 4,902,506. Other activation and conjugation methods may alternatively be used.

[0076] "Carrier protein" or "protein carrier" as used herein, refers to any protein molecule that may be conjugated to an antigen (such as the capsular polysaccharides) against which an immune response is desired. Conjugation of an antigen such as a polysaccharide to a carrier protein can render the antigen immunogenic. Carrier proteins are preferably proteins that are non-toxic and non-reactogenic and obtainable in sufficient amount and purity. Examples of carrier proteins are toxins, toxoids or any mutant cross-reactive material (CRM_{197}) of the toxin from tetanus, diphtheria, pertussis, *Pseudomonas* species, *E. coli*, *Staphylococcus* species, and *Streptococcus* species. Carrier proteins should be

amenable to standard conjugation procedures. In a particular embodiment of the present invention, CRM_{197} is used as the carrier protein.

[0077] CRM_{197} (Wyeth/Pfizer, Sanford, NC) is a non-toxic variant (i.e., toxoid) of diphtheria toxin isolated from cultures of *Corynebacterium diphtheria* strain C7 (β_{197}) grown in casamino acids and yeast extract-based medium. CRM_{197} is purified through ultra-filtration, ammonium sulfate precipitation, and ion-exchange chromatography. A culture of *Corynebacterium diphtheriae* strain C7 ($_{197}$), which produces CRM_{197} protein, has been deposited with the American Type Culture Collection, Rockville, Maryland and has been assigned accession number ATCC 53281. Other diphtheria toxoids are also suitable for use as carrier proteins.

[0078] Other suitable carrier proteins include inactivated bacterial toxins such as tetanus toxoid, pertussis toxoid, cholera toxoid (*e.g.*, as described in International Patent Application WO2004/083251), *E. coli* LT, *E. coli* ST, and exotoxin A from *Pseudomonas aeruginosa*. Bacterial outer membrane proteins such as outer membrane protein complex c (OMPC), porins, transferrin binding proteins, pneumolysin, pneumococcal surface protein A (PspA), pneumococcal adhesin protein (PsaA), C. *difficile* enterotoxin (toxin A) and cytotoxin (toxin B) or *Haemophilus influenzae* protein D, can also be used. Other proteins, such as ovalbumin, keyhole limpet hemocyanin (KLH), bovine serum albumin (BSA) or purified protein derivative of tuberculin (PPD) can also be used as carrier proteins.

[0079] After conjugation of the capsular polysaccharide to the carrier protein, the polysaccharide-protein conjugates are purified (enriched with respect to the amount of polysaccharide-protein conjugate) by a variety of techniques. These techniques include, e.g., concentration/diafiltration operations, precipitation/elution, column chromatography, and depth filtration. See examples below.

[0080] After the individual conjugates are purified, they may be combined to formulate an immunogenic composition of the present invention, which may be used, for example, in a vaccine. Formulation of the immunogenic composition of the present invention can be accomplished using art-recognized methods.

[0081] It is noted that in this disclosure, terms such as "comprises", "comprised", "comprising", "contains", "containing" and the like can have the meaning

attributed to them in U.S. patent law; *e.g.*, they can mean "includes", "included", "including" and the like. Such terms refer to the inclusion of a particular ingredients or set of ingredients without excluding any other ingredients. Terms such as "consisting essentially of" and "consists essentially of" have the meaning attributed to them in U.S. patent law, *e.g.*, they allow for the inclusion of additional ingredients or steps that do not detract from the novel or basic characteristics of the invention, *i.e.*, they exclude additional unrecited ingredients or steps that detract from novel or basic characteristics of the invention, and they exclude ingredients or steps of the prior art, such as documents in the art that are cited herein or are incorporated by reference herein, especially as it is a goal of this document to define embodiments that are patentable, *e.g.*, novel, non-obvious, inventive, over the prior art, *e.g.*, over documents cited herein or incorporated by reference herein. And, the terms "consists of" and "consisting of" have the meaning ascribed to them in U.S. patent law; namely, that these terms are close-ended. Accordingly, these terms refer to the inclusion of a particular ingredient or set of ingredients and the exclusion of all other ingredients.

[0082] A "conservative amino acid substitution" refers to the substitution of one or more of the amino acid residues of a protein with other amino acid residues having similar physical and/or chemical properties. Substitutes for an amino acid within the sequence may be selected from other members of the class to which the amino acid belongs. For example, the nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine. Amino acids containing aromatic ring structures are phenylalanine, tryptophan, and tyrosine. The polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine. The positively charged (basic) amino acids include arginine, lysine and histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid. Such alterations will not be expected to affect apparent molecular weight as determined by polyacrylamide gel electrophoresis, or isoelectric point. Particularly preferred substitutions are: Lys for Arg and vice versa such that a positive charge may be maintained; Glu for Asp and vice versa such that a negative charge may be

maintained; Ser for Thr such that a free --OH can be maintained; and Gln for Asn such that a free NH_2 can be maintained.

[0083] "Fragment" refers to proteins where only specific domains of a larger protein are included. For example, ClfA and ClfB proteins contain as many as 8 domains each if the signal sequences are included. A polypeptide corresponding to the N1N2N3, N2N3, N1N2, N1, N2, or N3 domains are each considered to be fragments of ClfA or ClfB. "Fragment" also refers to either a protein or polypeptide comprising an amino acid sequence of at least 4 amino acid residues (preferably, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 40 amino acid residues, at least 50 amino acid residues, at least 60 amino residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, or at least 150 amino acid residues) of the amino acid sequence of a parent protein or polypeptide or a nucleic acid comprising a nucleotide sequence of at least 10 base pairs (preferably at least 20 base pairs, at least 30 base pairs, at least 40 base pairs, at least 50 base pairs, at least 50 base pairs, at least 100 base pairs, at least 200 base pairs) of the nucleotide sequence of the parent nucleic acid.

[0084] "Functional activity" of an antibody or "functional antibody" as used herein refers to an antibody that, at a minimum, can bind specifically to an antigen. Additional functions are known in the art and may include additional components of the immune system that effect clearance or killing of the pathogen such as through opsonization, ADCC or complement-mediated cytotoxicity. After antigen binding, any subsequent antibody functions can be mediated through the Fc region of the antibody. The antibody opsonophagocytic assay (OPA) is an *in vitro* assay designed to measure *in vitro* Ig complement-assisted killing of bacteria with effector cells (white blood cells), thus mimicking a biological process. Antibody binding may also directly inhibit the biological function of the antigen it binds, e.g., antibodies that bind ClfA can neutralize its enzymatic function. In some embodiments, a "functional antibody" refers to an antibody that is functional as measured by the killing of bacteria in an animal efficacy model or an

opsonophagocytic killing assay that demonstrates that the antibodies kill the bacteria.

[0085] The molecular weight of the *S. aureus* capsule polysaccharides is a consideration for use in immunogenic compositions. For example, high molecular weight capsule polysaccharides may be able to induce certain antibody immune responses due to a higher valency of the epitopes present on the antigenic surface. The isolation of "high molecular weight capsular polysaccharides" is contemplated for use in the compositions and methods of the present invention. For example, in one embodiment of the invention, the isolation of type 5 high molecular weight polysaccharides ranging in size from about 50 to about 800 kDa in molecular weight is contemplated. In one embodiment of the invention, the isolation of type 5 high molecular weight polysaccharides ranging in size from about 20 to about 1000 kDa in molecular weight is contemplated. In one embodiment of the invention, the isolation and purification of type 5 high molecular weight capsular polysaccharides ranging in size from about 50 to about 300 kDa in molecular weight is contemplated. In one embodiment, the isolation and purification of type 5 high molecular weight capsular polysaccharide ranging from 70 kDa to 300 kDa in molecular weight is contemplated. In one embodiment, the isolation and purification of type 5 high molecular weight capsular polysaccharide ranging from 90 kDa to 250 kDa in molecular weight is contemplated. In one embodiment, the isolation and purification of type 5 high molecular weight capsular polysaccharide ranging from 90 kDa to 150 kDa in molecular weight is contemplated. In one embodiment, the isolation and purification of type 5 high molecular weight capsular polysaccharide ranging from 90 kDa to 140 kDa in molecular weight is contemplated. In one embodiment, the isolation and purification of type 5 high molecular weight capsular polysaccharide ranging from 80 kDa to 120 kDa in molecular weight is contemplated. Other ranges of high molecular weight serotype 5 capsular polysaccharide that can be isolated and purified by the methods of this invention include size ranges of about 70 kDa to about 100 kDa in molecular weight; 70 kDa to 110 kDa in molecular weight; 70 kDa to 120 kDa in molecular weight; 70 kDa to 130 kDa in molecular weight; 70 kDa to 140 kDa in molecular weight; 70 kDa to 150 kDa in molecular weight; 70 kDa to 160 kDa in molecular

weight; 80 kDa to 110 kDa in molecular weight; 80 kDa to 120 kDa in molecular weight; 80 kDa to 130 kDa in molecular weight; 80 kDa to 140 kDa in molecular weight; 80 kDa to 150 kDa in molecular weight; 80 kDa to 160 kDa in molecular weight; 90 kDa to 110 kDa in molecular weight; 90 kDa to 120 kDa in molecular weight; 90 kDa to 130 kDa in molecular weight; 90 kDa to 140 kDa in molecular weight; 90 kDa to 150 kDa in molecular weight; 90 kDa to 160 kDa in molecular weight; 100 kDa to 120 kDa in molecular weight; 100 kDa to 130 kDa in molecular weight; 100 kDa to 140 kDa in molecular weight; 100 kDa to 150 kDa in molecular weight; 100 kDa to 160 kDa in molecular weight; and similar desired molecular weight ranges.

[0086] As discussed above, the molecular weight of the *S. aureus* capsule polysaccharides is a consideration for use in immunogenic compositions. For example, high molecular weight capsule polysaccharides may be able to induce certain antibody immune responses due to a higher valency of the epitopes present on the antigenic surface. In one embodiment of the invention, the isolation and purification of type 8 high molecular weight capsular polysaccharides ranging from about 20 kDa to about 1000 kDa in molecular weight is contemplated. In one embodiment of the invention, the isolation and purification of type 8 high molecular weight capsular polysaccharides ranging from about 50 kDa to about 700 kDa in molecular weight is contemplated. In one embodiment of the invention, the isolation and purification of type 8 high molecular weight capsular polysaccharides ranging from 50 kDa to 300 kDa in molecular weight is contemplated. In one embodiment, the isolation and purification of type 8 high molecular weight capsular polysaccharide ranging from 70 kDa to 300 kDa in molecular weight is contemplated. In one embodiment, the isolation and purification of type 8 high molecular weight capsular polysaccharides ranging from 90 kDa to 250 kDa in molecular weight is contemplated. In one embodiment, the isolation and purification of type 8 high molecular weight capsular polysaccharides ranging from 90 kDa to 150 kDa in molecular weight is contemplated. In one embodiment, the isolation and purification of type 8 high molecular weight capsular polysaccharides ranging from 90 kDa to 120 kDa in molecular weight is contemplated. In one embodiment, the isolation and

purification of type 8 high molecular weight capsular polysaccharides ranging from 80 kDa to 120 kDa in molecular weight is contemplated. Other ranges of high molecular weight serotype 8 capsular polysaccharides that can be isolated and purified by the methods of this invention include size ranges of about 70 kDa to about 100 kDa in molecular weight; 70 kDa to 110 kDa in molecular weight; 70 kDa to 120 kDa in molecular weight; 70 kDa to 130 kDa in molecular weight; 70 kDa to 140 kDa in molecular weight; 70 kDa to 150 kDa in molecular weight; 70 kDa to 160 kDa in molecular weight; 80 kDa to 110 kDa in molecular weight; 80 kDa to 120 kDa in molecular weight; 80 kDa to 130 kDa in molecular weight; 80 kDa to 140 kDa in molecular weight; 80 kDa to 150 kDa in molecular weight; 80 kDa to 160 kDa in molecular weight; 90 kDa to 110 kDa in molecular weight; 90 kDa to 120 kDa in molecular weight; 90 kDa to 130 kDa in molecular weight; 90 kDa to 140 kDa in molecular weight; 90 kDa to 150 kDa in molecular weight; 90 kDa to 160 kDa in molecular weight; 100 kDa to 120 kDa in molecular weight; 100 kDa to 130 kDa in molecular weight; 100 kDa to 140 kDa in molecular weight; 100 kDa to 150 kDa in molecular weight; 100 kDa to 160 kDa in molecular weight; and similar desired molecular weight ranges.

[0087] An "immune response" to an immunogenic composition is the development in a subject of a humoral and/or a cell-mediated immune response to molecules present in the composition of interest (for example, an antigen, such as a protein or polysaccharide). For purposes of the present invention, a "humoral immune response" is an antibody-mediated immune response and involves the generation of antibodies with affinity for the antigens present in the immunogenic compositions of the invention, while a "cell-mediated immune response" is one mediated by T-lymphocytes and/or other white blood cells. A "cell-mediated immune response" is elicited by the presentation of antigenic epitopes in association with Class I or Class II molecules of the major histocompatibility complex (MHC). This activates antigen-specific CD4+ T helper cells or CD8+ cytotoxic T lymphocyte cells ("CTLs"). CTLs have specificity for peptide or lipid antigens that are presented in association with proteins encoded by the major histocompatibility complex (MHC) or CD1 and expressed on the surfaces of cells. CTLs help induce and promote the intracellular destruction of intracellular

microbes, or the lysis of cells infected with such microbes. Another aspect of cellular immunity involves an antigen-specific response by helper T-cells. Helper T-cells act to help stimulate the function, and focus the activity of, nonspecific effector cells against cells displaying peptide antigens in association with classical or nonclassical MHC molecules on their surface. A "cell-mediated immune response" also refers to the production of cytokines, chemokines and other such molecules produced by activated T-cells and/or other white blood cells, including those derived from CD4+ and CD8+ T-cells. The ability of a particular antigen or composition to stimulate a cell-mediated immunological response may be determined by a number of assays, such as by lymphoproliferation (lymphocyte activation) assays, CTL cytotoxic cell assays, by assaying for T-lymphocytes specific for the antigen in a sensitized subject, or by measurement of cytokine production by T cells in response to restimulation with antigen. Such assays are well known in the art. See, e.g., Erickson et al., *J. Immunol.* (1993) 151:4189-4199; Doe et al., *Eur. J. Immunol.* (1994) 24:2369-2376.

[0088] The term "immunogenic" refers to the ability of an antigen or a vaccine to elicit an immune response, either humoral or cell-mediated, or both.

[0089] An "immunogenic amount", or an "immunologically effective amount" or "dose", each of which is used interchangeably herein, generally refers to the amount of antigen or immunogenic composition sufficient to elicit an immune response, either a cellular (T cell) or humoral (B cell or antibody) response, or both, as measured by standard assays known to one skilled in the art.

[0090] The amount of a particular conjugate in a composition is generally calculated based on total polysaccharide, conjugated and non-conjugated for that conjugate. For example, a CP5 conjugate with 20% free polysaccharide will have about 80 mcg of conjugated CP5 polysaccharide and about 20 mcg of non-conjugated CP5 polysaccharide in a 100 mcg CP5 polysaccharide dose. The protein contribution to the conjugate is usually not considered when calculating the dose of a conjugate. The amount of conjugate can vary depending upon the staphylococcal serotype. Generally, each dose will comprise 0.01 to 100 mcg of polysaccharide, particularly 0.1 to 10 mcg, and more particularly 1 to 10 mcg. The "immunogenic amount" of the different polysaccharide components in the

immunogenic composition, may diverge and each may comprise 0.01 mcg, 0.1 mcg, 0.25 mcg, 0.5 mcg, 1 mcg, 2 mcg, 3 mcg, 4 mcg, 5 mcg, 6 mcg, 7 mcg, 8 mcg, 9 mcg, 10 mcg, 15 mcg, 20 mcg, 30 mcg, 40 mcg,50 mcg, 60 mcg, 70 mcg, 80 mcg, 90 mcg, or about 100 mcg of any particular polysaccharide antigen.

[0091] In another embodiment, the "immunogenic amount" of the protein components in the immunogenic composition, may range from about 10 mcg to about 300 mcg of each protein antigen. In a particular embodiment, the "immunogenic amount" of the protein components in the immunogenic composition, may range from about 20 mcg to about 200 mcg of each protein antigen. The "immunogenic amount" of the different protein components in the immunogenic composition may diverge, and each comprise 10 mcg, 20 mcg, 30 mcg, 40 mcg, 50 mcg, 60 mcg, 70 mcg, 80 mcg, 90 mcg, 100 mcg, 125 mcg, 150 mcg, 175 mcg or about 200 mcg of any particular protein antigen.

[0092] The effectiveness of an antigen as an immunogen can be measured by measuring the levels of B cell activity by measuring the levels of circulating antibodies specific for the antigen in serum using immunoassays, immunoprecipitation assays, functional antibody assays, such as *in vitro* opsonic assay and many other assays known in the art. Another measure of effectiveness of an antigen as an T-cell immunogen can be measured by either by proliferation assays, by cytolytic assays, such as chromium release assays to measure the ability of a T cell to lyse its specific target cell. Furthermore, in the present invention, an "immunogenic amount" may also be defined by measuring the serum levels of antigen specific antibody induced following administration of the antigen, or, by measuring the ability of the antibodies so induced to enhance the opsonophagocytic ability of particular white blood cells, as described herein. The level of protection of the immune response may be measured by challenging the immunized host with the antigen that has been injected. For example, if the antigen to which an immune response is desired is a bacterium, the level of protection induced by the "immunogenic amount" of the antigen can be measured by detecting the percent survival or the percent mortality after challenge of the animals with the bacterial cells. In one embodiment, the amount of protection may be measured by measuring at least one symptom associated with the bacterial

infection, for example, a fever associated with the infection. The amount of each of the antigens in the multi-antigen or multi-component vaccine or immunogenic compositions will vary with respect to each of the other components and can be determined by methods known to the skilled artisan. Such methods would include, for example, procedures for measuring immunogenicity and/or *in vivo* efficacy.

[0093] The term "immunogenic composition" relates to any pharmaceutical composition containing an antigen, *e.g.* a microorganism, or a component thereof, which composition can be used to elicit an immune response in a subject. The immunogenic compositions of the present invention can be used to treat a human susceptible to *S. aureus* infection, by means of administering the immunogenic compositions via a systemic transdermal or mucosal route. These administrations can include injection via the intramuscular (i.m.), intraperitoneal (i.p.), intradermal (i.d.) or subcutaneous routes; application by a patch or other transdermal delivery device; or via mucosal administration to the oral/alimentary, respiratory or genitourinary tracts. In one embodiment, intranasal administration is used for the treatment or prevention of nasopharyngeal carriage of *S. aureus*, thus attenuating infection at its earliest stage. In one embodiment, the immunogenic composition may be used in the manufacture of a vaccine or in the elicitation of a polyclonal or monoclonal antibodies that could be used to passively protect or treat an animal.

[0094] Optimal amounts of components for a particular immunogenic composition can be ascertained by standard studies involving observation of appropriate immune responses in subjects. Following an initial vaccination, subjects can receive one or several booster immunizations adequately spaced.

[0095] In one embodiment of the present invention, the *S. aureus* immunogenic composition comprises a recombinant *S. aureus* clumping factor A (ClfA) fragment (N1N2N3, or combinations thereof), an isolated capsular polysaccharides type 5 conjugated to CRM_{197} and an isolated capsular polysaccharides type 8 conjugated to CRM_{197}. In another embodiment, the *S. aureus* immunogenic composition is a sterile formulation (liquid, lyophilized, DNA vaccine, intradermal preparation) of recombinant *S. aureus* clumping factor (ClfA) fragment (N1N2N3, or combinations thereof), recombinant *S. aureus* clumping factor B (ClfB) fragment (N1N2N3, or combinations thereof), an isolated capsular polysaccharides

type 5 conjugated to CRM_{197} and an isolated capsular polysaccharides type 8 conjugated to CRM_{197}. In one embodiment of the present invention, the *S. aureus* immunogenic composition comprises a recombinant *S. aureus* clumping factor A (ClfA) fragment (N1N2N3, or combinations thereof), *S. aureus* iron binding protein MntC, an isolated capsular polysaccharides type 5 conjugated to CRM_{197} and an isolated capsular polysaccharides type 8 conjugated to CRM_{197}. In one embodiment, the *S. aureus* immunogenic composition is a sterile formulation (liquid, lyophilized, DNA vaccine, intradermal preparation) of recombinant *S. aureus* clumping factor (ClfA) fragment (N1N2N3, or combinations thereof), recombinant *S. aureus* clumping factor B (ClfB) fragment (N1N2N3, or combinations thereof), *S. aureus* iron binding protein MntC, an isolated capsular polysaccharides type 5 conjugated to CRM_{197} and an isolated capsular polysaccharides type 8 conjugated to CRM_{197}. In one embodiment of the present invention, the *S. aureus* immunogenic composition comprises a recombinant *S. aureus* clumping factor B (ClfB) fragment (N1N2N3, or combinations thereof), an isolated capsular polysaccharides type 5 conjugated to CRM_{197} and an isolated capsular polysaccharides type 8 conjugated to CRM_{197}. In one embodiment of the present invention, the *S. aureus* immunogenic composition comprises a recombinant *S. aureus* clumping factor B (ClfB) fragment (N1N2N3, or combinations thereof), *S. aureus* iron binding protein MntC, an isolated capsular polysaccharides type 5 conjugated to CRM_{197} and an isolated capsular polysaccharides type 8 conjugated to CRM_{197}. In one embodiment of the present invention, the *S. aureus* immunogenic composition comprises a *S. aureus* iron binding protein MntC, an isolated capsular polysaccharides type 5 conjugated to CRM_{197} and an isolated capsular polysaccharides type 8 conjugated to CRM_{197}.

[0096] The immunogenic compositions of the present invention can further comprise one or more additional "immunomodulators", which are agents that perturb or alter the immune system, such that either up-regulation or down-regulation of humoral and/or cell-mediated immunity is observed. In one particular embodiment, up-regulation of the humoral and/or cell-mediated arms of the immune system is preferred. Examples of certain immunomodulators include, for example, an adjuvant or cytokine, or ISCOMATRIX (CSL Limited, Parkville,

Australia), described in U.S. Patent No. 5,254,339 among others. Non-limiting examples of adjuvants that can be used in the vaccine of the present invention include the RIBI adjuvant system (Ribi Inc., Hamilton, Mont.), alum, mineral gels such as aluminum hydroxide gel, oil-in-water emulsions, water-in-oil emulsions such as, *e.g.*, Freund's complete and incomplete adjuvants, Block copolymer (CytRx, Atlanta Ga.), QS-21 (Cambridge Biotech Inc., Cambridge Mass.), SAF-M (Chiron, Emeryville Calif.), AMPHIGEN® adjuvant, saponin, Quil A or other saponin fraction, monophosphoryl lipid A, and Avridine lipid-amine adjuvant. Non-limiting examples of oil-in-water emulsions useful in the vaccine of the invention include modified SEAM62 and SEAM 1/2 formulations. Modified SEAM62 is an oil-in-water emulsion containing 5% (v/v) squalene (Sigma), 1% (v/v) SPAN® 85 detergent (ICI Surfactants), 0.7% (v/v) polysorbate ® 80 detergent (ICI Surfactants), 2.5% (v/v) ethanol, 200 µg/ml Quil A, 100 µg/ml cholesterol, and 0.5% (v/v) lecithin. Modified SEAM 1/2 is an oil-in-water emulsion comprising 5% (v/v) squalene, 1% (v/v) SPAN® 85 detergent, 0.7% (v/v) polysorbate 80 detergent, 2.5% (v/v) ethanol, 100 µg/ml Quil A, and 50 µg/ml cholesterol. Other "immunomodulators" that can be included in the vaccine include, *e.g.*, one or more interleukins, interferons, or other known cytokines or chemokines. In one embodiment, the adjuvant may be a cyclodextrin derivative or a polyanionic polymer, such as those described in U.S. patent numbers 6,165,995 and 6,610,310, respectively. It is to be understood that the immunomodulator and/or adjuvant to be used will depend on the subject to which the vaccine or immunogenic composition will be administered, the route of injection and the number of injections to be given.

[0097] *S. aureus* "invasive disease" is the isolation of bacteria from a normally sterile site, where there is associated clinical signs/symptoms of disease. Normally sterile body sites include blood, CSF, pleural fluid, pericardial fluid, peritoneal fluid, joint/synovial fluid, bone, internal body site (lymph node, brain, heart, liver, spleen, vitreous fluid, kidney, pancreas, ovary), or other normally sterile sites. Clinical conditions characterizing invasive diseases include bacteremia, pneumonia, cellulitis, osteomyelitis, endocarditis, septic shock and more.

[0098] The term "isolated" means that the material is removed from its original environment (*e.g.*, the natural environment if it is naturally occurring or from it's host organism if it is a recombinant entity, or taken from one environment to a different environment). For example, an "isolated" capsule polysaccharide, protein or peptide is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized, or otherwise present in a mixture as part of a chemical reaction. In the present invention, the proteins or polysaccharides may be isolated from the bacterial cell or from cellular debris, so that they are provided in a form useful in the manufacture of an immunogenic composition. The term "isolated" or "isolating" may include purifying, or purification, including for example, the methods of purification of the proteins or capsular polysaccharides, as described herein. The language "substantially free of cellular material" includes preparations of a polypeptide/protein in which the polypeptide/protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, a capsule polysaccharide, protein or peptide that is substantially free of cellular material includes preparations of the capsule polysaccharide, protein or peptide having less than about 30%, 20%, 10%, 5%, 2.5%, or 1%, (by dry weight) of contaminating protein or polysaccharide or other cellular material. When the polypeptide/protein is recombinantly produced, it is also preferably substantially free of culture medium, i.e., culture medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When polypeptide/protein or polysaccharide is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, i.e., it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein or polysaccharide. Accordingly, such preparations of the polypeptide/protein or polysaccharide have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than polypeptide/protein or polysaccharide fragment of interest.

[0099] A "non-conservative amino acid substitution" refers to the substitution of one or more of the amino acid residues of a protein with other amino acid residues

having dissimilar physical and/or chemical properties, using the characteristics defined above.

[0100] The term "pharmaceutically acceptable carrier" means a carrier approved by a regulatory agency of a Federal, a state government, or other regulatory agency, or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, including humans as well as non-human mammals. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the pharmaceutical composition is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin. Water, saline solutions and aqueous dextrose and glycerol solutions can be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting, bulking, emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, sustained release formulations and the like. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin. The formulation should suit the mode of administration.

[0101] The terms "protein", "polypeptide" and "peptide" refer to a polymer of amino acid residues and are not limited to a minimum length of the product. Thus, peptides, oligopeptides, dimers, multimers, and the like, are included within the definition. Both full-length proteins and fragments thereof are encompassed by the definition. The terms also include modifications, such as deletions, additions and substitutions (generally conservative in nature, but which may be non-conservative), to a native sequence, preferably such that the protein maintains the ability to elicit an immunological response within an animal to which the protein is administered. Also included are post-expression modifications, *e.g.* glycosylation, acetylation, lipidation, phosphorylation and the like.

[0102] A "protective" immune response refers to the ability of an immunogenic composition to elicit an immune response, either humoral or cell mediated, which

serves to protect the subject from an infection. The protection provided need not be absolute, i.e., the infection need not be totally prevented or eradicated, if there is a statistically significant improvement compared with a control population of subjects, *e.g.* infected animals not administered the vaccine or immunogenic composition. Protection may be limited to mitigating the severity or rapidity of onset of symptoms of the infection. In general, a "protective immune response" would include the induction of an increase in antibody levels specific for a particular antigen in at least 50% of subjects, including some level of measurable functional antibody responses to each antigen. In particular situations, a "protective immune response" could include the induction of a two fold increase in antibody levels or a four fold increase in antibody levels specific for a particular antigen in at least 50% of subjects, including some level of measurable functional antibody responses to each antigen. In certain embodiments, opsonising antibodies correlate with a protective immune response. Thus, protective immune response may be assayed by measuring the percent decrease in the bacterial count in an opsonophagocytosis assay, for instance those described below. Preferably, there is a decrease in bacterial count of at least 10%, 25%, 50%, 65%, 75%, 80%, 85%, 90%, 95% or more.

[0103] The term "recombinant" as used herein simply refers to any protein, polypeptide, or cell expressing a gene of interest that is produced by genetic engineering methods. The term "recombinant" as used with respect to a protein or polypeptide, means a polypeptide produced by expression of a recombinant polynucleotide. The proteins used in the immunogenic compositions of the invention may be isolated from a natural source or produced by genetic engineering methods, such as, for example recombinant ClfA, recombinant ClfB or recombinant MntC. "Recombinant," as used herein, further describes a nucleic acid molecule, which, by virtue of its origin or manipulation, is not associated with all or a portion of the polynucleotide with which it is associated in nature. The term "recombinant" as used with respect to a host cell means a host cell into which a recombinant polynucleotide has been introduced.

[0104] Recombinant ClfA (rClfA) and recombinant ClfB (rClfB) as used herein refers to forms of ClfA or ClfB for use in the immunogenic compositions of the

invention. In one embodiment, rClfA is a fragment of ClfA comprising one or more of the N domains, for example, N1N2N3, N2N3, N2 or N3 and is referred to herein as "recombinant ClfA" or "rClfA". In one embodiment, rClfB is a fragment of ClfB comprising one or more of the N domains of ClfB, for example, N1N2N3, N2N3, N2 or N3 and is referred to herein as "recombinant ClfB" or "rClfB".

[0105] The term "subject" refers to a mammal, bird, fish, reptile, or any other animal. The term "subject" also includes humans. The term "subject" also includes household pets. Non-limiting examples of household pets include: dogs, cats, pigs, rabbits, rats, mice, gerbils, hamsters, guinea pigs, ferrets, birds, snakes, lizards, fish, turtles, and frogs. The term "subject" also includes livestock animals. Non-limiting examples of livestock animals include: alpaca, bison, camel, cattle, deer, pigs, horses, llamas, mules, donkeys, sheep, goats, rabbits, reindeer, yak, chickens, geese, and turkeys.

[0106] As used herein, "treatment" (including variations thereof, for example, "treat" or "treated") refers to any one or more of the following: (i) the prevention of infection or reinfection, as in a traditional vaccine, (ii) the reduction in the severity of, or, in the elimination of symptoms, and (iii) the substantial or complete elimination of the pathogen or disorder in question. Hence, treatment may be effected prophylactically (prior to infection) or therapeutically (following infection). In the present invention, prophylactic or therapeutic treatments can be used. According to a particular embodiment of the present invention, compositions and methods are provided which treat, including prophylactically and/or therapeutically immunize, a host animal against a microbial infection (*e.g.* a bacterium such as *Staphylococcus* species). The methods of the present invention are useful for conferring prophylactic and/or therapeutic immunity to a subject. The methods of the present invention can also be practiced on subjects for biomedical research applications.

[0107] The terms "vaccine" or "vaccine composition", which are used interchangeably, refer to pharmaceutical compositions comprising at least one immunogenic composition that induces an immune response in an animal.

General Description

[0108] The present invention relates to immunogenic compositions comprising at least three antigens from a staphylococcal organism, for example *S. aureus*. The antigens may be isolated from the organism using biochemical isolation procedures, or they may be produced synthetically or by recombinant means. The antigens may be polypeptides, or polysaccharides, or a combination thereof. These immunogenic compositions may be used in the manufacture of a vaccine to immunize subjects against infections caused by a staphylococcal organism. The components suitable for use in these compositions are described in greater detail below.

Staphylococcal Immunogenic Compositions

[0109] *S. aureus* is the causative agent of a wide variety of human diseases ranging from superficial skin infections to life threatening conditions such as pneumonia, sepsis and endocarditis. See Lowy N. Eng. J. Med. 339:580-532(1998). In cases of invasive disease, *S. aureus* can be isolated from normally sterile body sites including blood, cerebral spinal fluid CSF, pleural fluid, pericardial fluid, peritoneal fluid, joint/synovial fluid, bone, internal body site (lymph node, brain, heart, liver, spleen, vitreous fluid, kidney, pancreas, ovary), or other normally sterile sites. This can lead to life threatening clinical conditions such as bacteremia, pneumonia, cellulitis, osteomyelitis, endocarditis, and septic shock. Adults, elderly and pediatric patients are most at risk for *S. aureus* infections.

[0110] Embodiments of the present invention describe selected antigens in immunogenic compositions including an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated *S. aureus* capsular polysaccharide type 5 conjugated to a carrier protein, an isolated *S. aureus* capsular polysaccharide type 8 conjugated to a carrier protein, an isolated *S. aureus* clumping factor B (ClfB), and recombinant *S. aureus* MntC protein. Next, the antigens were characterized in immunogenic compositions as a series of combinations, to demonstrate that specific combinations provide immune responses that may be superior to that produced using individual components for immunogenic compositions.

Accordingly, one combination provides an immunogenic composition comprising: an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated *S. aureus* capsular polysaccharide type 5 conjugated to a carrier protein, and an isolated *S. aureus* capsular polysaccharide type 8 conjugated to a carrier protein. A second combination provides an immunogenic composition comprising: an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated *S. aureus* clumping factor B (ClfB), isolated *S. aureus* capsular polysaccharide type 5 conjugated to a carrier protein, and an isolated *S. aureus* capsular polysaccharide type 8 conjugated to a carrier protein. A third combination provides an immunogenic composition comprising: an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated *S. aureus* clumping factor B (ClfB) polypeptide, an isolated *S. aureus* MntC protein, an isolated *S. aureus* capsular polysaccharide type 5 conjugated to a carrier protein, and an isolated *S. aureus* capsular polysaccharide type 8 conjugated to a carrier protein. A fourth combination provides an immunogenic composition comprising: an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated *S. aureus* MntC protein, an isolated *S. aureus* capsular polysaccharide type 5 conjugated to a carrier protein, and an isolated *S. aureus* capsular polysaccharide type 8 conjugated to a carrier protein. A fifth combination provides an immunogenic composition comprising: an isolated *S. aureus* clumping factor B (ClfB) polypeptide, an isolated *S. aureus* capsular polysaccharide type 5 conjugated to a carrier protein, and an isolated *S. aureus* capsular polysaccharide type 8 conjugated to a carrier protein. A sixth combination provides an immunogenic composition comprising: an isolated *S. aureus* clumping factor B (ClfB) polypeptide, an isolated *S. aureus* MntC protein, an isolated *S. aureus* capsular polysaccharide type 5 conjugated to a carrier protein, and an isolated *S. aureus* capsular polysaccharide type 8 conjugated to a carrier protein. A seventh combination provides an immunogenic composition comprising: an isolated *S. aureus* MntC protein, an isolated *S. aureus* capsular polysaccharide type 5 conjugated to a carrier protein, and an isolated *S. aureus* capsular polysaccharide type 8 conjugated to a carrier protein. An eighth combination provides an immunogenic composition comprising: an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated *S. aureus* clumping factor B (ClfB) polypeptide,

and an isolated *S. aureus* MntC protein. In some embodiments, the above combinations further comprise at least one of the following antigens: EkeS, DsqA, KesK, KrkN, KrkN2, RkaS, RrkN, KnkA, SdrC, SdrD, SdrE, Opp3a, DltD, HtsA, LtaS, IsdA, IsdB, IsdC, SdrF, SdrG, SdrH, SrtA, SpA, Sbi alpha-hemolysin (hla), beta-hemolysin, fibronectin-binding protein A (fnbA), fibronectin-binding protein B (fnbB), coagulase, Fig, map, Panton-Valentine leukocidin (pvl), alpha-toxin and its variants, gamma-toxin (hlg) and variants, ica, immunodominant ABC transporter, Mg2+ transporter, Ni ABC transporter, RAP, autolysin, laminin receptors, IsaA/PisA, IsaB/PisB , SPOIIIE, SsaA, EbpS, Sas A, SasF, SasH, EFB (FIB), SBI, Npase, EBP, bone sialo binding protein II, aureolysin precursor (AUR)/Sepp1, Cna, and fragments thereof such as M55, TSST-1, mecA, poly-N-acetylglucosamine (PNAG/dPNAG) exopolysaccharide, GehD, EbhA, EbhB, SSP-1, SSP-2, IIBP, vitronectin binding protein, HarA, EsxA, EsxB, Enterotoxin A, Enterotoxin B, Enterotoxin C1, and novel autolysin.

[0111] Epidemiological studies of *S. aureus* outbreaks indicate that evolution of *S. aureus* is clonal in nature, where a single clone that acquired a successful genotype has spread rapidly and caused many of the infections. Therefore, evolution is considered to be clonal. The bacterial genome is comprised of a larger more stable species core genome and a more diversified set of accessory genes. See Feil et al., Nature Reviews: Microbiology 2:483-495 (2004). The core genes are ubiquitously present in all clones of the species, and the accessory genes are not necessarily present in any given clone. Considering *S. aureus*, one study using a DNA microarray representing more than 90% of the *S. aureus* genome found that 78% of the genes in the genome was common to all *S. aureus* thus representing the "species core", and the remaining 22% are the "accessory genes". The accessory genes comprise dispensable genetic material much of which codes for virulence factors, proteins mediating antibiotic resistance and genes coding for proteins specific for interacting with a particular host environment. See Fitzgerald et al., PNAS 98:8821-8826 (2001); Feil et al., Nature Reviews: Microbiology 2:483-495 (2004). In general, the core genes are more slowly evolving and the accessory genes are polymorphic. See Kuhn et al., J. Bact. 188:169-178 (2006). Therefore,

appropriately selected core genes provide better target antigens for use in immunogenic compositions to prevent infection.

[0112] Surface expressed antigens from disease-causing isolates or clonal types of *S. aureus* offer a source for antigens able to induce immunity and functional antibodies. At the macromolecular level (either amino acid or polysaccharide sequence), conserved forms of the antigen expressed by the different disease isolates may be chosen to permit broad cross reactivity of antibodies to those strains that may possess antigenic variations of the vaccine target.

[0113] One important consideration for including an antigen in the multi-antigen immunogenic compositions described herein is whether the antigen has demonstrated efficacy when administered as an immunogenic composition by providing protection in one or more animal models of bacterial infection. There are numerous animal models for various *S. aureus* diseases. Each of these models has strengths and weaknesses.

[0114] Human clearance of bacterial infections can proceed via opsonic killing that is mediated after phagocyte uptake. There are many convincing examples for this from studies using Gram-positive polysaccharide antigens, such as Streptococcus pneumoniae capsular polysaccharide and *S. aureus* capsular polysaccharide. See Lee et al., Crit. Rev. Micro. 29:333-349 (2003). There is less evidence for opsonic activity induced by Gram-positive protein antigens. Uptake by phagocytes has been observed, but direct killing has been harder to demonstrate. Monoclonal antibodies to proteins have been shown to confer protection against *S. aureus* challenge in animal models of infection; and mechanisms other than opsonophagocytic killing may account for the protection observed.

[0115] The induction of antibodies having a measurable functional activity, such as opsonophagocytic activity (OPA) is one indicator of whether a particular antigen is useful for inclusion in the immunogenic compositions of the present invention. Other indicators include but are not limited to antigen expression on the cell surface during in vivo expression as measured using antigen specific antibodies or the ability of antibodies to inhibit/neutralize antigen function.

Species/ strains

[0116] The type of any particular hospital or disease strain is useful for determining the origin, clonal relatedness and monitoring the epidemiology of outbreaks. Numerous methods are available for typing *S. aureus* strains. The classical practical definition for a bacterial species is a group of strains that are characterized by over 70% genomic hybridization (DNA-DNA genomic hybridization of DDH) and over 97% of 16S ribosomal RNA gene sequence identity. See Vandamme et al., Microbiol. Rev. 60:407-438 (1996). Bacteriophage typing (BT) is a method of typing *S. aureus* strains based on their susceptibility to lysis by certain phage types. See Blair et al., Bull. W.H.O. 24:771-784 (1961). This older method suffers from a lack of reproducibility between laboratories and a failure to type 15-20% of isolates.

Single-Antigen vs Multi-Antigen Immunogenic Compositions

[0117] The question arises as to whether the optimal immunogenic composition to protect against infection of the predominant *S. aureus* strains should be comprised of a single component or multiple components. Numerous studies have shown that immunogenic compositions based on a single protein or carbohydrate component can offer some protection from challenge with a strain of *S. aureus* expressing that component in certain animal models. Importantly, it has also been demonstrated that protection from a single antigen can be dependent on the strain selected.

[0118] Surface proteins such as adhesins have been investigated as single component vaccines. For example, mice immunized with *S. aureus* ClfA developed less severe arthritis than did mice with a control protein. See Josefsson et al., J. Infect. Dis. 184:1572-1580 (2001). Fragments of the collagen binding adhesin (*cna*) offered protection in a mouse sepsis model. See Nilsson, et al., J. Clin. Invest., 101:2640-2649 (1998). Immunization of mice with the A domain of ClfB could reduce nasal colonization in a mouse model. See Schaffer et al., Infect. Immun. 74:2145-2153 (2006).

[0119] One of the fourteen *S. aureus* iron sequestering proteins known as IsdB is being investigated in a monovalent immunogenic formulation for protection from

S. aureus infection. This protein has shown a good protective effect in mice and good immunogenicity in non-human primates. See Kuklin et al., Infect. Immun. 74:2215-2223 (2006).

[0120] Due to the vast potential of *S. aureus* to evolve or substitute different proteins to perform the same or similar functions, the optimal immunogenic formulation for protecting the most people from the most *S. aureus* diseases is a multi-antigen formulation comprising 2 or more (e.g., 3, 4, 5, etc.) antigens properly selected and presented in an immunogenic formulation. In certain embodiments, an immunogenic composition of the invention comprises three or more antigens selected from an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated *S. aureus* clumping factor B (ClfB) polypeptide, an isolated *S. aureus* capsular polysaccharide type 5 (CP5) conjugated to a carrier protein, an isolated *S. aureus* capsular polysaccharide type 8 (CP8) conjugated to a carrier protein and an isolated *S. aureus* MntC protein. In certain embodiments, an immunogenic composition of the invention comprises four or more antigens selected from an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated *S. aureus* clumping factor B (ClfB) polypeptide, an isolated *S. aureus* capsular polysaccharide type 5 (CP5) conjugated to a carrier protein, an isolated *S. aureus* capsular polysaccharide type 8 (CP8) conjugated to a carrier protein and an isolated *S. aureus* MntC protein. In certain embodiments, an immunogenic composition of the invention comprises an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated *S. aureus* clumping factor B (ClfB) polypeptide, an isolated *S. aureus* capsular polysaccharide type 5 (CP5) conjugated to a carrier protein, an isolated *S. aureus* capsular polysaccharide type 8 (CP8) conjugated to a carrier protein and an isolated *S. aureus* MntC protein as antigens.

Adjuvants

[0121] Immunogenic compositions as described herein also comprise, in certain embodiments, one or more adjuvants. An adjuvant is a substance that enhances the immune response when administered together with an immunogen or antigen. A number of cytokines or lymphokines have been shown to have immune modulating activity, and thus are useful as adjuvants, including, but not limited to, the interleukins 1-α, 1-β, 2, 4, 5, 6, 7, 8, 10, 12 (see, *e.g.*, U.S. Patent No. 5,723,127),

13, 14, 15, 16, 17 and 18 (and its mutant forms); the interferons-α, β and γ; granulocyte-macrophage colony stimulating factor (GM-CSF) (see, *e.g.*, U.S. Patent No. 5,078,996 and ATCC Accession Number 39900); macrophage colony stimulating factor (M-CSF); granulocyte colony stimulating factor (G-CSF); and the tumor necrosis factors α and β. Still other adjuvants that are useful with the immunogenic compositions described herein include chemokines, including without limitation, MCP-1, MIP-1α, MIP-1β, and RANTES; adhesion molecules, such as a selectin, *e.g.*, L-selectin, P-selectin and E-selectin; mucin-like molecules, *e.g.*, CD34, GlyCAM-1 and MadCAM-1; a member of the integrin family such as LFA-1, VLA-1, Mac-1 and p150.95; a member of the immunoglobulin superfamily such as PECAM, ICAMs, *e.g.*, ICAM-1, ICAM-2 and ICAM-3, CD2 and LFA-3; co-stimulatory molecules such as B7-1, B7-2,CD40 and CD40L; growth factors including vascular growth factor, nerve growth factor, fibroblast growth factor, epidermal growth factor, PDGF, BL-1, and vascular endothelial growth factor; receptor molecules including Fas, TNF receptor, Flt, Apo-1, p55, WSL-1, DR3, TRAMP, Apo-3, AIR, LARD, NGRF, DR4, DR5, KILLER, TRAIL-R2, TRICK2, and DR6; and Caspase (ICE).

[0122] Suitable adjuvants used to enhance an immune response further include, without limitation, MPL™ (3-O-deacylated monophosphoryl lipid A, Corixa, Hamilton, MT), which is described in U.S. Patent No. 4,912,094. Also suitable for use as adjuvants are synthetic lipid A analogs or aminoalkyl glucosamine phosphate compounds (AGP), or derivatives or analogs thereof, which are available from Corixa (Hamilton, MT), and which are described in United States Patent No. 6,113,918. One such AGP is 2-[(R)-3-Tetradecanoyloxytetradecanoyl-amino] ethyl 2-Deoxy-4-O-phosphono-3-O-[(R)-3-tetradecanoyoxytetradecanoyl]-2-[(R)-3-tetradecanoyloxytetradecanoyl-amino]-b-D-glucopyranoside, which is also known as 529 (formerly known as RC529). This 529 adjuvant is formulated as an aqueous form (AF) or as a stable emulsion (SE).

[0123] Still other adjuvants include muramyl peptides, such as N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-normuramyl-L-alanine-2-(1'-2' dipalmitoyl-*sn*-glycero-3-hydroxyphosphoryloxy)-ethylamine (MTP-PE); oil-in-water emulsions, such as MF59 (U.S. Patent No. 6,299,884) (containing 5%

Squalene, 0.5% polysorbate 80, and 0.5% Span 85 (optionally containing various amounts of MTP-PE) formulated into submicron particles using a microfluidizer such as Model 110Y microfluidizer (Microfluidics, Newton, MA)), and SAF (containing 10% Squalene, 0.4% polysorbate 80, 5% pluronic-blocked polymer L121, and thr-MDP, either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion); incomplete Freund's adjuvant (IFA); aluminum salts (alum), such as aluminum hydroxide, aluminum phosphate, aluminum sulfate; Amphigen; Avridine; L121/squalene; D-lactide-polylactide/glycoside; pluronic polyols; killed *Bordetella*; saponins, such as Stimulon™ QS-21 (Antigenics, Framingham, MA.), described in U.S. Patent No. 5,057,540, ISCOMATRIX (CSL Limited, Parkville, Australia), described in U.S. Patent No. 5,254,339, and immunostimulating complexes (ISCOMATRIX); *Mycobacterium tuberculosis*; bacterial lipopolysaccharides; synthetic polynucleotides such as oligonucleotides containing a CpG motif (*e.g.*, U.S. Patent No. 6,207,646); IC-31 (Intercell AG, Vienna, Austria), described in European Patent Nos. 1,296,713 and 1,326,634; a pertussis toxin (PT) or mutant thereof, a cholera toxin or mutant thereof (*e.g.*, U.S. Patent Nos. 7,285,281, 7,332,174, 7,361,355 and 7,384,640); or an *E. coli* heat-labile toxin (LT) or mutant thereof, particularly LT-K63, LT-R72 (*e.g.*, U.S. Patent Nos. 6,149,919, 7,115,730 and 7,291,588).

Candidate Antigens:

ClfA: Domain organization

[0124] Clumping factor A (ClfA) is a *S. aureus* surface protein associated with binding to host matrix proteins via a fibrinogen binding site. ClfA is a member of a family of proteins containing the carboxyl terminal LPXTG (SEQ ID NO: 125) motif that enables the protein to become covalently linked to the cell surface. ClfA also belongs to another family of proteins (Microbial Surface Components Recognizing Adhesive Matrix Molecule, or MSCRAMMs) that are associated with binding host proteins such as fibrinogen (bound by ClfA), the fibronectin binding proteins (FnbA and FnbB), the collagen binding protein (Cna) and others. These proteins all share the amino terminal signal sequence that mediates transport to the

cell surface. The MSCRAMMs also include an A-domain that is the functional region containing the active site for ligand binding (*e.g.*, fibrinogen, fibronectin, elastin, keratin). The A-domain is followed by a region composed of serine aspartate repeats (SD repeat), which is thought to span the peptidoglycan layer. The SD repeat is followed by a membrane-spanning region that includes the LPXTG (SEQ ID NO: 125) motif for covalent linkage of the protein to peptidoglycan. ClfA is described in U.S. Pat. No. 6,008,341.

[0125] The ligand binding region of ClfA comprising N1N2N3 of the A domain (Figure 1) spans amino acids 40-559. The N domains of ClfA have been assigned as follows: N1 encompasses residues 45-220; N2 encompasses residues 229-369; and N3 encompasses residues 370-559. See Deivanayagam et al. EMBO J. 21:6660-6672 (2002). For ease of reference the N1N2N3 domains may be referred to as N123, likewise N2N3 may be referred to as N23. In preparations of recombinant N1N2N3, the N1 domain has been found to be protease sensitive and is easily cleaved or hydrolyzed to leave the N2N3 as a stable ligand binding recombinant fragment. See Deivanayagam et al. EMBO J. 21:6660-6672 (2002). The crystal structure of the fibrinogen binding N2N3 fragment of ClfA A domain, revealed that both N2 and N3 are dominated by anti-parallel beta strands. In addition to the anti-parallel beta strands, the N2 domain contains a single turn alpha helix and two 3_{10} helices and the N3 domain contains three 3_{10} helices. See Deivanayagam et al. EMBO J. 21:6660-6672 (2002). Sequence alignment of N2 and N3 reveals only 13% sequence identity and 36% sequence similarity over their lengths. See Deivanayagam et al. EMBO J. 21:6660-6672 (2002). The topology of the N2 and N3 domains are similar to the classic IgG fold and have been proposed to be novel variants of the IgG fold. See Deivanayagam et al. EMBO J. 21:6660-6672 (2002).

ClfA Sequence

[0126] The gene for clumping factor protein A, designated ClfA, has been cloned, sequenced and analyzed in detail at the molecular level (McDevitt et al., Mol. Microbiol. 11: 237-248 (1994); McDevitt et al., Mol. Microbiol. 16:895-907 (1995)). The sequence identifiers for the amino acid sequences of ClfA from 111 *S. aureus* disease-causing isolates are shown in Table 10. The amino acid

sequence of the full length (including the signal sequence) wild type ClfA from *S. aureus* strain PFESA0237, is shown in SEQ ID NO: 130. This sequence shows a tyrosine at position 338, which is changed to an alanine in the mutated form of ClfA. The full length gene encoding the wild type ClfA from *S. aureus* strain PFESA0237, comprising the N123 region, the repeat region and the anchor region is shown in SEQ ID NO: 131. The amino acid sequence of the Y338A mutated forms of ClfA is shown in SEQ ID NO: 123. However, it should be noted that the change from a tyrosine to an alanine, which occurs in the wild type ClfA at position 338 of SEQ ID NO: 130, and which is designated as Y338A, is shown in the mutated form of ClfA, in SEQ ID NO: 123 at position 310. Furthermore, the mutated form of ClfA shown in the amino acid sequence of SEQ ID NO: 123 is the mature form of ClfA without the signal sequence, thus accounting for the difference in position of this mutation between SEQ ID NO: 130 and SEQ ID NO: 123.

ClfB: Domain Organization

[0127] ClfB is a *S. aureus* protein having fibrinogen binding activity and triggers *S. aureus* to form clumps in the presence of plasma. ClfB is an MSCRAMM protein and displays the characteristic MSCRAMM domain organization including an A-domain that is the functional region containing the active site for ligand binding (*e.g.*, fibrinogen, fibronectin, elastin, keratin). The A-domain is followed by a region composed of serine aspartate repeats (SD repeat), which is thought to span the peptidoglycan layer. The SD repeat is followed by a membrane-spanning region that includes the LPXTG (SEQ ID NO: 125) motif for covalent linkage of the protein to peptidoglycan. ClfB is described in WO 99/27109 and in US patent 6,680,195.

[0128] The internal organization of ClfB N-terminal A domain is very similar organization as found in ClfA. The A domain is composed of three subdomains N1, N2, and N3. The ligand binding region of ClfB comprising N1N2N3 of the A domain (Figure 1) spans amino acids 44-585. For ease of reference the N1N2N3 domains may be referred to as N123, likewise N2N3 may be referred to as N23. The N domains of ClfB have been assigned as follows: N1 encompasses residues 44_{-197}; N2 encompasses residues 198-375; and N3 encompasses residues 375-585.

In ClfA, the crystal structure of the A domain was found to have a unique version of the immunoglobulin fold and by analogy the same may be speculated to be the case for ClfB. See Deivanayagam et al., EMBO J. 21:6660-6672 (2002). Even though organization of the A domains of ClfB and ClfA are similar, sequence identity is only 26%. See Ni Eidhin et al., Mol. Microbiol. 30:245-257 (2002).

ClfB Sequence

[0129] The gene encoding ClfB is classified as a core adhesion gene. ClfB sequences from 92 strains of *S. aureus* associated with multiple disease states are summarized in Table 11. Additional sequences were obtained from GenBank.

Other MSCRAMMS

[0130] Other MSCRAMMS may be considered for use in an immunogenic composition of the present invention. For example, the serine-aspartate repeat (Sdr) proteins, SdrC, SdrD, and SdrE are related in primary sequence and structural organization to the ClfA and ClfB proteins and are localized on the cell surface. The SdrC, SdrD and SdrE proteins are cell wall-associated proteins, having a signal sequence at the N-terminus and an LPXTG (SEQ ID NO:125) motif, hydrophobic domain and positively charged residues at the C-terminus. Each also has an SD repeat containing region R of sufficient length to allow, along with the B motifs, efficient expression of the ligand binding domain region A on the cell surface. With the A region of the SdrC, SdrD and SdrE proteins located on the cell surface, the proteins can interact with proteins in plasma, the extracellular matrix or with molecules on the surface of host cells. The Sdr proteins share some limited amino acid sequence similarity with ClfA and ClfB. Like ClfA and ClfB, SdrC, SdrD and SdrE also exhibit cation-dependent ligand binding of extracellular matrix proteins.

[0131] The sdr genes are closely linked and tandemly arrayed. The Sdr proteins (of SdrC, SdrD, SdrE, ClfA, and ClfB) characteristically comprise an A region where there is highly conserved amino acid sequence that can be used to derive a consensus TYTFTDYVD (SEQ ID NO: 126) motif. The motif exhibits slight variation between the different proteins. This variation, along with the consensus sequence of the motif is described in US patent number 6,680,195. In the Clf-Sdr

proteins, this motif is highly conserved. The motif can be used in immunogenic compositions to impart broad spectrum immunity to bacterial infections, and also can be used as an antigen in the production of monoclonal or polyclonal antibodies. Such an antibody can be used to impart broad spectrum passive immunity.

[0132] The Sdr proteins differ from ClfA and ClfB by having two to five additional 110-113 residue repeated sequences (B-motifs) located between region A and the R-region. Each B-motif contains a consensus Ca^{2+} -binding EF-hand loop normally found in eukaryotic proteins. The structural integrity of a recombinant protein comprising the five B-repeats of SdrD was shown by bisANS fluorescence analysis to be Ca^{2+} -dependent, suggesting that the EF-hands are functional. When Ca^{2+} was removed the structure collapsed to an unfolded conformation. The original structure was restored by addition of Ca^{2+}. The C-terminal R-domains of the Sdr proteins contain 132-170 SD residues. These are followed by conserved wall-anchoring regions characteristic of many surface proteins of Gram positive bacteria.

[0133] In the Sdr and Clf proteins this B motif is highly conserved while a degenerate version occurs in fibronectin binding MSCRAMMS, as well as the collagen binding protein Cna. The B motifs, in conjunction with the R regions, are necessary for displaying the ligand-binding domain at some distance from the cell surface. The repeated B motifs are one common denominator of the sub-group of SD repeat proteins described herein. These motifs are found in different numbers in the three Sdr proteins from strain PFESA0237. There are clear distinctions between the individual B motifs. The most conserved units are those located adjacent to the R regions (SdrC B2, SdrD B5 and SdrE B3). They differ from the rest at several sites, especially in the C-terminal half. A noteworthy structural detail is that adjacent B repeats are always separated by a proline residue present in the C-terminal region, but a proline never occurs between the last B repeats and the R region. Instead this linker is characterized by a short acidic stretch. These differences are evidence that the end units have a different structural or functional role compared to the other B motifs. The N-terminal B motifs of SdrD and SdrE have drifted apart from the others, and there are numerous amino acid alterations,

including small insertions and deletions whereas the remaining internal B motifs are more highly conserved. Note that each of the three Sdr proteins has at least one B motif of each kind.

[0134] The C-terminal R-domains of the Sdr proteins contain 132-170 SD residues. These are followed by conserved wall-anchoring regions characteristic of many surface proteins of Gram positive bacteria.

[0135] Other candidate SdrD molecules may be derived from various species of organisms for use in an immunogenic composition of the invention, some of which include the following SdrD from *S. aureus*: strain USA300 FPR3757 (protein accession number SAUSA300 0547); strain NCTC8325 (protein accession number SAOUHSC 00545); strain MW2 (protein accession number MW0517); strain MSSA476 (protein accession number SAS0520; and strain Mu50 (protein accession number SAV0562).

[0136] Further MSCRAMMS which may be considered for use in an immunogenic composition of the present invention include EkeS, DsqA, KesK, KrkN, KrkN2, RkaS, RrkN, and KnkA. These MSCRAMMS are described in WO 02/102829, which is hereby incorporated by reference. Additional MSCRAMMS, identified by GenBank Accession No., include NP_373261.1, NP_373371.1, NP_374246.1, NP_374248.1, NP_374841.1, NP_374866.1, NP_375140.1, NP_375614.1, NP_375615.1, NP_375707.1, NP_375765.1, and NP_375773.1.

Capsule Polysaccharides Type 5 and Type 8

[0137] Staphylococcal microorganisms capable of causing invasive disease generally also are capable of producing a capsule polysaccharide (CP) that encapsulates the bacterium and enhances its resistance to clearance by host innate immune system. The CP serves to cloak the bacterial cell in a protective capsule that renders the bacteria resistant to phagocytosis and intracellular killing. Bacteria lacking a capsule are more susceptible to phagocytosis. Capsular polysaccharides are frequently an important virulence factor for many bacterial pathogens, including *Haemophilus influenzae*, *Streptococcus pneumoniae* and Group B streptococci.

[0138] The capsule polysaccharide can be used to serotype a particular species of bacteria. Typing is usually accomplished by reaction with a specific antiserum or monoclonal antibody generated to a specific structure or unique epitope characteristic of the capsule polysaccharide. Encapsulated bacteria tend to grow in smooth colonies whereas colonies of bacteria that have lost their capsules appear rough. Colonies producing a mucoid appearance are known as Heavily Encapsulated. Types 1 and 2 of *S. aureus* are heavily encapsulated and are rarely associated with disease.

[0139] Most clinical isolates of *S. aureus* are encapsulated with either serotypes 5 or 8. The type 5 (CP5) and type 8 (CP8) capsular polysaccharides have similar trisaccharide repeating units comprised of N-acetyl mannosaminuronic acid, N-acetyl L-fucosamine, and N-acetyl D-fucosamine. See Fournier, J.M. et al., Infect. Immun. 45:97-93 (1984) and Moreau, M., et al., Carbohydrate Res. 201:285-297 (1990). The two CPs, which have the same sugars, but differ in the sugar linkages and in sites of O acetylation to produce serologically distinct patterns of immunoreactivity.

[0140] In some embodiments, the serotype 5 and/or 8 capsular polysaccharides of the invention are O-acetylated. In some embodiments, the degree of O-acetylation of type 5 capsular polysaccharide or oligosaccharide is 10-100%, 20-100%, 30-100%, 40-100%, 50-100%, 60-100%, 70-100%, 80-100%, 90-100%, 50- 90%, 60-90%, 70-90% or 80-90%. In some embodiments, the degree of O-acetylation of type 8 capsular polysaccharide or oligosaccharide is 10-100%, 20-100%, 30-100%, 40-100%, 50-100%, 60-100%, 70-100%, 80-100%, 90-100%, 50-90%, 60-90%, 70-90% or 80-90%. In some embodiments, the degree of O-acetylation of type 5 and type 8 capsular polysaccharides or oligosaccharides is 10-100%, 20-100%, 30-100%, 40-100%, 50-100%, 60-100%, 70-100%, 80-100%, 90-100%, 50-90%, 60-90%, 70-90% or 80-90%.

[0141] The degree of O-acetylation of the polysaccharide or oligosaccharide can be determined by any method known in the art, for example, by proton NMR (Lemercinier and Jones 1996, Carbohydrate Research 296; 83-96, Jones and Lemercinier 2002, J Pharmaceutical and Biomedical Analysis 30; 1233-1247, WO

05/033148 or WO 00/56357). Another commonly used method is described by Hestrin (1949) J. Biol. Chem. 180; 249-261.

[0142] In some embodiments, the serotype 5 and/or 8 capsular polysaccharides of the invention are used to generate antibodies that are functional as measured by the killing of bacteria in an animal efficacy model or an opsonophagocytic killing assay that demonstrates that the antibodies kill the bacteria. Such functionality may not be observed using an assay that monitors the generation of antibodies alone, which is not indicative of the importance of O-acetylation in efficacy.

Capsule Epidemiology

[0143] The association of particular capsule serotypes with disease is possible through monitoring of clinical isolates. Of the eight different serotypes of *S. aureus* identified (Karakawa and Vann (1982) only serotypes 1 and 2 are heavily encapsulated, and these are rarely isolated. See Capsular Polysaccharides of *Staphylococcus aureus*, p. 285-293. In J.B. Robbins, J.C. Hill and J.C. Sadoff (ed.), Seminars in infectious disease, vol. 4, Bacterial Vaccines. Thieme Stratton, Inc. New York). Surveys have shown that approximately 85-90% of *S. aureus* clinical isolates express CP5 or CP8 (Arbeit RD, et al., Diagn. Microbiol. Infect. Dis. (1984) Apr;2(2):85-91; Karakawa WW, et al., J. Clin. Microbiol. (1985) Sep;22(3):445-7; Essawi T, et al., Trop. Med. Int. Health. (1998) Jul;3(7):576-83; Na'was T, et al., J. Clin. Microbiol. (1998) 36(2):414-20. Most of CP5 and CP8 non-typeable strains are genetically type 5 or type 8 containing mutations in *cap5/8* locus (Cocchiaro, Gomez et al., (2006), Mol. Microbiol. Feb. 59(3):948-960). Capsulation for some strains is lost rapidly within few passages *in vitro* which is due to a repressive effect of high phosphate concentration in media used in clinical diagnosis on capsule production. It was also reported that non-capsulated isolates recover capsule expression after passing through cows. See Opdebeck, J.P. et al., J. Med. Microbiol. 19:275-278 (1985). Some non-typeable strains become capsule positive under appropriate growth conditions.

CP5 and CP8 Structure

[0144] The repeat unit of both CP5 and CP8 is comprised of 2-acetamido-2-deoxy-D-mannuronic acid, 2-acetamido-2-deoxy-L-fucose and 2-acetamido-2-

deoxy-D-fucose. See C. Jones et al., Carbohydr. Res. 340:1097-1106 (2005). Although CP5 and CP8 have the same sugar composition, they have been demonstrated to be immunologically distinct. They differ in glycosidic linkages and site of O-acetylation of uronic acid. Strain dependent incomplete N-acetylation of one of the FucNAc residues was observed. See Tzianabos et al., PNAS V98: 9365(2001).

S. aureus *Capsule Polysaccharide in an Immunogenic Composition*

[0145] The molecular weight of the *S. aureus* capsule polysaccharides is an important consideration for use in immunogenic compositions. High molecular weight capsule polysaccharides are able to induce certain antibody immune responses due to a higher valency of the epitopes present on the antigenic surface. The methods described herein provide for isolation and purification of much higher molecular weight capsule polysaccharide type 5 and type 8 than was previously available.

MntC/SitC /Saliva Binding Protein

[0146] MntC/SitC /Saliva Binding Protein is an ABC transporter protein and has homologues in *S. epidermidis* and *S. aureus*. It is referred to in the present invention as MntC. This protein is a 32 kDa lipoprotein and is located in the bacterial cell wall. See Sellman et al., and Cockayne et al., Infect. Immun. 66: 3767(1998). In *S. epidermidis*, it is a component of an iron-regulated operon. It shows considerable homology to both adhesins including FimA of *S. parasanguis*, and with lipoproteins of a family of ABC transporters with proven or putative metal iron transport functions. (See Table 12 for strains of *S. aureus* and sequences.)

S. aureus *MntC protein*

[0147] The *S. aureus* homologue of MntC is known as saliva binding protein and was disclosed in U.S. Pat. No. 5,801,234 and can be included in an immunogenic composition of the invention. The protein sequence for the *S. aureus* homologue of MntC/SitC/Saliva Binding Protein is found in GenBank accession number NP_371155 for strain Mu50. (Also known as SAV0631.) The sequence identifier

is SEQ ID NO: 119. The accession number for the nucleotide sequence for the complete genome of strain Mu50 is NC_002758.2 (coordinates 704988-705917).

S. epidermidis *SitC protein*

[0148] The *S. epidermidis* homologue of MntC/SitC/Saliva Binding Protein is known as SitC and was disclosed in Sellman et al., (Sellman et al., Infect. Immun. 2005 October; 73(10): 6591- 6600). The protein sequence for the *S. epidermidis* homologue of MntC/SitC/Saliva Binding Protein is found in GenBank accession number YP_187886.1. (Also known as SERP0290.). The sequence identifier is SEQ ID NO: 121.

[0149] The accession number for the nucleotide sequence for the complete genome of strain RP62A, is NC_002976 (coordinates 293030-293959). Other candidate SitC molecules may be derived from various species of organisms for use in an immunogenic composition of the invention, some of which are listed in Table 1 below.

Table 1

Protein	Species	Example strain	Protein Accession
SitC	S. haemolyticus	JCSC1435	BAE03450.1
SitC	S. epidermidis	ATCC 12228	AAO04002.1
SitC	S. saprophyticus	ATCC 15305	BAE19233.1
SitC	S. xylosus	DSM20267	ABR57162.1
SitC	S. carnosus	TM300	CAL27186.1

S. aureus Iron Binding Proteins

[0150] Another potential candidate antigen to be considered for use in the immunogenic compositions of the invention include the *S. aureus* surface protein iron surface determinant B (IsdB). This MSCRAMM was described by Mazmanian et al. (Mazmanian, SK et al. Proc. Natl. Acad. Sci.. USA 99:2293-2298 (2002)) and it has subsequently been tested and shown to be effective as a vaccine candidate in a murine model of infection and a rhesus macaque immunogenicity study by Kuklin, et al. (Kuklin. NA. et al. Infection and Immunity, Vol. 74, No. 4, 2215-2223, (2006)). This IsdB molecule is present in various strains of *S. aureus*, including strain MRSA252 (protein accession number CAG40104.1); strain

Newman (protein accession number BAF67312.1); strain MSSA476 (protein accession number CAG42837.1); strain Mu3 (protein accession number BAF78003.1); strain RF122 (protein accession number CAI80681.1).

Candidate Antigens:

[0151] The immunogenic compositions of the present invention may also include one or more of the following antigens: Opp3a, DltD, HtsA, LtaS, IsdA, IsdC, SdrF, SdrG, SdrH, SrtA, SpA, Sbi alpha-hemolysin (hla), beta-hemolysin, fibronectin-binding protein A (fnbA), fibronectin-binding protein B (fnbB), coagulase, Fig, map, Panton-Valentine leukocidin (pvl), alpha-toxin and its variants, gamma-toxin (hlg) and variants, ica, immunodominant ABC transporter, Mg^{2+} transporter, Ni ABC transporter, RAP, autolysin, laminin receptors, IsaA/PisA, IsaB/PisB , SPOIIIE, SsaA, EbpS, Sas A, SasF, SasH, EFB (FIB), SBI, Npase, EBP, bone sialo binding protein II, aureolysin precursor (AUR)/Sepp1, Cna, and fragments thereof such as M55, TSST-1, mecA, poly-N-acetylglucosamine (PNAG/dPNAG) exopolysaccharide, GehD, EbhA, EbhB, SSP-1, SSP-2, HBP, vitronectin binding protein, HarA, EsxA, EsxB, Enterotoxin A, Enterotoxin B, Enterotoxin C1, and novel autolysin. In certain embodiments of the invention, when the immunogenic composition comprises certain forms of CP5 and/or CP8, it may not further comprise PNAG.

Immunogenic Composition Formulations

[0152] In one embodiment, the immunogenic compositions of the invention further comprise at least one of an adjuvant, a buffer, a cryoprotectant, a salt, a divalent cation, a non-ionic detergent, an inhibitor of free radical oxidation, a diluent or a carrier.

[0044] The immunogenic compositions of the invention may further comprise one or more preservatives in addition to a plurality of staphylococcal protein antigens and capsular polysaccharide-protein conjugates. The FDA requires that biological products in multiple-dose (multi-dose) vials contain a preservative, with only a few exceptions. Vaccine products containing preservatives include vaccines containing benzethonium chloride (anthrax), 2-phenoxyethanol (DTaP, HepA, Lyme, Polio (parenteral)), phenol (Pneumo, Typhoid (parenteral), Vaccinia) and

thimerosal (DTaP, DT, Td, HepB, Hib, Influenza, JE, Mening, Pneumo, Rabies). Preservatives approved for use in injectable drugs include, e.g., chlorobutanol, m-cresol, methylparaben, propylparaben, 2-phenoxyethanol, benzethonium chloride, benzalkonium chloride, benzoic acid, benzyl alcohol, phenol, thimerosal and phenylmercuric nitrate.

[0153] Formulations of the invention may further comprise one or more of a buffer, a salt, a divalent cation, a non-ionic detergent, a cryoprotectant such as a sugar, and an anti-oxidant such as a free radical scavenger or chelating agent, or any multiple combination thereof. The choice of any one component, e.g., a chelator, may determine whether or not another component (e.g., a scavenger) is desirable. The final composition formulated for administration should be sterile and/or pyrogen free. The skilled artisan may empirically determine which combinations of these and other components will be optimal for inclusion in the preservative containing immunogenic compositions of the invention depending on a variety of factors such as the particular storage and administration conditions required.

[0154] In certain embodiments, a formulation of the invention which is compatible with parenteral administration comprises one or more physiologically acceptable buffers selected from, but not limited to, Tris (trimethamine), phosphate, acetate, borate, citrate, glycine, histidine and succinate. In certain embodiments, the formulation is buffered to within a pH range of about 6.0 to about 9.0, preferably from about 6.4 to about 7.4.

[0155] In certain embodiments, it may be desirable to adjust the pH of the immunogenic composition or formulation of the invention. The pH of a formulation of the invention may be adjusted using standard techniques in the art. The pH of the formulation may be adjusted to be between 3.0 and 8.0. In certain embodiments, the pH of the formulation may be, or may adjusted to be, between 3.0 and 6.0, 4.0 and 6.0, or 5.0 and 8.0. In other embodiments, the pH of the formulation may be, or may adjusted to be, about 3.0, about 3.5, about 4.0, about 4.5, about 5.0, about 5.5, about 5.8, about 6.0, about 6.5, about 7.0, about 7.5, or about 8.0. In certain embodiments, the pH may be, or may adjusted to be, in a range from 4.5 to 7.5, or from 4.5 to 6.5, from 5.0 to 5.4, from 5.4 to 5.5, from 5.5

to 5.6, from 5.6 to 5.7, from 5.7 to 5.8, from 5.8 to 5.9, from 5.9 to 6.0, from 6.0 to 6.1, from 6.1 to 6.2, from 6.2 to 6.3, from 6.3 to 6.5, from 6.5 to 7.0, from 7.0 to 7.5 or from 7.5 to 8.0. In a specific embodiment, the pH of the formulation is about 5.8.

[0156] In certain embodiments, a formulation of the invention which is compatible with parenteral administration comprises one or more divalent cations, including but not limited to $MgCl_2$, $CaCl_2$ and $MnCl_2$, at a concentration ranging from about 0.1 mM to about 10 mM, with up to about 5 mM being preferred.

[0157] In certain embodiments, a formulation of the invention which is compatible with parenteral administration comprises one or more salts, including but not limited to sodium chloride, potassium chloride, sodium sulfate, and potassium sulfate, present at an ionic strength which is physiologically acceptable to the subject upon parenteral administration and included at a final concentration to produce a selected ionic strength or osmolarity in the final formulation. The final ionic strength or osmolality of the formulation will be determined by multiple components (e.g., ions from buffering compound(s) and other non-buffering salts. A preferred salt, NaCl, is present from a range of up to about 250 mM, with salt concentrations being selected to complement other components (e.g., sugars) so that the final total osmolarity of the formulation is compatible with parenteral administration (e.g., intramuscular or subcutaneous injection) and will promote long term stability of the immunogenic components of the immunogenic composition formulation over various temperature ranges. Salt-free formulations will tolerate increased ranges of the one or more selected cryoprotectants to maintain desired final osmolarity levels.

[0158] In certain embodiments, a formulation of the invention which is compatible with parenteral administration comprises one or more cryoprotectants selected from but not limited to disaccharides (e.g., lactose, maltose, sucrose or trehalose) and polyhydroxy hydrocarbons (e.g., dulcitol, glycerol, mannitol and sorbitol).

[0159] In certain embodiments, the osmolarity of the formulation is in a range of from about 200 mOs/L to about 800 mOs/L, with a preferred range of from about 250 mOs/L to about 500 mOs/L, or about 300 mOs/L - about 400 mOs/L. A

salt-free formulation may contain, for example, from about 5% to about 25% sucrose, and preferably from about 7% to about 15%, or about 10% to about 12% sucrose. Alternatively, a salt-free formulation may contain, for example, from about 3% to about 12% sorbitol, and preferably from about 4% to 7%, or about 5% to about 6% sorbitol. If salt such as sodium chloride is added, then the effective range of sucrose or sorbitol is relatively decreased. These and other such osmolality and osmolarity considerations are well within the skill of the art.

[0160] In certain embodiments, a formulation of the invention which is compatible with parenteral administration comprises one or more free radical oxidation inhibitors and/or chelating agents. A variety of free radical scavengers and chelators are known in the art and apply to the formulations and methods of use described herein. Examples include but are not limited to ethanol, EDTA, a EDTA/ethanol combination, triethanolamine, mannitol, histidine, glycerol, sodium citrate, inositol hexaphosphate, tripolyphosphate, ascorbic acid/ascorbate, succinic acid/succinate, malic acid/maleate, desferal, EDDHA and DTPA, and various combinations of two or more of the above. In certain embodiments, at least one non-reducing free radical scavenger may be added at a concentration that effectively enhances long term stability of the formulation. One or more free radical oxidation inhibitors/chelators may also be added in various combinations, such as a scavenger and a divalent cation. The choice of chelator will determine whether or not the addition of a scavenger is needed.

[0161] In certain embodiments, a formulation of the invention which is compatible with parenteral administration comprises one or more non-ionic surfactants, including but not limited to polyoxyethylene sorbitan fatty acid esters, Polysorbate-80 (Tween 80), Polysorbate-60 (Tween 60), Polysorbate-40 (Tween 40) and Polysorbate-20 (Tween 20), polyoxyethylene alkyl ethers, including but not limited to Brij 58, Brij 35, as well as others such as Triton X-100; Triton X-114, NP40, Span 85 and the Pluronic series of non-ionic surfactants (e.g., Pluronic 121), with preferred components Polysorbate-80 at a concentration from about 0.001% to about 2% (with up to about 0.25% being preferred) or Polysorbate-40 at a concentration from about 0.001% to 1% (with up to about 0.5% being preferred).

[0162] In certain embodiments, a formulation of the invention comprises one or more additional stabilizing agents suitable for parenteral administration, e.g., a reducing agent comprising at least one thiol (-SH) group (e.g., cysteine, N-acetyl cysteine, reduced glutathione, sodium thioglycolate, thiosulfate, monothioglycerol, or mixtures thereof). Alternatively or optionally, preservative-containing immunogenic composition formulations of the invention may be further stabilized by removing oxygen from storage containers, protecting the formulation from light (e.g., by using amber glass containers).

[0163] Preservative-containing immunogenic composition formulations of the invention may comprise one or more pharmaceutically acceptable carriers or excipients, which includes any excipient that does not itself induce an immune response. Suitable excipients include but are not limited to macromolecules such as proteins, saccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, sucrose (Paoletti et al, 2001, *Vaccine*, 19:2118), trehalose, lactose and lipid aggregates (such as oil droplets or liposomes). Such carriers are well known to the skilled artisan. Pharmaceutically acceptable excipients are discussed, e.g., in Gennaro, 2000, Remington: The Science and Practice of Pharmacy, 20th edition, ISBN:0683306472.

[0164] Compositions of the invention may be lyophilized or in aqueous form, i.e. solutions or suspensions. Liquid formulations may advantageously be administered directly from their packaged form and are thus ideal for injection without the need for reconstitution in aqueous medium as otherwise required for lyophilized compositions of the invention.

[0165] Direct delivery of immunogenic compositions of the present invention to a subject may be accomplished by parenteral administration (intramuscularly, intraperitoneally, intradermally, subcutaneously, intravenously, or to the interstitial space of a tissue); or by rectal, oral, vaginal, topical, transdermal, intranasal, ocular, aural, pulmonary or other mucosal administration. In a preferred embodiment, parenteral administration is by intramuscular injection, e.g., to the thigh or upper arm of the subject. Injection may be via a needle (e.g., a hypodermic needle), but needle free injection may alternatively be used. A typical intramuscular dose is 0.5mL. Compositions of the invention may be prepared in

various forms, e.g., for injection either as liquid solutions or suspensions. In certain embodiments, the composition may be prepared as a powder or spray for pulmonary administration, e.g., in an inhaler. In other embodiments, the composition may be prepared as a suppository or pessary, or for nasal, aural or ocular administration, e.g., as a spray, drops, gel or powder.

[0166] Optimal amounts of components for a particular immunogenic composition may be ascertained by standard studies involving observation of appropriate immune responses in subjects. Following an initial vaccination, subjects can receive one or several booster immunizations adequately spaced.

Packaging and Dosage Forms

[0167] Immunogenic compositions of the invention may be packaged in unit dose or multi-dose form (e.g. 2 doses, 4 doses, or more). For multi-dose forms, vials are typically but not necessarily preferred over pre-filled syringes. Suitable multi-dose formats include but are not limited to: 2 to 10 doses per container at 0.1 to 2 mL per dose. In certain embodiments, the dose is a 0.5 ml. dose. See, e.g., International Patent Application WO2007/127668, which is incorporated by reference herein.

Compositions may be presented in vials or other suitable storage containers, or may be presented in pre-filled delivery devices, e.g., single or multiple component syringes, which may be supplied with or without needles. A syringe typically but need not necessarily contains a single dose of the preservative-containing immunogenic composition of the invention, although multi-dose, pre-filled syringes are also envisioned. Likewise, a vial may include a single dose but may alternatively include multiple doses.

[0168] Effective dosage volumes can be routinely established, but a typical dose of the composition for injection has a volume of 0.5 mL. In certain embodiments, the dose is formulated for administration to a human subject. In certain embodiments, the dose is formulated for administration to an adult, teen, adolescent, toddler or infant (i.e., no more than one year old) human subject and may in preferred embodiments be administered by injection.

[0169] Liquid immunogenic compositions of the invention are also suitable for reconstituting other immunogenic compositions which are presented in lyophilized

form. Where an immunogenic composition is to be used for such extemporaneous reconstitution, the invention provides a kit with two or more vials, two or more ready-filled syringes, or one or more of each, with the contents of the syringe being used to reconstitute the contents of the vial prior to injection, or vice versa.

[0170] Alternatively, immunogenic compositions of the present invention may be lyophilized and reconstituted, e.g., using one of a multitude of methods for freeze drying well known in the art to form dry, regular shaped (e.g., spherical) particles, such as micropellets or microspheres, having particle characteristics such as mean diameter sizes that may be selected and controlled by varying the exact methods used to prepare them. The immunogenic compositions may further comprise an adjuvant which may optionally be prepared with or contained in separate dry, regular shaped (e.g., spherical) particles such as micropellets or microspheres. In such embodiments, the present invention further provides an immunogenic composition kit comprising a first component that includes a stabilized, dry immunogenic composition, optionally further comprising one or more preservatives of the invention, and a second component comprising a sterile, aqueous solution for reconstitution of the first component. In certain embodiments, the aqueous solution comprises one or more preservatives, and may optionally comprise at least one adjuvant (see, e.g., WO2009/109550 (incorporated herein by reference).

[0171] In yet another embodiment, a container of the multi-dose format is selected from one or more of the group consisting of, but not limited to, general laboratory glassware, flasks, beakers, graduated cylinders, fermentors, bioreactors, tubings, pipes, bags, jars, vials, vial closures (e.g., a rubber stopper, a screw on cap), ampoules, syringes, dual or multi-chamber syringes, syringe stoppers, syringe plungers, rubber closures, plastic closures, glass closures, cartridges and disposable pens and the like. The container of the present invention is not limited by material of manufacture, and includes materials such as glass, metals (e.g., steel, stainless steel, aluminum, etc.) and polymers (e.g., thermoplastics, elastomers, thermoplastic-elastomers). In a particular embodiment, the container of the format is a 5 mL Schott Type 1 glass vial with a butyl stopper. The skilled artisan will appreciate that the format set forth above is by no means an exhaustive list, but

merely serve as guidance to the artisan with respect to the variety of formats available for the present invention. Additional formats contemplated for use in the present invention may be found in published catalogues from laboratory equipment vendors and manufacturers such as United States Plastic Corp. (Lima, OH), VWR.

Evaluation of Immunogenic Compositions

[0172] In one embodiment, the present invention provides immunogenic compositions comprising at least three antigens from a *S. aureus* organism.

[0173] Various *in vitro* tests are used to assess the immunogenicity of the immunogenic compositions of the invention. For example, an *in vitro* opsonic assay is conducted by incubating together a mixture of staphylococcal cells, heat inactivated serum containing specific antibodies to the antigens in question, and an exogenous complement source. Opsonophagocytosis proceeds during incubation of freshly isolated polymorphonuclear cells (PMN's) or differentiated effector cells such as HL60s and the antibody/complement/staphylococcal cell mixture. Bacterial cells that are coated with antibody and complement are killed upon opsonophagocytosis. Colony forming units (cfu) of surviving bacteria that are recovered from opsonophagocytosis are determined by plating the assay mixture. Titers are reported as the reciprocal of the highest dilution that gives 50% bacterial killing, as determined by comparison to assay controls.

[0174] A whole cell ELISA assay is also used to assess *in vitro* immunogenicity and surface exposure of the antigen, wherein the bacterial strain of interest (*S. aureus*) is coated onto a plate, such as a 96 well plate, and test sera from an immunized animal is reacted with the bacterial cells. If any antibody, specific for the test antigen, is reactive with a surface exposed epitope of the antigen, it can be detected by standard methods known to one skilled in the art.

[0175] Any antigen demonstrating the desired *in vitro* activity is then tested in an *in vivo* animal challenge model. In certain embodiments, immunogenic compositions are used in the immunization of an animal (*e.g.*, a mouse) by methods and routes of immunization known to those of skill in the art (*e.g.*, intranasal, parenteral, oral, rectal, vaginal, transdermal, intraperitoneal, intravenous, subcutaneous, etc.). Following immunization of the animal with a particular *Staphylococcus sp.* immunogenic composition, the animal is challenged

with a *Staphylococcus sp.* and assayed for resistance to the staphylococcal infection.

[0176] In one embodiment, pathogen-free mice are immunized and challenged with *S. aureus*. For example, mice are immunized with one or more doses of the desired antigen in an immunogenic composition. Subsequently, the mice are challenged with *S. aureus* and survival is monitored over time post challenge.

Methods of Immunizing

[0177] Provided also are methods for immunizing a host to prevent staphylococcal infection. In a preferred embodiment, the host is human. Thus, a host or subject is administered an immunogenic amount of an immunogenic composition as described herein. An immunogenic amount of an immunogenic composition can be determined by doing a dose response study in which subjects are immunized with gradually increasing amounts of the immunogenic composition and the immune response analyzed to determine the optimal dosage. Starting points for the study can be inferred from immunization data in animal models. The dosage amount can vary depending upon specific conditions of the individual. The amount can be determined in routine trials by means known to those skilled in the art. In some embodiments, the method of immunizing a host to prevent staphylococcal infection, disease or condition comprises human, veterinary, animal, or agricultural treatment. Another embodiment provides a method of immunizing a host to prevent staphylococcal infection, disease or condition associated with a *Staphylococcus sp.* in a subject, the method comprising generating a polyclonal or monoclonal antibody preparation from the immunogenic composition described herein, and using said antibody preparation to confer passive immunity to the subject.

[0178] An immunologically effective amount of the immunogenic composition in an appropriate number of doses is administered to the subject to elicit an immune response. The treated individual should not exhibit the more serious clinical manifestations of the staphylococcal infection. The dosage amount can vary depending upon specific conditions of the individual, such as age and weight. This amount can be determined in routine trials by means known to those skilled in the art.

[0179] In one embodiment, patients being administered immunogenic compositions of the invention show a reduction in *S. aureus* carriage rates. Such reduction in carriage or a prolonged interval of time spent as a non-carrier following administration of an immunogenic composition is significant from a medical need perspective. For example, reduction in overall *S. aureus* carriage in carriers may be assessed following one dose of *S. aureus* multi-antigen vaccine. For example, 1 day prior to administration of an immunogenic composition, a group of adults aged 18-50 years may be screened for carriage by nasal and throat swabs followed by cultivation to determine their carriage state. Next, the group can be administered an immunogenic composition of the invention with a group receiving a control. Nasal and throat swabs performed weekly over a 12 week period, and monthly up to 6 months post administration of the immunogenic composition are performed and compared to placebo. One primary endpoint is to compare carriage rates in patients after administration of an immunogenic composition versus placebo at 3 month intervals post immunization.

Animal Models of Staphylococcal Infection

[0180] Several animal models are described below for use in assessing the efficacy of any one of the immunogenic compositions described herein.

Murine Sepsis Model (Passive or Active)

Passive Immunization Model

[0181] Mice are passively immunized intraperitoneally (i.p.) with immune IgG or monoclonal antibody. The mice are subsequently challenged 24 hours later with a lethal dose of *S. aureus*. The bacterial challenge is administered intravenously (i.v.) or i.p. ensuring that any survival could be attributed to the specific *in vivo* interaction of the antibody with the bacteria. The bacterial challenge dose is determined to be the dose required to achieve lethal sepsis of approximately 20% of the unimmunized control mice. Statistical evaluation of survival studies can be carried out by Kaplan-Meier analysis.

Active Immunization Model

[0182] In this model, mice (e.g. Swiss Webster mice) are actively immunized intraperitoneally (i.p.) or subcutaneously (s.c.) with a target antigen at 0, 3 and 6 weeks (or other similar appropriately spaced vaccination schedule) and subsequently challenged with *S. aureus* at week 8 by the intravenous route. The bacterial challenge dose is calibrated to achieve approximately 20% survival in the control group over a 10-14 day period. Statistical evaluation of survival studies can be carried out by Kaplan-Meier analysis.

Infectious Endocarditis Model (Passive or Active)

[0183] A passive immunization model for infectious endocarditis (IE) caused by *S. aureus* has previously been used to show that ClfA can induce protective immunity. See Vernachio et al., Antmicro. Agents & Chemo. 50:511-518 (2006). In this model of IE, rabbits or rats are used to simulate clinical infections that include a central venous catheter, bacteremia, and hematogenous seeding to distal organs. Catheterized rabbits or rats with sterile aortic valve vegetations are administered a single or multiple intravenous injection of a monoclonal or polyclonal antibody specific for the target antigen. Subsequently, the animals are challenged i.v. with a *S. aureus* or *S. epidermidis* strain. Then after challenge, heart, cardiac vegetations, and additional tissues, including kidneys, and blood are harvested and cultured. The frequency of staphylococcal infection in cardiac tissue, kidneys, and blood is then measured. In one study, when animals were challenged with either MRSE ATCC 35984 or MRSA 67-0, significant reductions in infection rate were shown using either the polyclonal antibody preparation or the monoclonal antibody to ClfA. See Vernachio et al., Antmicro. Agents & Chemo. 50:511-518 (2006).

[0184] The infectious endocarditis model has also been adapted for active immunization studies in both rabbits and rats. Rabbits or rats are immunized intramuscularly or subcutaneously with target antigen and challenged with *S. aureus* two weeks later via the intravenous route.

Pyelonephritis Model

[0185] In the pyelonephritis model, mice are immunized on wks 0, 3 and 6 (or other appropriately spaced immunization schedule) with the target antigens. Subsequently, the animals are challenged i.p. or i.v. with *S. aureus* PFESA0266. After 48 hrs, the kidneys are harvested and bacterial CFU are enumerated.

Antibodies and Antibody Compositions

[0186] The invention further provides antibodies and antibody compositions which bind specifically and selectively to one or more antigens of an immunogenic composition of the present invention. In some embodiments, antibodies are generated upon administration to a subject of an immunogenic composition of the present invention. In some embodiments, the invention provides purified or isolated antibodies directed against one or more of the antigens of an immunogenic composition of the present invention. In some embodiments, the antibodies of the present invention are functional as measured by killing bacteria in either an animal efficacy model or via an opsonophagocytic killing assay. In some embodiments, the antibodies of the invention confer passive immunity to a subject. The present invention further provides polynucleotide molecules encoding an antibody or antibody fragment of the invention, and a cell or cell line (such as hybridoma cells or other engineered cell lines for recombinant production of antibodies) and a transgenic animal that produces an antibody or antibody composition of the invention, using techniques well-known to those of skill in the art.

[0187] Antibodies or antibody compositions of the invention may be used in a method of treating or preventing a Staphylococcal infection, disease or condition associated with a *Staphylococcus sp.* in a subject, the method comprising generating a polyclonal or monoclonal antibody preparation, and using said antibody or antibody composition to confer passive immunity to the subject. Antibodies of the invention may also be useful for diagnostic methods, e.g., detecting the presence of or quantifying the levels of one or more antigens of the immunogenic compositions of the present invention.

EXAMPLES

[0188] The following examples demonstrate some embodiments of the present invention. However, it is to be understood that these examples are for illustration only and do not purport to be wholly definitive as to conditions and scope of this invention. It should be appreciated that when typical reaction conditions (*e.g.*, temperature, reaction times, etc.) have been given, the conditions both above and below the specified ranges can also be used, though generally less conveniently. All parts and percents referred to herein are on a weight basis and all temperatures are expressed in degrees centigrade unless otherwise specified.

[0189] Furthermore, the following examples were carried out using standard techniques, which are well known and routine to those of skill in the art, except where otherwise described in detail. As noted above, the following examples are presented for illustrative purpose, and should not be construed in any way limiting the scope of this invention.

Example 1: Production of Antigens ClfA and ClfB

[0190] Clumping factor A (ClfA) and B (ClfB) are *S. aureus* surface proteins responsible for binding to host proteins including fibrinogen (ClfA, ClfB) and cytokeratin 10 (ClfB). ClfA and ClfB are members of a family of proteins containing the carboxyl terminal LPXTG (SEQ ID NO: 125) motif that enables the protein to become covalently linked to the cell surface. Both ClfA and ClfB belong to family of proteins (Microbial Surface Components Recognizing Adhesive Matrix Molecule, or MSCRAMMs) that recognize and bind host extracellular matrix proteins such as fibrinogen (ClfA and ClfB), fibronectin (FnbA and FnbB), collagen (Cna), and others. These proteins all share the amino terminal signal sequence that mediates transport to the cell surface. The MSCRAMMs also include an A-domain that is the functional region containing ligand-binding site for fibrinogen, fibronectin, elastin, and keratin. The A-domain can be followed by a region composed of serine-aspartate repeats (SD repeat), which is thought to span the peptidoglycan layer. The SD repeat is followed by a membrane-spanning region that includes the LPXTG (SEQ ID NO: 125) motif for covalent linkage of the protein to peptidoglycan.

[0191] The ligand binding regions of ClfA and ClfB comprising N1N2N3 of the A domain spans amino acids 40-559. The N domains of ClfA / ClfB have been assigned as follows: N1 encompasses residues 45-220; N2 encompasses residues 229-369; and N3 encompasses residues 370-559. See Deivanayagam et al. EMBO J. 21:6660-6672 (2002). In preparations of recombinant ClfA N1N2N3, the N1 domain has been found to be protease sensitive and is easily cleaved or hydrolyzed to leave the N23 as a stable ligand binding recombinant fragment. See Deivanayagam et al. EMBO J. 21:6660-6672 (2002). Similarly, it was demonstrated that N1 domain of ClfB is also protease-sensitive and could be easily cleaved by *S. aureus* metalloprotease (McAleese, F. M. et al. J. Biol. Chem. 2001, 276, pp. 29969-29978). The crystal structure of the fibrinogen binding N23 fragment of ClfA A domain, revealed that both N2 and N3 are dominated by anti-parallel beta strands. In addition to the anti-parallel beta strands, the N2 domain contains a single turn alpha helix and two 3_{10} helices and the N3 domain contains three 3_{10} helices. See Deivanayagam et al. EMBO J. 21:6660-6672 (2002).

[0192] Sequence alignment of N2 and N3 reveals only 13% sequence identity and 36% sequence similarity over their lengths. See Deivanayagam et al. EMBO J. 21:6660-6672 (2002). The topology of the N2 and N3 domains are similar to the classic IgG fold and have been proposed to be novel variants of the IgG fold. See Deivanayagam et al. EMBO J. 21:6660-6672 (2002).

Recombinant forms of ClfA used in the immunogenic compositions described herein are fragments of ClfA comprising one or more of the N domains, for example, N1N2N3, N2N3 and are referred to herein as "recombinant ClfA" or "rClfA". In addition, any rClfA should be one that maintains the native structure of the individual N domains and critical epitopes but does not interfere with normal processes of the immunized individual after administration (i.e., does not bind fibrinogen). Mutational studies have shown that mutating Y338A (N2) completely eliminated binding of the N23 fragment to fibrinogen. (This Y338A position refers to a change from a tyrosine to an alanine at position 338 in the immature form of the polypeptide sequence with the leader sequence still attached. This change can be seen at position 310 in the mature form of the mutated ClfA polypeptide of SEQ ID NO: 123 that demonstrates a lack of binding to fibrinogen). See Deivanayagam

et al. EMBO J. 21:6660-6672 (2002). Therefore, the Y338A mutation has been adopted for all fragments of ClfA in the following studies.

[0193] Similarly, recombinant forms of ClfB used in the immunogenic compositions described herein are fragments of ClfB comprising one or more of the N domains, for example, N1N2N3, N2N3 and are referred to herein as "recombinant ClfB" or "rClfB". In addition, any rClfB should be one that maintains the native structure of the individual N domains and critical epitopes but does not interfere with normal processes of the immunized individual after administration (i.e., does not bind fibrinogen). (See, for example, Walsh, E.J. et al. Microbiology (2008), 154, 550-558).

ClfA and ClfB: Overview of Cloning Strategy

[0194] The different forms of rClfA protein used to generate preclinical efficacy data include $HisClfA_{(N123)}$; $T7ClfA_{(N123)}$; $T7ClfA_{(N123)}$; Y338A; $ClfA_{(N23)}$ and $ClfA_{(N23)}$Y338A. See Figure 1. The ClfA gene contains the A region coding sequence from *S. aureus* PFESA0237 corresponding to residues 40-559. The reading frame cloned from *S. aureus* was fused to the N-terminal HisTag and linker sequences of the vector (MRGSHHHHHHGS SEQ ID NO: 127) along with three additional coding sequences (KLN) introduced at the C-terminus. (See below for detailed procedure.) Protein expressed from this vector was used for all experiments where it is referred to as $HisClfA_{(N123)}$.

[0195] The different forms of rClfA were derived from the A region (residues 40-559 of ClfA expressed by *S. aureus* PFESA0237 (top row). The $HisClfA_{(N123)}$ is expressed using the T5 promoter contained in pQE30 and all other forms are expressed using the T7 based pET expression system.

[0196] Two forms of ClfB (T7ClfB N1N2N3 and ClfB N23) were utilized for preclinical animal studies.

ClfA Cloning Procedure

[0197] The ClfA coding sequence corresponding to amino acid residues 40-559 from *S. aureus* strain PFESA0237 was cloned and the mutation, Y338A, was introduced to eliminate fibrinogen binding. The mutated ClfA gene was introduced into a T7 RNA polymerase expression vector, pET9a (Novagen) to provide

plasmid, pLP1179. The DNA sequence of the region comprising the T7 promoter and coding region in pLP1179 is SEQ ID:124. The expression vector was transformed into *E. coli* BLR(DE3) (Novagen) for production of recombinant ClfA.

[0198] The construction of T7ClfA$_{(N123)}$Y338A involved several steps. A summary of the cloning steps used to construct the final expression plasmid, pLP1179 is shown in Figure 2.

[0199] The *clfA* DNA sequence present in pQEClf40 correspond to amino acid residues 40-559 of ClfA that was originally cloned into the BamHI/HindIII cloning site of pQE30. This creates a HisTag fusion at the N-terminal end of ClfA and the addition of three residues at the C-terminus. The ClfA coding region present in (AmpR) pQEClf40 was sub-cloned into the KanR pET 27b vector (Novagen) to create pLP1137. In addition the *clfA* DNA sequence corresponding to amino acid residues 221-559 was cloned into the NdeI-HindIII cloning site of pET27b to create pLP1134. The N-terminal HisTag of ClfA was replaced with the N-terminal T7 by subcloning the BamH-BlpI DNA fragment from pQEClf40 into pET9a (Novagen) to create pLP1153. The coding sequence of T7ClfA$_{(N123)}$ present in pLP1153 contains 11 N-terminal amino acid residues from the T7 tag of pET9a followed by three amino acid residues from linker sequences plus the three C-terminal linker derived residues originally present in pQE30Clf40. The Y338A mutation was first introduced into the ClfA$_{(N23)}$ coding sequence of pLP1134 to create pLP1168. Later a PstI-SnaBI DNA fragment containing the Y338A mutation from ClfA$_{(N23)}$ of pLP1168 was replaced into PstI-SnaBI of T7ClfA$_{(N123)}$ coding sequence of pLP1153 to create pLP1171. An internal ribosome binding site present in the coding sequence of T7ClfA$_{(N123)}$Y338A of pLP1171 was altered by silent mutations at DNA positions 339 and 342 of the T7 rClfA Y338A ORF, changing from G to T and G to A, respectively. The resulting plasmid, pLP1176, was then used to remove the three extraneous residues, originally derived from pQE30Clf40, between the T7 tag and the start of the ClfA coding region. The three linker derived C-terminal residues were also removed at this time.

[0200] The rClfA expressed by the resulting plasmid, pLP1179 (Figures 2 and 3), contains only the 11 N-terminal amino acids fused to residue 40-559 of

$ClfA_{(N123)}$Y338A. The DNA sequence of the region comprising the T7 promoter and the coding sequence of T7 r$ClfA_{(N123)}$Y338A of pLP1179 is SEQ ID NO 124.

Bacterial Strains and Plasmids

[0201] The plasmid backbone pET9a (obtained from Novagen) was used for construction of pLP1179, which expresses T7$ClfA_{(N123)}$Y338A from a T7 promoter. The plasmid contains the kanamycin resistance gene (KanR) for positive selection. The BL21(DE3) *E. coli* host strain [F- *ompT hsdS*$_B$ ($r_B^-m_B^-$) *gal dcm* (DE3)] (Novagen) was originally used to obtain expression of T7$ClfA_{(N123)}$Y338A. The DE3 designation denotes the lambda lysogen containing the T7 RNA polymerase gene under control of the *lacUV5* (IPTG inducible) promoter that is used for induced expression of T7 RNA polymerase and subsequent transcription from the T7 promoter proximal to the $ClfA_{(N123)}$Y338A coding sequence present in pLP1179. Upon receiving information that the BL21(DE3) lysogenic host strain is capable of inducing lytic phage upon large scale fermentations, the host strain was changed to the *recA* BLR(DE3) host strain [F- *ompT hsdS*$_B$ ($r_B^-m_B^-$) *gal dcm* Δ(*srl-recA*)306::Tn*10*(Tc*R*) (DE3)] (Novagen).

Production and Purification of ClfA

[0202] For the production of ClfA, *E. coli* BLR(DE3)/pLP1179 was grown in defined medium in glucose fed-batch mode in bioreactors. When the culture reached an optical density (OD_{600}) between 30-50, the expression of ClfA was induced by the addition of IPTG. The culture was harvested between 3-16 hours post induction.

[0203] The cells were disrupted and the clarified soluble fraction was collected. After the addition of ammonium sulfate, the material was applied to a column containing Phenyl-Sepharose resin and eluted. Fractions containing ClfA were identified, dialyzed and loaded onto an anion exchange column (Q-Sepharose). After elution with a salt gradient, fractions containing ClfA were identified, concentrated by ultrafiltration and loaded on to a size-exclusion column (Superdex-75). Fractions containing ClfA were identified and pooled. The purity of the ClfA at this point was about 98% as measured by SDS-PAGE.

Cloning and Purification of ClfB N1N2N3

[0204] The ClfB coding sequence corresponding to amino acid residues 44-542 was cloned into a T7 RNA polymerase expression vector, pET28a (Novagen) to provide plasmid pPX1189. The expression vector was transformed into *E. coli* BLR(DE3) (Novagen) for the production of recombinant ClfB. (See Walsh, et al., Microbiology 154: 550-558 (2008).)

[0205] For the production of ClfB, *E. coli* BLR(DE3)/pLP1179 was grown in defined medium in glucose fed-batch mode in bioreactors. When the culture reached an optical density (OD_{600}) between 30-50, the expression of ClfB was induced by the addition of IPTG. The culture was harvested between 3-16 hours post induction.

[0206] The cells were disrupted and the clarified soluble fraction was collected. The pH of the soluble fraction was adjusted to about pH 3.2 and the precipitated impurities were removed. The pH of the soluble fraction containing ClfB was readjusted to about pH 8.0 and dialyzed to remove salts. After the addition of ammonium sulfate, the material was applied to a column containing Phenyl-Sepharose resin and eluted. Fractions containing ClfB were identified, dialyzed and loaded onto an anion exchange column (Q-Sepharose). After elution with a salt gradient, fractions containing ClfB were identified, concentrated by ultrafiltration and loaded on to a size-exclusion column (Superdex-75). Fractions containing ClfB were identified and pooled. The purity of the ClfB at this point was about 94% as measured by SDS-PAGE.

Example 2: Productions of Antigens: *Staph Aureus* MntC

Cloning *S. aureus* Lipidated MntC

[0207] Recombinant MntC was originally cloned from *S. aureus* strain Mu50. The rMntC coding sequence was amplified by PCR from *S. aureus* Mu50 genomic DNA. Two pairs of nested primers were used for the amplification (Table 2). The first pair of primers, 5'SA926-MntC ups and 3'SA926-MntC down, align to the sequence upstream and downstream of the open reading frame of rMntC. The second set of primers align to the coding sequence of rMntC allowing to amplify the sequence corresponding to amino acid residues 19-309. Restriction enzymes

sites were incorporated at the 5' ends of these primers to facilitate directional cloning. PCR was carried out in a Peltier Thermal Cycler (MJ Research Inc, Waltham, MA) with TaKaRa PrimeSTAR HS DNA Polymerase Premix (Takara Bio USA, Madison, WI). PCR product was purified by QIAEX II (Qiagen, Valencia, CA), cleaved with the appropriate restriction endonucleases (New England BioLabs, Ipswich, MA) and sub-cloned into the araBAD promoter-driven expression vector pBAD18Cm. This vector also contains the signal peptide of the lipoprotein P4 from *H. influenza*. The *MntC* PCR product was sub-cloned in frame downstream from the P4 signal peptide to create pLP1194. The DNA sequence of the MntC coding region of pLP1194 is shown in SEQ ID NO: 120. The MntC expressed from pLP1194 is a lipoprotein. The recombinant plasmid DNA was sequenced by ABI PRISM BigDye™ Terminator V.3.1 (Applied Biosystems, Foster City, CA) and the recombinant protein was expressed in *E. coli* BLR (NOVAGEN) for the production of lipidated rMntC.

Production and Purification of Lipidated MntC

[0208] For the production of lipidated MntC, *E. coli* BLR/pLP1194 was grown in defined medium in glucose fed-batch mode in bioreactors. When the culture reached an optical density (OD_{600}) of about 60, the expression of rMntC was induced by switching the feed to a mixture of glucose and arabinose. The culture was harvested about 24 hours post induction.

[0209] The cells were disrupted and the insoluble fraction was collected. Lipidated MntC was found associated with the cell membranes due to the lipid modification. MntC was extracted from the membrane fraction with a detergent (Zwittergent ZW-312). After removal of the insoluble debris, the lipidated MntC was found in the soluble fraction. The soluble fraction was applied to a column containing a mixed-mode resin and eluted with a linear salt and pH gradient. Fractions containing MntC were identified and pooled. Ammonium sulfate was added to the pool and the material was applied to a column containing Butyl-Sepharose and eluted. Fractions containing MntC were identified, desalted and loaded onto a cation exchange column (SP-Sepharose). After elution with a salt gradient, fractions containing rMntC were identified and pooled.

Cloning *S. aureus* Non-Lipidated MntC

[0210] The DNA sequence employed to express non-lipidated rMntC was isolated by PCR amplification from plasmid pLP1194. The resulting sequence corresponds to amino acid residues 19-309 and does not contain the signal sequence that directs secretion and lipidation. The DNA sequence of the rMntC coding region of pLP1215 is found in DNA SEQ ID NO: 120.

[0211] To create pLP1215, MntC was amplified by PCR from pLP1194. The MntC DNA sequence present in pLP1215 corresponds to amino acid residues 19-309 and the first codon for this construct was introduced in the forward primer used in the amplification of the gene. The primers used for PCR also contain restriction enzymes sites at the 5' ends to facilitate directional cloning (Table 2). PCR and purification of the amplified gene was carried out as described above. Purified PCR product was cleaved with the appropriate restriction endonucleases (New England BioLabs, Ipswich, MA) and sub-cloned into the T7 promoter-driven expression vector pET28a (Novagen, Madison, WI). The recombinant plasmid DNA pLP1215 was sequenced by ABI PRISM BigDye™ Terminator V.3.1 (Applied Biosystems, Foster City, CA) and the recombinant protein was expressed in *E. coli* BLR(DE3). Plasmid DNA for pLP1215 was purified and used to transform *E. coli* HMS174(DE3) to evaluate protein expression.

Table 2: MntC primers.

Expression constructs	Primer name	Sequence (5'-3')
Lipidated MntC (pLP1194)	5'SA926-MntCups	CAC AAA ATT TAC GAA TAG AAA GAA ACG AG (SEQ ID NO: 109)
	3'SA926-MntCdown	AAA ATA TTG GAG ATA CCA ATA TTT TAG GTT G (SEQ ID NO: 110)
	5'BamHISA926 MntC	TTT CTT GGA TCC GGT ACT GGT GGT AAA CAA AGC AGT G (SEQ ID NO: 111)
	3'SphISA926 MntC	TTT CTT GCA TGC TTA TTT CAT GCT TCC GTG TAC AGT TTC (SEQ ID NO: 112)

Expression constructs	Primer name	Sequence (5'-3')
Non lipidated MntC (pLP1215)	5'NcoIMntC	TTT CTT CCA TGG GTA CTG GTG GTA AAC AAA GCA G (SEQ ID NO: 113)
	3'BlpIMntC	TTT CTT GCT CAG CAT TAT TTC ATG CTT CCG TGT ACA G (SEQ ID NO: 114)

[0212] Synthetic oligonucleotides used to generate rMntC constructs. Restriction endonuclease sites are underlined. The nucleotides in boldface indicate the first codon for the nonlipidated rMntC construct.

Production and Purification of Non-Lipidated rMntC

[0213] For the production of non-lipidated rMntC. *E. coli* HMS174(DE3)/pLP1215 was grown in defined medium in glucose fed-batch mode in bioreactors. When the culture reached an optical density (OD_{600}) of about 60 to 80, the expression of rMntC was induced by addition of IPTG. The culture was harvested about 24 hours post induction. The cells were disrupted and the clarified soluble fraction was collected. The lysate was applied to a column containing a cation exchange resin (SP-Sepharose) and eluted with a linear salt gradient. Fractions containing MntC were identified. After the addition of ammonium sulfate, the material was applied to a column containing Phenyl-Sepharose resin and eluted. After elution, fractions containing rMntC were identified, pooled, and desalted. The purity of the rMntC at this point was >95% as measured by SDS-PAGE.

Example 3: Production of Capsule Polysaccharides CP5 and CP8

[0214] In this example, production of various sizes of *S. aureus* capsule polysaccharides type 5 and 8 is described. The structures of the CP5 and CP8 polysaccharides are shown in Figure 4. The methods described herein are effective in producing CP5 and CP8 with molecular weights ranging from about 50 kDa to 800 kDa. Based on growth characteristics and the quantity of capsule produced, strain PFESA0266 was chosen for CP5 production while strains PFESA0005 or PFESA0286 were used for the production of CP8. The capsules isolated from strains PFESA0005 and PFESA0286 were shown to be identical.

[0215] For production of capsular polysaccharides, the strains were grown in a complex medium consisting primarily of a carbon source (either lactose or sucrose), hydrolyzed soyflour as the nitrogen source, and trace metals. The strains were grown in bioreactors for 2 to 5 days.

[0216] Purification of CP5 and CP8 used for the preparation of conjugates was performed by two different methods that rely on elevated temperature and low pH to effect the release of capsule from the cell and reduce the molecular weight of the polysaccharide. The resulting molecular weight is dependent on the time, temperature and pH of the hydrolysis step.

[0217] Characterization of CP5 and CP8 was performed using the techniques specified in Table 3. Capsule polysaccharides produced by this procedure result in pure polysaccharides with low levels of protein, NA, peptidoglycan and TA contaminants. See Tables 4 and 5.

Table 3: Characterization Assays for Purified *S. aureus* CP5 and CP8

Specificity	Assay
Residual Protein	Lowry colorimetric assay
Residual Nucleic acids	260nm scan
Residual Teichoic Acid	Phosphate colorimetric assay
Residual Peptidoglycan	HPAEC-PAD
Size	SEC-MALLS
Composition	HPAEC-PAD
Identity	HH-NMR or reaction with specific mAb
O-acetylation	1H-NMR
Concentration	MALLS-RI or HPAEC-PAD

[0218] In the first method, following release of the capsule from the cell and reduction of molecular weight, the capsule preparation is treated with a cocktail of enzymes (ribonuclease, deoxyribonuclease, lysozyme, and protease) to digest impurities. After incubation, residual impurities are precipitated by the addition of ethanol (final concentration about 25%). After removal of the residual ethanol, solution containing capsule was loaded onto an anion exchange column (Q-Sepharose) and eluted with a linear salt gradient. Fractions containing capsule

were pooled and treated with sodium meta-periodate. This treatment resulted in the oxidative hydrolysis of residual teichoic acid contaminant, but did not affect the CP5 or CP8. The reaction was quenched by the addition of ethylene glycol. The material was concentrated and diafiltered against dH20 to remove any residual reagents and by-products.

[0219] The second method was used to produce capsules did not involve the use of enzymes to digest the various cell-derived impurities. In this method, following release of the capsule from the cell and reduction of molecular weight the hydrolyzed fermentation broth was clarified by microfiltration followed by ultrafiltration and diafiltration. The solution was treated with activated carbon to remove impurities. After carbon treatment, the material was treated with sodium meta-periodate to oxidize residual teichoic acid followed by quenching with propylene glycol. The material was concentrated and diafiltered against dH_2O to remove any residual reagents and by-products.

[0220] Capsules produced using either method result in pure polysaccharides with low levels of protein, nucleic acid and teichoic acid contaminants. The methods described can be used to produce specific ranges of the desired high molecular weight polysaccharides simply by varying the conditions of hydrolysis. A particularly advantageous range of high molecular weight polysaccharides, ranging from 70 to 150 kDa, is useful in making immunogenic compositions by conjugating polysaccharide to a carrier protein.

[0221] Examples of High Molecular Weight Capsule Polysaccharide obtainable by the methods described herein are shown in Table 4 below. Batches of purified higher MW CP5 also had high purity as indicated by no TA, peptidoglycan and low residual protein. See Table 4. The range of molecular weights in these examples spanned 132.7 kDa to 800 kDa and the purified polysaccharides were highly O-acetylated, ranging from 90-100%, and 100% for N-Acetylation. See Table 4.

[0222] Examples of lower Molecular Weight Capsule Polysaccharide obtainable by the methods described herein are shown in Table 5 below. Batches of purified lower MW CP8 had high purity as indicated by no teichoic acid (TA), peptidoglycan and low residual protein. See Table 5. The range of lower

molecular weights spanned 20.4 kDa to 65.1 kDa and the purified polysaccharides were highly O-acetylated, ranging from 75-96%. The levels of nucleic acid contamination was low, ranging from 0.5-%-2.45%. See Table 5.

Table 4: Characterization of CP5 Preparations

SA CP-5	MW (kDa)	CP (mg/ml)	O-acetyl (%) NMR	Identity NMR	N-acetyl (%) NMR
1	800.1	3.164	100	Pass	100
2	132.7	1.172	90	Pass	100
3	335.4	0.975	90	Pass	100
4	366.8	0.865	90	Pass	ND

Table 5: Characterization of CP8 Preparations

SA CP-8	Total CP Purified mg	MW (kDa) (g/mol)	Protein (Lowry) % (w/w)	NA (260nm scan) % (w/w)	O-Acetyl NMR %
5	310	27.0	1.2	0.94	100
6	438	29.0	2.4	2	100
7	179	20.4	0.37	0.12	108
8	101	46.9	Below Detection	0.5	94
9	91	65.1	1.15	2.45	96
10	578	35.5	2.47	0.65	75

Molecular Weight Selection of Capsular Polysaccharides

[0223] This kinetic analysis demonstrates that a broad range of molecular weights of capsule polysaccharides can be generated by the methods described herein. Initially, larger polysaccharides were produced by the bacterial cells, and subsequently, a desired molecular weight range may be selected and then purified by manipulation of the pH and heat conditions of the heat and hydrolysis steps.

[0224] Heat treatment of *S. aureus* fermentation broth was a process step between fermentation and CP recovery. This process step uses heat to treat pH-adjusted broth for a specified period. The goals of the heat treatment at low pH were to kill cells, inactivate enterotoxins, release cell bound polysaccharide, and reduce molecular weight to the desired size. Among these goals, the reduction of molecular weight was the slowest in terms of processing time required in this step. Therefore, the other goals were inevitably achieved within the treatment time considered.

Heat Treatment

[0225] Temperature and pH conditions for selecting various molecular weight ranges of capsule polysaccharides were determined. The broth pH was adjusted with concentrated sulfuric acid. Then, the broth temperature was raised to the set value. The heat treatment time started as soon as the temperature reached the set point. When the desired treatment time was reached, the broth was cooled to room temperature. In-process samples were taken to determine polysaccharide concentration and molecular weight by HPLC and SEC-MALLS systems, respectively. The MW data was used in the kinetic analysis. The MW profiles were determined over time of CP5 at pH 4.0, 4.5 and 5.0 and CP8 at pH 3.5, 4.0, and 5.0. See Figures 5A and 5B.

[0226] The kinetics of mild acid hydrolysis of polysaccharides was conducted using purified CP-5 and CP-8 obtained from the process. The purified polysaccharide solution was adjusted to the desired pH for the experiment with sulfuric acid. The samples were placed in an oil bath equipped with a precision temperature control system. Each sample was taken out at a predetermined time interval and was quenched in an ice bucket. At the end of the experiment, an aliquot of 1M Tris buffer (pH 7.5) was added to the sample to adjust the pH back to about 7. The samples were analyzed by a SEC-MALLS system. The MW data was used in the kinetic analysis. The effect of temperature on MW profiles of CP5 at pH 4.5 and CP8 at pH 3.5 was determined over time. See Figures 6A and 6B. This acid hydrolysis procedure may be implemented using the fermenter culture or at an intermediate stage of purification or, as shown here, using the purified polysaccharide. Other molecular weight reduction steps, such as sonication or sheer, may be similarly be implemented.

Results

[0227] The effect of pH on the reduction of MW in heat treatment is shown in Figures 5A and 5B for CP-5 and CP-8, respectively. It can be seen that a lower pH was more effective in reducing the size of polysaccharide. The data also suggest that CP-5 was more difficult to hydrolyze than CP-8 at the same pH. Considering the CP8 profiles, ranges of molecular weights between 300 kDa and

600 kDa can be generated using a pH of 5 at 95 °C for between 15 minutes and 120 minutes. Likewise, choosing a pH of 4 at 95 °C for between 15 minutes and 120 minutes can yield CP8 polysaccharide molecular weight ranges between 250 kDa and 450 kDa. In addition, choosing a pH of 3.5 at 95 °C for between 15 minutes and 120 minutes can yield CP8 polysaccharide molecular weight ranges between 120 kDa and 450 kDa.

[0228] The effect of temperature on MW reduction was conducted using the purified polysaccharides recovered from the recovery process. The results are shown in Figures 6A and 6B. As shown, the higher the temperature, the faster the rate of hydrolysis and broader the range of the molecular weights of polysaccharide produced with time. Use of a lower temperature, 55°C versus 95°C at the same pH, produces a narrower range of polysaccharide molecular weights.

[0229] Furthermore, Figure 7 demonstrates the correlation between the molecular weight of purified CP5 and CP8 with the treatment time for mild acid hydrolysis. The purified polysaccharide is the final product obtained from the recovery process detailed previously. As shown in Figure 7, the increase in time of heat treatment of the *S. aureus* PFESA0266 strain at pH 4.5 results in the generation of smaller molecular weight CP5 polysaccharides, whereas shorter heat treatment times at pH 4.5 result in the generation of higher molecular weight CP5 polysaccharides. The size of the CP5 polysaccharides ranged from about 90 kDa to about 220 kDa depending on the length of time of heat treatment at low pH (4.5). Likewise, the increase in time of heat treatment of the *S. aureus* PFESA0005 strain at pH 3.5 results in the generation of smaller molecular weight CP8 polysaccharides, whereas shorter heat treatment times at pH 3.5 result in the generation of higher molecular weight CP8 polysaccharides. The size of the CP8 polysaccharides ranged from about 80 kDa to about 220 kDa depending on the length of time of heat treatment at low pH (3.5). The correlation between the time of heat treatment at low pH and the size of the purified CP5 and CP8 polysaccharides, as shown in this study, allows for an estimation of the treatment time required to produce purified polysaccharide with a specified range of molecular weight.

[0230] It is important to note that as demonstrated above the full range of molecular weights of capsule polysaccharides for both CP5 and CP8 from 20 kDa

to more than 800 kDa can be produced, released and purified. The methods described may be used to produce specific ranges of desired high molecular weight capsule polysaccharides. A particularly advantageous range of high molecular weight capsule polysaccharide type 5 and type 8 can be generated from these methods having molecular weights ranging from 70 to 150 kDa. See Table 6. This range of molecular weights of capsule polysaccharide is useful in making immunogenic compositions by conjugating the polysaccharide to a carrier protein. Alternatively, this advantageous range of high molecular weight capsule polysaccharide ranges from 80 to 140 kDa of CP5 and CP8. See Table 6. Another advantageous range of high molecular weight capsule polysaccharide CP5 and CP8 is from 90 to 130 kDa, or from 90 to 120 kDa of CP5 and CP8. See Table 6. The conditions used to generate the CP5 capsule polysaccharide having a molecular weight range of from about 100 to 140 kDa are as follows: 95°C, pH 4.5 for 135 minutes. The conditions used to generate the CP8 capsule polysaccharide having a molecular weight range of from about 80 to 120 kDa are as follows: 95°C, pH 3.5 for 300 minutes.

Table 6: Production of Specific Range of High Molecular Weight CP5 and CP8

Run	CP8 MW (kDa)	CP5 MW (kDa)
1	98	142
2	89	108
3	108	142
4	108	108
5	89	ND
6	100	ND
7	99	63
8	113	72
9	105	74
10	100	63
11	87	ND

ND= not done

Example 4: Conjugation of Capsule Polysaccharides CP5 and CP8 to CRM_{197}

[0231] This example describes processes and characterization assays used in the production of *S. aureus* CP5- CRM_{197} and CP8- CRM_{197} conjugates. Several conjugation chemistries were evaluated for conjugating *S. aureus* capsule

polysaccharides CP5 and CP8 to a carrier protein. Conjugation using PDPH (3-2-pyridyldithio)-propionyl hydrazide) results in covalent thioether bond and CDI/CDT (1,1-carboyldiimidazole/1,1-carboyl-di-1,2,4-triazole) results in a one-carbon or zero-carbon linker between CP and carrier protein.

Conjugation of CP to CRM_{197} by PDPH Conjugation Chemistry

[0232] The PDPH conjugation chemistry is a multi-step process that involves activation of the polysaccharide, removal of the thiol protecting group, purification of the activated polysaccharide intermediate, activation and purification of the CRM_{197} protein, and conjugation of the activated components followed by purification. After introduction of a thiol group containing linker to the polysaccharide and a haloacetyl group to the CRM_{197} protein carrier, *S. aureus* CP5 and CP8 polysaccharides were linked to the protein carrier through a thioether bond. Bromoacetyl groups were introduced into the CRM_{197} protein by reaction of amine groups with the N-hydroxysuccimide ester of bromoacetic acid. To generate thiolated CP, the carbodiimide activated carboxylate groups of N-acetylmannosaminouronic acid in CP were coupled to the hydrazide group of the sulfhydryl-reactive hydrazide heterobifunctional linker 3-(2-pyridyldithio)-propionyl hydrazide (PDPH). Thiols of PDPH-thiolated CP, generated by reduction with DTT and purified by SEC on a Sephadex G25 column, reacted with bromoacetyl groups of activated protein resulting in covalent thioether linkage formed by bromine displacement between CP and the protein. Non-reacted bromoacetyl groups were "capped" with cysteamine hydrochloride (2-aminoethanethiol hydrochloride). The reaction mixture was then concentrated and diafiltered. The remaining unconjugated bromoacetyl groups were capped with cysteamine hydrochloride to ensure no reactive bromoacetyl groups were left after conjugation. This formed a covalent bond between the thiol end of cysteamine and the acetyl group on the lysine residue after displacement of bromine.

Thiolation of *S. aureus* Capsular Polysaccharide with PDPH

[0233] The polysaccharide was first activated by thiolation with PDPH. The polysaccharide was mixed with a freshly prepared PDPH stock solution (250 mg/mL in DMSO), an EDAC stock solution (90 mg/mL in diH_2O), and MES

buffer stock solution (0.5M, pH 4.85) to make the final solution 0.1 M MES, and 2 and 4 mg CP/mL while maintaining a CP:PDPH:EDAC ratio by weight of 1:5:3 for CP 5 and 1:0.6:1.25 for CP 8. This mixture was incubated for 1 hour at room temperature and then dialyzed against a 1000X volume of distilled H_2O four times using a 3500 MWCO dialysis device at between 4° and 8°C to remove unreacted PDPH. The PDPH-linked polysaccharide was made 0.2 M DTT and incubated at room temperature for 3 hours or overnight at between 4 and 8°C. Excess DTT as well as the by-products of the reaction were separated from the activated saccharide by SEC using Sephadex G25 resin and distilled water as the mobile phase. Fractions were assayed by the DTDP assay for thiol groups and thiol-positive fractions that eluted near the void volume of the column were pooled. The pool of fractions was assayed by the PAHBAH and the O-acetyl assays to determine the degree of activation which is expressed as a molar percent of the repeat units containing a thiol group (molar concentration of thiols/molar concentration of repeat units). The activated polysaccharide was lyophilized and stored at -25°C until needed for conjugation.

Carrier protein activation

[0234] Separately, the carrier protein was activated by bromoacetylation. CRM_{197} was diluted to 5 mg/mL with 10 mM phosphate buffered 0.9% NaCl pH 7 (PBS) and then made 0.1 M $NaHCO_3$ pH 7.0 using 1 M stock solution. The N-hydroxysuccinimide ester of bromoacetic acid (BAANS) was added at a CRM_{197} :BAANS ratio 1:0.25 (w:w) using a BAANS stock solution of 20 mg/mL DMSO. This reaction mixture was incubated at between 4 and 8°C for 1 hour then purified using SEC on Sephadex G-25. The purified activated CRM_{197} was assayed by the Lowry assay to determine the protein concentration and then diluted with PBS to 5 mg/mL. Sucrose was added to 5% wt/vol as a cryoprotectant and the activated protein was frozen and stored at -25°C until needed for conjugation.

Coupling Reaction

[0235] Once the activated capsule polysaccharide and activated carrier protein were prepared, the two were combined in a conjugation reaction. The lyophilized and thiolated polysaccharide was dissolved in 0.16 M borate pH 8.95, mixed with

thawed bromoacetylated CRM_{197} and distilled water to make the final solution 0.1 M borate, 1:1 wt/wt ratio of CRM_{197}:CP, and 1 mg/mL polysaccharide for CP8 and 2 mg/mL polysaccharide for CP5. This mixture was incubated at room temperature for between 16 and 24 hours. Unreacted bromoacetyl groups on the protein were capped by adding cysteamine hydrochloride at a ratio of CRM_{197}:cysteamine of 1:2 (wt/wt) using a 135 mg/mL stock solution of cysteamine dissolved in 0.1 M borate pH 8.95 and incubated for 4 hours at room temperature. The capsule polysaccharide-CRM_{197} conjugate (conjugate) was purified by diafiltering 50-fold against 0.9% NaCl using a 100K polyethersulfone ultrafilter.

[0236] The results from the reproducibility of CP5 and CP8 thiolation studies with PDPH demonstrated that the degree of activation of CP5 was in the range 11 to 19 % which corresponds to approximately one linker molecule attached per ten CP repeat units to one linker molecule per five repeat units. The CP8 activation was in the range of 12 to 16%, which was very similar to activation of CP5.

[0237] Bromoacetylation of lysine residues of CRM_{197} was very consistent, resulting in the activation of 19 to 25 lysines from 39 lysines available. The reaction produced high yields of activated protein.

Conjugation of CP to CRM_{197} by CDI/CDT Conjugation Chemistry

[0238] CDI and CDT afford a one-step conjugation process where the polysaccharide is activated in an anhydrous environment (DMSO) to form imidazole or triazole carbamate moieties with available hydroxyls and acylimidazole or acyltriazole moieties with carboxylic acids. Addition of a protein carrier (in DMSO) leads to the nucleophilic displacement of the imidazole or triazole by lysine and formation of a carbamate linkage (for activated hydroxyls) and the amide linkage (for activated carboxylic acids). The reaction solution is diluted 10-fold into an aqueous solution to remove unreacted activation groups and then purified by diafiltration.

[0239] Both conjugation chemistries produced CP covalently linked to the carrier protein, which was indicated by the presence of the saccharide and protein in the fractions from size exclusion chromatography, and by amino acid analysis of glycolaldehyde capped or cysteamine hydrochloride capped conjugate.

[0240] Summary of the results from the preparation of several lots of conjugates prepared by both PDPH and CDI/CDT chemistries for both capsular serotypes with polysaccharide size in the range of 20 to 40 kDa are shown in Table 7 below. There were no significant differences in the free capsule polysaccharide, ratio of CP:Protein and yields of conjugates generated by these two conjugation methods. The antigenicity of conjugated CP was not altered by conjugation as portrayed by identity precipitin line between conjugates and native CP.

Table 7: Characterization of SA CP5-CRM_{197} and CP8-CRM_{197} Prepared by Two Conjugation Chemistries

Conjugate	Chemistry	CP Yield (%)	Protein Yield (%)	Output Ratio	Free saccharide (%)	Free Protein (%)	Lysines Modified	Size (Mw or Kd (% less than 0.3), sacc/prot))
SA CP5-CRM_{197}	CDT	19-27	35	0.5-0.8	10-40	<1	18-22	38/61 to 76/74
	PDPH	26-52	40-99	0.4-1.0	23-50	ND	ND	7.5×10^5 to 2.3×10^6
SA CP8-CRM_{197}	CDI	46-62	54-55	0.8-0.9	22-25	<1	7-8	34/57 to 60/57
	PDPH	34-70	61-83	0.6-0.9	15-41	ND	11-16	74 92%

[0241] As shown above, the methods described herein may be used to produce specific ranges of desired high molecular weight capsule polysaccharides. The aim of this study was to prepare conjugates from a pre-selected range of high molecular weights that could be filtered and purified CP for use in immunogenic compositions. In this example, eight batches where the CP5 capsule polysaccharide ranged in molecular weight from about 90 kDa to about 120 kDa were selected and conjugation was performed using activation with triazole (CDT). See Table 8. The molecular weights of the resulting conjugates ranged from 1533 kDa to 2656 kDa. The number of conjugated lysines per CRM_{197} ranged from a high of 22 to a low of 15. The free capsule polysaccharide ranged from a high of 18% to a low of 11 %. See Table 8.

Table 8 Conjugates With Preselected MW Range of CP5

Run	Poly MW (kDa)	Sacc Yield (%)	Free saccharide (%)	MW by SEC-MALLS (kDa)	Lysines Modified
1	121	63	11	2130	19
2	92	72	16	1533	22
3	119	74	14	2656	15
4	115	63	18	1911	15

[0242] Table 9 summarizes the analysis of CP8 conjugates where the CP8 capsule polysaccharide ranged in molecular weight from about 87 kDa to 113 kDa and the imidazole conjugation chemistry was utilized. The molecular weights of the resulting conjugates ranged from 595 kDa to 943 kDa. The number of conjugated lysines per CRM_{197} ranged from a high of 9 to a low of 3. The free capsule polysaccharide ranged from a high of 6% to a low of 2%. See Table 9.

Table 9 Conjugates With Preselected MW Range of CP8

Run	Poly MW (kDa)	Sacc Yield (%)	Free saccharide (%)	MW by SEC-MALLS (kDa)	Lysines Modified
1	99	88	6	943	4
2	113	73	5	841	3
3	105	79	3	719	7
4	100	86	2	630	9
5	87	90	3	595	6

[0243] Both conjugation chemistries produce CP covalently linked to carrier protein. There were no significant differences in free capsule polysaccharide, ratio of CP:Protein and yields of conjugates generated by these two methods.

Example 5: Sequence Diversity of Polypeptide Fragments N1, N2 and N3 of ClfA

[0244] In this example the protein sequence heterogeneity of ClfA polypeptide fragments N1, N2 and N3 from disease causing isolates obtained from various sources was evaluated. ClfA genes were sequenced from strains of *S. aureus* associated with multiple disease states. Sequence information from additional strains was obtained from GenBank to generate sequences from relevant strains. Table 10 lists different ClfA sequences.

[0245] The sequence alignment of ClfA proteins from different disease-causing strains of *S. aureus* is shown in Figure 8A-8E. The protein sequences were aligned using MUSCLE. See Edgar, R.C. Nucleic Acids Research 32 (5):1792-1797 (2004). The alignments were displayed using SHOWALIGN. See Rice, P. et al., "EMBOSS: The European Molecular Biology Open Software Suite" Trends in Genetics, 16 (6): 276-277 (2000). Many of the sequences recurred multiple times without variation. For clarity each unique sequence was placed in the alignment only once. See Figure 8A-8E. Only unique sequences were included in the sequence listing. For example, the protein sequence of ClfA_001 was obtained from multiple different strains without any variation. See Figure 8A-8E. The sequence listing number for any sequence can also be obtained from Table 10: ClfA strains and Sequence Listings. Table 10 lists one example strain that contained this same ClfA_001 protein sequence. This sequence is shown in the first row of the alignment in Figure 8A-8E. This alignment of unique sequences of the ClfA antigen indicates that polymorphisms were distributed throughout the entire A region (N1-N2-N3) of ClfA. In some cases, for any given unique protein sequence of ClfA, more than one nucleotide sequence, encoding the same protein, was discovered. Only the most frequently occurring DNA sequence was included in the sequence listing and in Table 10. For ClfA, the following sequences are disclosed herein and are not found in GenBank: ClfA_003, ClfA_005, ClfA_008, ClfA_009, ClfA_013, ClfA_014, ClfA_015, ClfA_016, ClfA_017, ClfA_018, ClfA_019, ClfA_020, ClfA_021, ClfA_022, ClfA_023, and ClfA_024.

Table 10: ClfA strains and Sequence Listings

Example Strain	DNA-ClfA	NT SEQ ID NO:	Protein-ClfA	AA SEQ ID NO:	% Identity to Antigen
PFESA0131	clfA_001-1	61	clfA_001	62	99
PFESA0074	clfA_002-1	63	clfA_002	64	92
PFESA0072	clfA_003-1	65	clfA_003	66	99
PFESA0159	clfA_004-1	67	clfA_004	68	94
PFESA0154	clfA_005-1	69	clfA_005	70	91
PFESA0096	clfA_006-1	71	clfA_006	72	91
PFESA0269	clfA_007-1	73	clfA_007	74	91
PFESA0081	clfA_008-1	75	clfA_008	76	97
PFESA0005	clfA_009-1	77	clfA_009	78	95
PFESA0139	clfA_010-1	79	clfA_010	80	99

Example Strain	DNA-ClfA	NT SEQ ID NO:	Protein-ClfA	AA SEQ ID NO:	% Identity to Antigen
PFESA0237	clfA_011-1	81	clfA_011	82	100
PFESA0157	clfA_012-1	83	clfA_012	84	96
PFESA0069	clfA_013-1	85	clfA_013	86	92
PFESA0002	clfA_014-1	87	clfA_014	88	98
PFESA0147	clfA_015-1	89	clfA_015	90	91
PFESA0094	clfA_016-1	91	clfA_016	92	98
PFESA0143	clfA_017-1	93	clfA_017	94	97
PFESA0129	clfA_018-1	95	clfA_018	96	99
PFESA0128	clfA_019-1	97	clfA_019	98	92
PFESA0148	clfA_020-1	99	clfA_020	100	91
PFESA0140	clfA_021-1	101	clfA_021	102	98
PFESA0152	clfA_022-1	103	clfA_022	104	91
PFESA0141	clfA_023-1	105	clfA_023	106	96
PFESA0160	clfA_024-1	107	clfA_024	108	94

[0246] The phylogeny of the ClfA protein sequences was examined and a phylogenetic tree was constructed. Sequences were aligned using ClustalW. See Chenna R, Sugawara H, Koike T, et al. Nucleic Acids Research. 31(13):3497-3500 (2003). Neighbor-joining trees were bootstrapped 1000 times and were displayed with MEGA 4.0. See Tamura K, et al., Molecular Biology & Evolution. 24(8):1596-1599 (2007). Bootstrap values, indicated on the branches, are the number of times that branch was reproduced in 1,000 trials. Values less than 500 (50% reproducibility) are considered to be poorly supported.

[0247] The ClfA sequences form a tree with 2 major branches. See Figure 9. The separation of these two groups is very well supported in the phylogeny. One branch (top) includes 9 sequences that are fairly closely related to one another (96-99% identity) but more distantly related to the candidate sequence clfA_011, to which they are 91-92% identical. The second group, which includes clfA_011, is more diverse and the phylogeny in this group is not as well supported. These protein sequences range from 93-99% identical to one another.

Example 6: Sequence Diversity of Polypeptide Fragments N1, N2 and N3 of ClfB

[0248] In this example, the protein sequence heterogeneity of ClfB N1, N2 and N3 polypeptide fragments from 92 disease-causing isolates obtained from various sources was evaluated. ClfB genes were sequenced from strains of *S. aureus*

associated with multiple disease states. See Table 11. Information from additional strains was obtained from GenBank to generate additional sequences.

[0249] The sequence alignment of ClfB proteins from different disease-causing strains of *S. aureus* is shown in Figure 10A-10E. The protein sequences were aligned using MUSCLE. See Edgar, R.C. Nucleic Acids Research 32 (5):1792-1797 (2004). The alignments were displayed using SHOWALIGN. See Rice, P. et al., "EMBOSS: The European Molecular Biology Open Software Suite" Trends in Genetics, 16 (6): 276-277 (2000). See Figure 10A-10E ClfB align. As with ClfA, many of the sequences recurred multiple times without variation. For clarity, each unique sequence was placed in the alignment only once. See Figure 10A-10E. Only unique ClfB sequences were included in the sequence listing. For example, the sequence of ClfB_006 was obtained from multiple different strains without any variation. This sequence is shown in the first row of the alignment in Figure 10A-10E. The sequence listing number for any sequence can also be obtained from Table 11. This alignment of representative unique sequences of the ClfB antigen indicates that polymorphisms were distributed throughout the entire A region (N1-N2-N3) of ClfB. Similar to ClfA, for any given unique protein sequence of ClfB, more than one nucleotide sequence encoding the same protein was discovered. Only the most frequently occurring DNA sequence was included in the sequence listing and in Table 11. For ClfB, the following sequences are disclosed herein and are not found in GenBank: ClfB_001, ClfB_004, ClfB_005, ClfB_010, ClfB_011, ClfB_013, ClfB_014, ClfB_015, ClfB_016, ClfB_017, ClfB_018, ClfB_019, ClfB_020, ClfB_021, ClfB_022, ClfB_023, and ClfB_024. The phylogenetic tree is shown in Figure 11.

Table 11: ClfB Strains and Sequence Listings

Example Strain	DNA-ClfB	SEQ ID NO:	Protein-ClfB	SEQ ID NO:	% Identity to Antigen
PFESA0286	clfB_001-1	15	clfB_001	16	95
PFESA0159	clfB_002-1	17	clfB_002	18	95
RF122	clfB_003-1	19	clfB_003	20	94
PFESA0271	clfB_004-1	21	clfB_004	22	95
PFESA0081	clfB_005-1	23	clfB_005	24	95
PFESA0080	clfB_006-1	25	clfB_006	26	100
PFESA0270	clfB_007-1	27	clfB_007	28	99

Example Strain	DNA-ClfB	SEQ ID NO:	Protein-ClfB	SEQ ID NO:	% Identity to Antigen
PFESA0269	clfB_008-1	29	clfB_008	30	95
PFESA0145	clfB_009-1	31	clfB_009	32	94
PFESA0069	clfB_010-1	33	clfB_010	34	95
PFESA0002	clfB_011-1	35	clfB_011	36	96
PFESA0128	clfB_013-1	37	clfB_013	38	96
PFESA0129	clfB_014-1	39	clfB_014	40	95
PFESA0136	clfB_015-1	41	clfB_015	42	99
PFESA0139	clfB_016-1	43	clfB_016	44	99
PFESA0140	clfB_017-1	45	clfB_017	46	96
PFESA0141	clfB_018-1	47	clfB_018	48	94
PFESA0144	clfB_019-1	49	clfB_019	50	97
PFESA0150	clfB_020-1	51	clfB_020	52	96
PFESA0152	clfB_021-1	53	clfB_021	54	96
PFESA0156	clfB_022-1	55	clfB_022	56	96
PFESA0163	clfB_023-1	57	clfB_023	58	94
PFESA0211	clfB_024-1	59	clfB_024	60	99

Example 7: Sequence Diversity Of MntC In Disease-Causing Clones of *S. aureus*

[0250] In this example, the protein sequence heterogeneity of MntC genes from 104 disease-causing isolates obtained from various sources was evaluated. MntC genes were sequenced from strains of *S. aureus* associated with multiple disease states. See Table 12. Information from additional strains was obtained from GenBank to generate strain sequences.

[0251] The sequence alignment of MntC proteins from different disease-causing strains of *S. aureus* is shown in Figure 12A-12B. The protein sequences were aligned using MUSCLE. See Edgar, R.C. Nucleic Acids Research 32 (5):1792-1797 (2004). The alignments were displayed using SHOWALIGN. See Rice, P. et al., "EMBOSS: The European Molecular Biology Open Software Suite" Trends in Genetics, 16 (6): 276-277 (2000). See Figure 12. As with ClfA, many of the sequences recurred multiple times without variation. For clarity, each unique sequence was placed in the alignment only once. See Figure 12. Only unique MntC sequences were included in the sequence listing. For example, the sequence of MntC_001 was obtained from different strains without any variation. See Figure 12. This sequence is shown in the first row of the alignment in Figure 12. The sequence listing number for any sequence can also be obtained from Table 12.

Only the most frequent corresponding DNA sequence was included in the sequence listing. For MntC, the following sequences are disclosed herein and are not found in GenBank: MntC_002, MntC_006, MntC_007, MntC_008, and MntC_009.

Table 12: MntC strains and Sequence Listings

Strain	DNA-MntC	SEQ ID NO:	Protein-MntC	SEQ ID NO:	% Identity to Antigen
PFESA0129	MntC_001-1	1	MntC_001	2	99
PFESA0142	MntC_002-1	3	MntC_002	4	99
PFESA0139	MntC_003-1	5	MntC_003	6	99
PFESA0286	MntC_006-1	7	MntC_006	8	99
PFESA0136	MntC_007-1	9	MntC_007	10	99
PFESA0150	MntC_008-1	11	MntC_008	12	99
PFESA0153	MntC_009-1	13	MntC_009	14	99

Example 8: Surface Expression of ClfA, CP5, CP8 And MntC *In vivo* During Infection

[0252] *S. aureus* is responsible for causing a diverse array of human infections. Consequently the bacteria must adapt to different environmental niches by differential expression of virulence factors required for infection. The expression of target antigens was studied in three *in vivo* rodent assays to assess their expression during infection: a wound model to measure expression of the antigen at the primary site of infection, a bacteremia model that monitors antigen expression in the blood, and an indwelling chamber model that monitors antigen expression during nutrient/oxygen limited conditions. For all these models the rodents were challenged with bacteria at the site of study. Following infection, bacteria were harvested at various time-points and antigen expression (ClfA, CP5, CP8, MntC) was assessed using immunofluorescent microscopy (wound and bacteremia) or flow cytometry (chamber).

MATERIALS AND METHODS

Expression in the Wound Model

[0253] Wound infection experiments consist of 5 animals/group and up to 5 groups for a maximum of 25 animals/experiment. Six to eight week (wk) old C57BL/6 male mice underwent surgery to embed a loop of suture into a thigh

muscle incision. This provides a foreign-body substrate for bacterial attachment and significantly reduces the minimum infectious dose needed to produce a staphylococcal wound infection. Five µL of either *S. aureus* or sterile saline were introduced into the incision under the deep tissue suture of 4-0 silk. The skin was closed with 4-0 Prolene sutures or surgical adhesive (*e.g.*, cyanoacrylate). The animals were euthanized at time points between 30 min and 10 days following infection and the thigh muscle excised, homogenized and the bacteria enumerated. Bacteria at the sight of infection were analyzed for antigen expression by immunofluorescent (IF) confocal microscopy.

Expression in the Bacteremia Model

[0254] Groups of 10 four-wk old CD-1 or Balb/C mice were immunized with 1 µg of protein or CP conjugate by subcutaneous injection on wks 0, 3 and 6. The animals were bled on wks 0 and 8 followed by an intraperitoneal challenge with *S. aureus* grown to late log phase in TSB. Three hours following challenge the animals were euthanized and blood collected for IF confocal microscopy.

Expression in the Indwelling Dialysis Tubing Model

[0255] *S. aureus* isolates were grown overnight on TSA plates at 37°C. Bacteria were scraped from the plates and resuspended in sterile PBS and the OD_{600} adjusted to 1, approximately 10^9 colony forming units (cfu) /mL. Bacteria were diluted to a concentration of 10^5 cfu/mL and inoculated into dialysis tubing. An aliquot of the suspension was plated to determine the actual number of cfu. Dialysis tubing with 3.5 kDa MWCO was prepared for implant by sterilizing in 70% ethanol for 30 minutes followed by extensive rinsing in sterile water and then sterile saline. A 2 mL aliquot of the bacterial suspension was transferred to the dialysis tubing, the bag closed with a knot, and then rinsed extensively with sterile saline. Male Sprague Dawley rats (6 weeks old) were anaesthetized and a 2-3 cm incision made along the dorsal midline. Pockets were created at the site of incision by gently separating the skin from the underlying tissue. Tubing was implanted in the pockets and skin was closed using surgical staples. After 24 h, rats were euthanized, the tubing removed, and the bacteria recovered for flow cytometric analysis.

Immunofluorescent Microscopy (IF)

[0256] The blood from 5 mice was pooled into ice-cold sodium citrate, pH 7.0 (final concentration, 0.4%). The eukaryotic cells were lysed with 1% NP-40 (Pierce Biotechnology). The bacteria were washed with PBS and incubated overnight at 4°C with rabbit immune or preimmune serum (1:100) and detected with ALEXA488 conjugated goat-α-rabbit antibody (1:250, Invitrogen). The labeled bacteria were dried on a microscope slide and a coverslip was mounted with Vectashield HardSet medium (Vector Laboratories, Inc.). Images were obtained with a Leica TCS SL spectral confocal microscope (Leica Microsystems).

Flow Cytometric Analysis

[0257] *S. aureus* isolates were grown as described in the rat dialysis tubing model procedure. Approximately 10^7 bacterial cells were blocked in staining buffer (Hank's balanced salt solution with 10% goat sera) for 1 hour on ice. Bacterial cells were centrifuged for 5 minutes at 10,000 rpm, supernatant removed, and cells incubated with mouse antibody or isotype control antibody for 30 minutes on ice. Cells were then washed and stained with FITC conjugated goat anti-mouse IgG (Jackson ImmunoResearch) on ice for 30 minutes. Bacteria were washed with staining buffer, fixed with 2% paraformaldehyde and data acquired and analyzed using FACS Caliber flow cytometer and Cell quest software (Becton, Dickinson and Co.). A total of 30,000 events were collected for each sample.

Table 13a: Antigen Expression Profiles in *S. aureus* CP Type 5 Isolates.

Antigen		CP						ClfA						MntC					
Time [h]		T_0	1	4	6	24	72	T_0	1	4	6	24	72	T_0	1	4	6	24	72
PFESA0266	bacteremia	+	-	+	+	/	/	+	-	+	+	/	/	NT	NT	NT	NT	NT	NT
	wound	+	-	-	-	+	+	+	-	±	+	+	+	-	±	±	±	±	+
PFESA0272	bacteremia	+	+	+	+	/	/	+	-	+	+	/	/	-	-	+	+	/	/
	wound	+	-	-	-	+	!	+	-	±	+	±	!	-	-	-	±	!	!
PFESA0094	bacteremia	+	-	+	+	/	/	+	-	±	!	/	/	-	-	-	-	/	/
	wound	+	-	-	+	+	+	+	-	-	+	+	+	-	-	-	±	±	+
PFESA0093	bacteremia	+	-	±	+	/	/	+	-	±	+	/	/	NT	NT	NT	NT	NT	NT
	wound	+	-	-	+	+	+	+	-	-	-	!	±	-	-	-	±	±	±

PFESA0028	bacteremia	+	-	-	+	/	/	+	-	±	±	/	/	-	-	±	±	/	/
	wound	+	-	-	-	-	-	+	-	-	±	±	±	-	-	-	±	±	-
PFESA0029	bacteremia	-	-	±	+	/	/	+	-	-	+	/	/	-	-	-	+	/	/
	wound	-	-	-	-	±	±	+	-	-	-	-	±	-	-	-	±	±	-

/= bacteremia experiments were conducted for 6 hours != animal died during experiment NT= not tested

Table 13b: Antigen Expression Profiles in *S. aureus* CP Type 8 Isolates.

Antigen		CP						ClfA						MntC					
Time (h)		T0	1	4	6	24	72	T0	1	4	6	24	72	T0	1	4	6	24	72
PFESA0003	Bacteremia	+	±	+	+	/	/	+	-	±	+	/	/	NT	NT	NT	NT	NT	NT
	Wound	+	-	±	+	+	+	+	-	±	+	+	!	NT	NT	NT	NT	NT	NT
PFESA0286	Bacteremia	+	-	-	+	/	/	+	-	-	+	/	/	NT	NT	NT	NT	NT	NT
	Wound	+	-	-	+	!	!	+	-	+	+	!	!	NT	NT	NT	NT	NT	NT
PFESA0005	Bacteremia	+	-	±	±	/	/	+	-	+	+	/	/	NT	NT	NT	NT	NT	NT
	Wound	NT	NT			!	!	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
PFESA0002	Bacteremia	+	-	-	-	/	/	+	±	-	-	/	/	-	±	±	+	/	/
	Wound	+	-	-	+	+	!	+	-	-	-	±	NT	-	-	±	±	±	+
PFESA0269	Bacteremia	+	-	-	-	/	/	+	-	-	-	/	/	-	-	+	+	/	/
	Wound	+	-	-	±	-	+	+	-	-	±	±	NT	-	-	-	-	±	±
PFESA0268	Bacteremia	+	+	+	-	/	/	+	+	-	-	/	/	-	±	-	+	/	/
	Wound	+	-	-	-	+	+	+	-	-	-	±	NT	-	-	-	±	±	-
PFESA0025	Bacteremia	+	-	-	-	/	/	+	+	-	-	/	/	NT	NT	NT	NT	NT	NT
	Wound	+	-	-	-	+	±	+	-	-	-	-	NT	-	-	-	-	±	+
PFESA0283	Bacteremia	+	-	-	-	/	/	+	+	+	-	/	/	±	+	±	±	/	/
	Wound	+	-	-	+	!	!	+	-	-	+	!	NT	-	-	-	±	±	±
PFESA0027	Bacteremia	+	-	-	±	/	/	+	-	±	±	/	/	NT	NT	NT	NT	NT	NT
	Wound	+	-	±	±	+	+	+	-	-	±	+	NT	-	-	-	-	±	+
PFESA0001	Bacteremia	+	-	-	-	/	/	+	-	-	-	/	/	NT	NT	NT	NT	NT	NT
	Wound	+	-	-	±	±	+	+	-	-	-	±	NT	-	-	-	-	-	±
PFESA0095	Bacteremia	+	-	-	±	/	/	+	-	-	+	/	/	NT	NT	NT	NT	NT	NT
		+	-	-	-	+	+	+	-	-	-	±	NT	-	-	-	-	±	
PFESA0271	Bacteremia	+	-	-	-	/	/	+	+	-	-	/	/	NT	NT	NT	NT	NT	NT
	Wound	+	-	-	-	+	+	+	-	-	+	+	NT	-	-	±	±	±	+
PFESA0271	Bacteremia	+	-	±	+	/	/	+	-	±	±	/	/	NT	NT	NT	NT	NT	NT
	Wound	+	-	-	-	+	+	+	-	-	-	+	NT	-	-	-	-	±	±

/= bacteremia experiments were conducted for 6 hours. != animal died during experiment NT= not tested

Table 13c. Expression of *S. aureus* antigens in the Indwelling Dialysis Tubing.

Frequency of positive cells (% of total)

***S. aureus* PFESA0266**	**Time (hrs)**	**0**	**3**	**6.0**	**9.0**	**13.0**	**18.0**	**30.0**
	ClfA	69.8	13.7	8.5	8.0	12.5	8.8	16.4
	CP5	28.0	1.9	1.8	6.1	7.1	5.2	9.6
	MntC	91.4	4.3	5.6	2.9	20.8	37.0	33.2
***S. aureus* PFESA0005**	**Time (hrs)**	**0**	**3**	**6.0**	**9.0**	**13.0**	**18.0**	**24.0**
	ClfA	98.6	63.9	69.7	24.3	36.1	98.6	99.0
	CP8	77.3	43.0	18.0	7.5	11.8	96.4	94.0
	MntC	5.9	7.7	12.5	2.6	2.9	9.3	9.9

Results

[0258] A combination of nineteen *S. aureus* isolates were tested for expression of ClfA, CP5, CP8, or MntC on the *S. aureus* cell surface during infection (Table 13a, 13b, and 13c). These isolates included recent clinically relevant strains and were diverse as monitored by MLST. Antigen expression was dependent on the strain, time point, and the infection model. The variation in antigen expression between isolates in different *in vivo* environments (bloodstream vs. wound) supports the use of a multi-antigen immunogenic composition to induce broad coverage of staphylococcal isolates in a variety of different infections. The antigens were surface expressed within the first 24 hours of infection and are thus valid components for an anti-staphylococcal immunogenic composition. Protein antigens ClfA and MntC were accessible to staining in the presence of capsule expression indicating that the presence of capsule does not mask the proteins from antibodies directed against them.

[0259] Most of the tested type 8 isolates did not express CP in the blood until later time points post-challenge (> 4 hour) (See Table 13a-c). These results demonstrate that in *S. aureus* CP is differentially regulated depending on the *in vivo* microenvironment, i.e., site of infection. These results may explain the inconsistent efficacy results reported for CP8 conjugates in animal models.

[0260] *In vivo* expression results suggest that no single antigen immunogenic formulation will provide broad coverage against the majority of *S. aureus* infections. There is too much diversity of expression phenotypes by individual strains within *in vivo* microenvironments. Therefore, an immunogenic

composition consisting of more than one antigen is required to prevent *S. aureus* disease.

Example 9: Immunogenicity of Multi-Antigen Formulations Containing ClfA, CP5- and CP8-CRM_{197} Conjugates

[0261] In this example, we evaluated the immunogenicity of combinations of ClfA, CP5-CRM_{197} and CP8-CRM_{197}.

A. Bi-antigen (CP5-CRM_{197}/CP8-CRM_{197}) immunogenic composition formulation – dose effect on the anti-capsular antibody responses in rabbit

[0262] In this example, the dose effect on the immunogenicity of the combined CP5-CRM_{197} and CP8-CRM_{197} immunogenic formulation in rabbits was evaluated. Rabbits were immunized on week 0, 3 and 6 with bivalent conjugate plus 125 μg $AlPO_4$ administered by subcutaneous injection. The doses evaluated in this study were 0.1 μg, 1 μg, or 10 μg each of CP5-CRM_{197} and CP8-CRM_{197} (final combined CP- CRM_{197} doses of 0.2 μg, 2 μg, and 20 μg). The dose of the conjugate reflects the total polysaccharide component of the protein polysaccharide conjugate. Rabbits were bled on week 0, 3, 6 and 8. ELISA was performed on pooled and individual sera. Endpoint antibody titers were determined as the reciprocal dilution at 0.1 OD_{405}. Statistical analysis was performed on individual week 8 titers. The results demonstrated that the highest CP5 and CP8 specific antibody titers of 5×10^5 for CP5 and 1×10^6 for CP8 were induced by vaccination of rabbits with bivalent immunogenic formulation at 1 μg CP dose of each component (Data not shown.).

B. Tri-antigen formulation (CP5-CRM_{197} + CP8-CRM_{197} + rClfA) - rClfA dose range study with fixed dose (1 μg) of each conjugate in rabbits

[0263] The effect of a combination of rClfA and CP5 and CP8 conjugates on immune response to each component was tested. Three groups were immunized with bivalent *S. aureus* CP5-CRM_{197} + CP8-CRM_{197} (1μg dose of each conjugate) combined with T7-ClfA (N1N2N3) at three different doses 1, 10 and 100 μg. The control group was immunized with unconjugated CP5 and CP8 (50 μg each) combined with 100 μg of T7-ClfA (N1N2N3). Each immunogenic composition was formulated with 500 μg of adjuvant $AlPO_4$. Immunogenic compositions were

administered by subcutaneous injection in the neck. Rabbits were bled on week 0, 6 and 8. ELISA was performed on pooled and individual sera and endpoint antibody titers were determined as the reciprocal dilution at 0.1 OD_{405}.

[0264] Results showed that increased amount of rClfA when combined with bivalent conjugate did not affect capsular antibody responses. The antibody levels to both capsular serotypes were in the same range as in rabbits immunized with bivalent conjugate only (Data not shown). The antibody levels to CP5 and CP8 were 2.5 fold lower at 10 (103 K) and 100 µg (106 K) dose compared to 1 µg dose of rClfA (273 K). There was a booster effect after the second and third injection. Unconjugated bivalent polysaccharide immunogenic formulation (CP5 + CP8, 50 µg each) combined with 100 µg of rClfA did not induce CP specific antibodies. The rClfA specific antibody response was also not greatly affected by the dose, where titers were between 1 X 10^5 and 1 X 10^6 after three doses for 1, 10 and 100 µg doses (Data not shown.). Also the levels of anti-ClfA response achieved when administered with conjugated or unconjugated CP5 and CP8 polysaccharides were similar.

Example 10: Tri-Antigen Formulation - Immunogenicity In Rabbits With High Pre-Immunization CP5, CP8 and ClfA Ab Titers.

[0265] The staphylococcal immunogenic composition is targeted for adult populations that have pre-existing antibodies to *S. aureus* surface components. To study the effect of pre-existing antibodies to immunogenic formulation components on the response to the immunogenic formulation, we selected rabbits with high titers of naturally acquired anti-CP5, anti-CP8, and anti-ClfA antibody titers. Two groups of rabbits (n=6/7) were immunized on week 0, 3 and 6 with tri-antigen immunogenic formulation (CP5-CRM_{197} (1 µg) and CP8-CRM_{197} (1 µg) and T7-ClfA (N1N2N3)Y338A (10µg)). One group was immunized with the immunogenic composition formulated with 500 µg $AlPO_4$ as adjuvant and the second group was immunized with immunogenic composition formulation containing no adjuvant. Immunogenic compositions were administered by subcutaneous injection. Rabbits were bled on wk. 0, 3, 6 and 8. Antibody titers to CP5, CP8 and rClfA were determined by ELISA as endpoint antibody titers on pooled and individual sera (determined as the reciprocal dilution at 0.1 OD_{405}).

[0266] Results showed that rabbits with pre-existing antibody titers induced by natural infection responded to trivalent immunogenic formulation with an increase in levels of antibodies to all immunogenic formulation components CP5, CP8 and rClfA. An increase of Ab levels to each antigen of between 5 fold to 10 fold was shown even in animals with antibody titers of $1x10^6$. Presence of the adjuvant in the immunogenic formulation resulted in higher antibody titers compared to the group immunized without adjuvant (Data not shown).

Example 11: Effect Of The Adjuvant On Responses To Capsule Polysaccharide Components

A. Effect of Two Different Doses of $AlPO_4$ on Response to Bivalent CP5-CRM_{197}/CP8-CRM_{197} Conjugate Immunogenic Composition in Rabbits

[0267] The dose effect of the adjuvant $AlPO_4$ on the anti CP5 and CP8 responses in rabbits was studied. Rabbits were immunized on week 0, 3 and 6 with bivalent *S. aureus* CP5-CRM_{197} + CP8-CRM_{197} (1 µg dose of each conjugate). One group (n=5/group) was immunized with immunogenic composition formulated with 125 µg and a 2nd group with 500 µg of $AlPO_4$ as adjuvant. Immunogenic compositions were administered by subcutaneous injection in neck. Rabbits were bled on week 0, 6 and 8 and anti-capsular antibodies were determined by ELISA as endpoint antibody titers determined as the reciprocal dilution at 0.1 OD_{405}. Results indicated that there was no difference in CP8 specific antibody responses in rabbits immunized with either 125 µg or 500 µg of $AlPO_4$. The formulation with 125 µg of adjuvant gave higher CP5 antibody responses. Also, all rabbits in the 125 µg group responded with higher CP5 antibody responses, while in the 500 µg adjuvant group, there were two rabbits with low response to the formulation.

B. Effect of $AlPO_4$ on The Immunogenicity of Tri-Antigen Formulation

[0268] Rabbits (NZW, n=6/7 rabbits per group) were immunized on week 0, 3 and 6 with Tri-antigen formulation comprised of CP5-CRM_{197} (1 µg) and CP8-CRM_{197} (1µg) and T7-ClfA (N1N2N3)Y338A (10 µg). One group of rabbits was immunized with immunogenic formulation with 500 µg $AlPO_4$, a second group was formulated with no adjuvant, the third group was immunized at week 0 with

immunogenic formulation with 500 μg $AlPO_4$ and weeks 3 and 6 with immunogenic formulation with no adjuvant. Immunogenic formulations were administered by subcutaneous injection, rabbits were bled on week 0, 3, 6 and 8 and sera evaluated by antigen specific ELISA. Results showed that the presence of adjuvant in the immunogenic formulation did not have an effect on anti-CP5 or anti-CP8 responses in rabbits (Data not shown.). The GMT titers of Abs to both capsules were comparable. However, there was an adjuvant effect on ClfA specific antibody response shown in groups immunized with adjuvant present in all three vaccinations. The second and third boost with immunogenic formulation not containing $AlPO_4$ in the rabbits primed with the immunogenic formulation containing adjuvant gave higher ClfA responses compared to group with no adjuvant.

Examples 12-29: Preclinical Evaluation of *S. Aureus* ClfA, MntC, CP5-CRM_{197} and CP8-CRM_{197}:

[0269] Described below in Examples 12 through 29 are the results of the preclinical evaluation of the CP5 and CP8 conjugates, ClfA and MntC. The examples demonstrate the efficacy of these antigens in preclinical animal models. The examples also demonstrate that antibodies generated by the CP conjugates, ClfA and MntC have functional activity in *in vitro* assays.

[0270] Two different chemistries were used to conjugate CP to CRM_{197}, but no difference was observed in efficacy for the conjugates prepared by the different methods. O-acetylation of the capsular polysaccharides was shown to impact eliciting functional antibodies. Evaluation of a combined immunogenic composition comprising CP5-CRM_{197}, CP8-CRM_{197} and ClfA showed no interference on specific antibody (Ab) levels to each immunogenic formulation component.

Materials and Methods

ELISA

[0271] Maxisorp microtiter ELISA plates (Nalge Nunc International, Rochester, NY) were coated 18 hours at 4°C or for 90 min at 37°C with 1 μg/mL of ClfA antigen in PBS pH 7.5. The plates were washed five times in PBST (1X PBS,

0.1% polysorbate 20) and blocked with 1% (w/v) non-fat milk in PBS, with 0.05% polysorbate 20 for 1 h at room temperature. Plates were washed with PBST, and serially diluted (3-fold) and individual week 0, 3, 6 and 8 rabbit anti-sera were added to the plates and incubated either overnight at 4°C or 2 h at 37°C. The plates were washed, and bound primary antibodies were detected with horseradish peroxidase-conjugated goat anti-rabbit IgG (1:1000 dilution) in PBST. The plates were incubated for 1 h at 37°C then washed and developed with ABTS-peroxidase substrate solution, (KPL, Inc., Gaithersburg, MD), at room temperature for approximately 20 minutes. The reaction was stopped by the addition of a 1% (v/v) SDS solution. Absorbance was measured at 405 nm in an automated plate reader (Molecular Devices Corporation, Sunnyvale, CA). Antibody titers were expressed as the reciprocal of the highest serum dilution with an absorbance value of 0.1. Student's t-test using JMP Software (SAS Institute, Cary, NC) was used to determine differences in antibody titers between the different groups. A probability of less than 0.05 was considered to indicate a statistically significant difference.

Murine Sepsis Models

[0272] The murine sepsis model mimics blood borne disease. For passive immunization, groups of 15 Swiss-Webster mice were treated intraperitoneally (i.p.) with IgG. Twenty four hours later mice were challenged with *S. aureus* 659-018 via by a single intravenous (i.v.) injection (0.1 ml) via the tail vein. All animals were followed for 14 to 15 days, at which point all remaining mice were sacrificed.

[0273] For active immunization, mice were immunized with antigen at 0, 2 and 4 weeks and challenged at week 6 by the intravenous route with *S. aureus*.

Active Immunization Rabbit Endocarditis model

[0274] Adult New Zealand White rabbits were immunized intramuscularly 4 times with 25 µg antigen. One day post-surgery, animals are challenged i.v. with a bolus of *S. aureus* and the number of colony forming units (cfu) in the heart tissue are determined 24 hours post-challenge.

Murine bacteremia

[0275] A 3 hr bacteremia model was used to determine the effect of vaccination on bacterial numbers early during an infection. Mice were immunized at weeks 0, 3, and 6 with antigen followed by i.p. challenge with *S. aureus* on week 8. Animals were exsanguinated 3 hours later and serial dilutions of blood plated to enumerate the bacteria.

Murine pyelonephritis model

[0276] The murine pyelonephritis model mimics the dissemination of *S. aureus* from bacteremia. Groups of 10 four week-old female CD-1 mice were immunized at 0, 3 and 6 weeks with antigen. The mice were challenged by i.p., injection of *S. aureus*. Forty-eight hours following challenge the mice were sacrificed and the bacteria were enumerated in the kidney and blood.

Rat endocarditis model

[0277] The rat endocarditis model mimics human endocarditis in which colonization occurs after a blood borne infection leads to colonization of damaged heart tissue. Five 5 week-old male Sprague-Dawley rats (Charles River, Kingston, NY) were immunized on wks 0, 2 and 4 with 1 μg of CP5- CRM_{197} conjugate formulated with 100 μg of $AlPO_4$. The animals were bled prior to vaccination on wk 0 and at the end of wk 5. Seventy-two hours later, a catheter (PE-10 tubing) was surgically placed through the carotid artery into the left ventricle of the heart. Placement of the catheter results in the formation of a sterile vegetation to which the staphylococci can attach upon infection. To prevent infection resulting from the surgical procedure, the animals were treated with the antibiotic Baytril (5mg/kg) at the time of surgery and 8 hr following surgery. Forty-eight hours after surgery, the rats were challenged with PFESA0266 (approximately 4×10^8 cfu) or SA315 (approximately 1×10^9 cfu) by intraperitoneal injection. Forty-eight hours following challenge the rats were euthanized and the hearts and kidneys removed and placed into 3mL of phosphate buffered saline (PBS). The organs were then homogenized with a tissue homogenizer (Kinematica AG, Luzernerstrasse,

Germany) and brought to 10mL with PBS. The homogenates were then serially diluted and plated for bacterial enumeration.

Monitoring functional antibodies using opsonophagocytic killing assays

[0278] Differentiated effector cells from a cell line (e.g. HL60s) or polymorphonuclear cells (PMNs) isolated from donor human blood using LYMPHOLYTE®-poly solution (Cedarlane laboratories limited, Ontario, Canada) as per manufacturer's protocol can be used for this assay. Effector cells were resuspended in assay buffer (Modified Eagle's media containing 1% bovine serum albumin) at approximately 2 X 10^7 cells/ml concentration and placed in 37° C incubator until ready to use. *S. aureus* strain PFESA0266 was grown overnight on tryptic soy agar plates. Bacterial cells were scraped, washed twice and resuspended in assay buffer containing 5% glycerol to an OD_{600} = 1, which equals to approximately 5 X 10^8 cfu/ml concentration. One ml aliquots of the bacterial suspension were frozen and stored at -40°C until ready to use. Frozen bacterial suspension were thawed and adjusted to a concentration of 10^6 cfu/ml in assay buffer and placed on ice. The assay was performed using a sterile 96 deep well 1 ml polypropylene plates. Two fold serial dilutions of antibody samples (50 µl) were prepared and followed by addition of 300 µl of assay buffer to the antibody mix. Bacteria were added (50 µl) to the plates and placed on a rotary shaker at 4 °C for 30 minutes. The opsonization step was followed by addition of 50 µl of human complement (1% final concentration). Finally, 50 µl of effector cells (10^7 cells/ml concentration) were added to the plate and the suspension mixed well by repeated pipetting. A 50µl aliquot of the suspension was 10 fold serially diluted in sterile 1% saponin solution, vortexed to minimize bacterial clumping and plated on tryptic soy agar in duplicate. The assay plate was incubated at 37°C for 1 hour with continuous mixing using rotisserie style shaker. At the end of the incubation a 50µl aliquot of suspension was 10 fold serially diluted in sterile 1% saponin solution, mixed by vortexing to minimize bacterial clumping and plated on tryptic soy agar in duplicate. The percentage killing was calculated by determining the ratio of the number of cfu surviving at 60 minutes in wells with bacteria, antibodies, complement and effector cells to the number of cfu surviving in tubes

lacking antibodies but containing bacteria, complement and effector cells. Controls containing bacteria, complement, and sera were included to adjust for any reduction in cfu due to clumping.

Complement adsorption

[0279] Serum from human donors adsorbed against *S. aureus* strains PFESA0266, PFESA0286 and PFESA0270 can be used as a source of complement in the assay. *S. aureus* strains were grown overnight on TSA plates at 37°C. Cells were scraped from the plate and resuspended in sterile PBS. Bacterial cells were centrifuged at 10,000 rpm for 10 minutes at 4°C and cell pellet was resuspended in human serum for adsorption. Serum was incubated with bacteria on a nutator at 4°C for 30 minutes. Cells were centrifuged, serum transferred to another tube containing bacteria and the adsorption step repeated again for 30 minutes. Finally, the cells were centrifuged and the serum passed through a 0.2 micron filter before 0.5 ml aliquots were frozen down in liquid nitrogen.

Method II - OPA using HL-60 cells

[0280] HL-60 cells were differentiated according to S. Romero-Steiner, et al., Clin Diagn Lab Immunol 4 (4) (1997), pp. 415–422. Harvested HL-60 cells were resuspended in assay buffer (Modified Eagle's media containing 1% bovine serum albumin) at approximately 10^8 cells/ml and placed in 37 °C incubator until ready to use. *S. aureus* was grown overnight on tryptic soy agar plates. Bacterial cells were scraped, washed twice and resuspended in assay buffer containing 5% glycerol to an $OD_{650} = 1$, which equals to approximately 5 X 10^8cfu/ml. One ml aliquots of the bacterial suspension were frozen and stored at -40°C until ready to use. Frozen bacterial suspension were thawed and adjusted to a concentration of 10^6 cfu/ml in assay buffer and placed on ice. The assay was performed using a sterile 96 deep well 1 ml polypropylene plates. Two fold serial dilutions of monoclonal antibody samples (25µl) were prepared and followed by addition of 150 µl of assay buffer to the antibody suspension. Bacteria were added (25µl) to the plates and placed on a rotary shaker at 4 °C for 30 minutes followed by addition of 25 µl of human complement (1% final concentration). Finally, 25µl of

HL-60 cells (10^7 cells/ml) were added to the plate and the suspension mixed well by repeated pipetting. A 25µl aliquot of the suspension was 10 fold serially diluted in sterile 1% saponin solution, mixed by vortexing to minimize bacterial clumping and plated on tryptic soy agar in duplicates. The assay plate was incubated at 37°C for 1 hour with continuous mixing using rotisserie style shaker. At the end of incubation a 25µl aliquot of suspension was 10 fold serially diluted in sterile 1% saponin solution, mixed by vortexing to and plated on tryptic soy agar in duplicate. The percentage killing was calculated by determining the ratio of the number of cfu surviving at 60 minutes in wells with bacteria, antibodies, complement and HL-60 cells to the number of cfu surviving in tubes lacking antibodies but containing bacteria, complement and HL-60 cells. Controls containing bacteria, complement and mAb was included to adjust for any reduction in cfu due to clumping.

Example 12: Demonstration of a Protective Effect by ClfA in *In Vivo* Animal Models

[0281] To evaluate whether polyclonal rabbit antibodies elicited against ClfA were capable of reducing *S. aureus* colony counts in a murine sepsis model, purified rabbit polyclonal anti-ClfA IgG was used at two dosages (0.8 mg and 1.6 mg) in a passive immunization study (Figure 13). The *S. aureus* challenge strain was a recent clinical isolate, 659-018. Both antibody dosages resulted in a significant reduction of bacterial colony counts in the murine sepsis model ($p=0.0134$ for 1.8 mg dose and $p=0.0013$ for 0.8 mg dose). This experiment has been repeated with additional *S. aureus* isolates with similar results (data not shown).

Example 13: Active Immunization With ClfA Reduced Colonization of the Heart by *S. Aureus*

[0282] Active immunization of rabbits with ClfA resulted in protection in the rabbit endocarditis model. We found a 3–4 log reduction in *S. aureus* cfu recovered from cardiac vegetations for animals immunized with ClfA compared to negative control (PBS or $AlPO_4$) immunized animals (Figure 14).

Example 14: Protective Effect of MntC in *In Vivo* Animal Models

[0283] Active immunization with MntC has shown consistent protection of mice from at early time points following *S. aureus* challenge. Bacterial counts in the blood of mice receiving i.p. *S. aureus* challenge were significantly reduced as compared to controls immunized with PBS (Figures 15A and 15B). Four out of six individual studies showed a significant reduction in cfu/ml blood in immunized animals. Protection mediated by MntC immunization was demonstrated using 2 different *S. aureus* challenge strains, PFESA0237 (Figure 15A) and PFESA0266 (Figure 15B).

Example 15: CP5 Conjugates Protect in Murine Pyelonephritis Model

[0284] CP5 conjugates were evaluated for their ability to protect mice in an active immunization pyelonephritis model. Figure 16 shows the results from several studies. Bacterial counts in the blood of mice receiving i.p. *S. aureus* challenge were significantly reduced as compared to controls immunized with pbs (Figure 16). Six out of six individual studies showed a significant reduction in cfu/ml kidneys in immunized animals. The data showed consistent reduction of kidney colonization after active immunization with CP5 conjugate.

Example 16: CP5 Conjugates Prepared by Different Conjugation Chemistries Protect Mice Against Experimental Infections

[0285] Active immunization studies in the murine pyelonephritis model were conducted using CP5 conjugate prepared either by PDPH or CDT chemistry. The methods for conjugating CP5 or CP8 to CRM_{197} were described above. Results showed that both conjugates significantly reduce colonization in mice compared to the sham immunized animals (Table 14).

Table 14: Effect of PDPH vs. CDT Conjugation in Pyelonephritis Model

Study #	Antigens	Strain/Dose	logCFU/Kidney	Significance
Study 1	Saline+$AlPO_4$	PFESA0266	5.53 ± 1.90	--
	1 µg CP5- CRM_{197} (PDPH) +$AlPO_4$	2×10^8	3.01 ± 1.83	$p < 0.001$
	1 µg CP5- CRM_{197} (CDT) +$AlPO_4$		1.67 ± 0.23	$p < 0.0001$
Study 2	Saline+$AlPO_4$	PFESA0266	6.17 ± 1.76	--
	1 µg CP5- CRM_{197} (PDPH) +$AlPO_4$	2.7×10^8	3.06 ± 1.69	$p < 0.0001$
	1 µg CP5- CRM_{197} (CDT) +$AlPO_4$		1.87 ± 0.69	$p < 0.0001$

Example 17: CP5 Conjugate Protects in a Rat Endocarditis Model

[0286] Four studies were conducted with CP5-CRM_{197} PDPH conjugate and an unrelated conjugate (PP5-CRM_{197}) at 1 µg dose. The CP5 conjugates significantly reduced colonization in both the heart and kidneys in 2 of 3 experiments in which the challenge Type 5 challenge strain was PFESA0266 (Table 15). In the third study, the Geometric Mean Titer (GMT) anti-CP5 titer was the lowest of the three experiments, but it was only slightly lower than the titer in the previous experiment (51,000 vs. 67,000).

Table 15: CP5-CRM_{197} Immunization Reduces cfu in Rat Endocarditis Model

		logCFU Recovered		Significance		GMT
Immunogenic Composition	**Challenge Strain/Dose**	**Heart**	**Kidney**	**Heart**	**Kidney**	**CP Titer**
1 µg CP5-CRM_{197}	PFESA0266	4.34± 1.78	3.92±1.73			103,000
1 µg PP5-CRM_{197}	2.21 x 10^8 cfu	7.94± 0.78	6.77± 0.79	p<0.001	p<0.05	
1 µg CP5-CRM_{197}	PFESA0266	4.43± 2.30	3.109± 2.33			51,000
Saline	6.5 x 10^7 cfu	5.63± 2.48	4.19± 2.05	No	No	
1 µg CP5-CRM_{197}	PFESA0266	4.01± 2.49	3.90± 1.92			67,000
Saline	4.0 x 10^8 cfu	7.52± 1.38	6.52± 1.17	p<0.0002	p<0.0002	
1 µg CP5-CRM_{197}	SA315	8.17± 1.02	6.92± 1.20			186,000
Saline	1 x 10^9 cfu	8.25± 0.60	6.74± 0.95	No	No	

Example 18: CP5-CRM_{197} Conjugates in a Pyelonephritis Model

[0287] Initial studies investigating efficacy of conjugates were performed with 25 kDa MW CP5. Improvements in fermentation process resulted in production of the high MW polysaccharide, which was conjugated to protein carrier and tested side by side with 25 kDa CP5 conjugate. Conjugates comprising CP with MW of 25 kDa (Low MW) and 300 kDa (High MW) were prepared using CDT

conjugation chemistry and evaluated in the murine pyelonephritis model. Three doses (0.01, 0.1 and 1 μg) of the HMW conjugates were tested and compared to the control LMW CP5-CRM_{197} and an unrelated conjugate (PP5-CRM_{197}) at 1 μg dose. The results showed a significant reduction in CFU of *S. aureus* PFESA0266 recovered from the kidneys at a 1 μg dose. There was no statistical difference between protection from conjugates prepared with different size CP5 at the 1 μg dose (Table 16). The lower doses (0.01 μg and 0.1 μg) of the conjugate failed to elicit an immune response sufficient to significantly reduce the infection. The experiment was repeated using an identical immunization and challenge procedure. In the repeated experiment, only the 1 μg dose of LMW CP5-CRM_{197} resulted in a significant reduction in colonization (p=0.01). The 1 μg dose of HMW CP5-CRM_{197} lowered cfu in kidneys, however the reduction was not statistically significant (p=0.056).

Table 16. CP5 Conjugates Protect in a Mouse Pyelonephritis Model.

Study	Antigen	Strain/Dose	logCFU/Kidney	Significance (p value)
1	1 μg PP5-CRM_{197}	PFESA0266 1.7×10^8	5.34	0.0048
	1μg 25kDa CP5-CRM_{197}		2.94	
	1 μg 300kDa CP5-CRM_{197}		2.74	0.0056
	0.1 μg 300kDa CP5-CRM_{197}		5.59	
	0.01 μg 300kDaCP5-CRM_{197}		4.70	
2	1 μg PP5-CRM_{197}	PFESA0266 1.7×10^8	5.35	
	1μg 25kDa CP5-CRM_{197}		3.25	0.01
	1 μg 300kDa CP5-CRM_{197}		3.78	0.06
	0.1 μg 300kDa CP5-CRM_{197}		4.45	
	0.01 μg 300kDa CP5-CRM_{197}		6.08	

Example 19: Polysaccharide O-Acetylation is Important for Induction of Protective Antibody Response to CP5 Conjugate Immunogenic Formulation

[0288] To evaluate the importance of O-Acetylation of CP5, the native CP5 was de-O-acetylated (dOAc) and conjugated to CRM_{197} (dOAc-CRM_{197}) using PDPH

conjugation chemistry. The efficacy of dOAcCP-CRM_{197} conjugate was compared side by side with CP5-CRM_{197} in a murine pyelonephritis model. The results showed that conjugate lacking O-acetyl groups (dOAc CP5- CRM_{197}) is not efficacious in this model as demonstrated by no significant change in the bacterial colonization in kidneys. These data (Table 17) indicate that O- acetylation was important for elicitation of functional antibodies against CP5.

Table 17: Immunization With de-O-acetylated CP5- CRM_{197} Does Not Protect Mice From Kidney Colonization

Study #	Antigens	Strain/Dose	logCFU/Kidney	Significance
Study 1	1 µg PP5- CRM_{197}	PFESA0266	3.89 ± 2.24	
	1 µg dOAc CP5- CRM_{197}	7×10^8	4.20 ± 1.75	
	1 µg CP5- CRM_{197}		1.75 ± 0.39	p-value < 0.008
Study 2	Saline	PFESA0266	5.08 ± 1.96	
	1 µg dOAc CP5- CRM_{197}	2.4×10^9	5.89 ± 1.29	
	1 µg CP5- CRM_{197}		2.93 ± 2.11	p-value < 0.02

Example 20: Immunization with CP8-Conjugate Reduces Death in a Sepsis Model

[0289] The efficacy of CP8-CRM_{197} conjugate was evaluated in the murine sepsis model after challenge with *S. aureus* PFESA0268 (Type 8). Swiss Webster mice (n=30) were actively immunized by subcutaneous injection with 1µg CP8-CRM_{197} and saline both formulated with 100 µg $AlPO_4$. The study showed a significant reduction of sepsis (p=0.0308) as compared to mice immunized with $AlPO_4$ alone. See Figure 17.

Example 21: Evaluation of the Conjugated Native and Base Treated CP8 in the Murine Bacteremia Model

[0290] The importance of O-Acetyl groups present on native CP8 before conjugation for induction of functional antibody responses was evaluated for CP8 conjugate. CP8 polysaccharide was de-O-Acetylated under mild basic conditions and both NMR and Ion Chromatography (IC) confirmed absence of O-Acetylation in CP8 de-O-Ac - CRM_{197}.

[0291] The murine bacteremia model was used to evaluate efficacy of the native versus base treated CP8 conjugated to CRM_{197}. Groups of female BALB/c mice

(15/group) were immunized at weeks 0, 3 and 6, with 1 μg CP8 de-O-Ac - CRM_{197} or 1 μg CP8 O-Ac - CRM_{197}. Immunogenic formulations were formulated with 22 μg $AlPO_4$. Animals were challenged with *S. aureus* PFESA0003. Three hours post challenge the mice were sacrificed and the bacteria were enumerated in blood. The data showed that there was a statistically significant ($p=0.0362$) reduction in bacterial cfu recovered from the blood of animals immunized with untreated native CP8 conjugate as determined by the student t test (Table 18). In animals that were immunized with base treated CP8 conjugate the bacterial cfu recovered from blood were similar to the saline control group.

Table 18: CP8-CRM_{197} Conjugate Reduces Bacteremia *S. aureus* PFESA0003 in Mice.

Antigen	Strain/Dose	logCFU/Blood	Significance (p value)
Saline	PFESA0003 1.14×10^8	4.35	
CP8 de-O-Ac - CRM_{197}		4.45	
CP8 O-Ac - CRM_{197}		3.93	0.03

Example 22: Confirmation of the Importance of O-Acetylation as Functional Epitope of CP5 by OPA Using MAbs With Known Specificities

[0292] CP5 monoclonal antibodies with specificities to CP5 OAc+ (CP5-7-1), CP5 OAc+/- (CP5-5-1) and CP5 OAc- (CP5-6-1) were evaluated for OP killing activity against type 5 strain PFESA0266 (Table 19). MAb CP8-3-1 specific to CP8 OAc+ was used as negative control. Results showed that CP5-7-1 mAb (CP5 OAc+ specific) mediates killing of both type 5 strains tested. Also mAb CP5-5-1 recognizing epitopes shared by both CP5 OAc+ and CP5 OAc- mediated killing of PFESA0266 strain. The MAb specific for epitopes present on CP5 OAc- polysaccharide did not mediate killing of PFESA0266 strain. These results indicate that O-Acetyl epitopes on CP5 are involved in functional activity of CP5 specific antibodies.

Table 19 mAbs Specific to O-Acetylated (+) CP5 and O- and de-O-Acetylated (+/-) CP5 are Opsonic against *S. aureus* PFESA0266 (Type 5).

	CP5-5-1 (O-Ac +/-) (µg)				CP5-6-1 (O-Ac -) (µg)				CP5-7-1 (O-Ac +) (µg)				CP8-3-1 (neg. control) (µg)			
µg	20	10	5	2.5	20	10	5	2.5	20	10	5	2.5	20	10	5	2.5
% kill	28	33	30	21	-12	-5	-12	-5	31	46	49	55	-18	-3	-13	-5

Data reported as percent killing and was calculated by determining the ratio of the number of cfu surviving at 60 minutes in wells with bacteria, antibodies, complement and HL-60 cells to the number of cfu surviving in wells lacking antibodies but containing bacteria, complement and HL-60 cells.

Example 23: Opsonic Activity of Mouse Antibodies Induced to High and Low MW CP5 Conjugates

[0293] Sera from mice (n=5) with high CP5 ELISA titers from 1 µg high molecular weight and low molecular weight groups from Example 18 were compared for opsonic activity using *S. aureus* PFESA0266. OPA results showed that both conjugates elicited opsonic antibodies in mice (Table 20). There was a trend observed for high MW conjugates to elicit higher titer opsonic antibodies. Data shown as a mean % killing ±SEM for 5 individual mouse sera. Antibodies need to be functional as measured by killing of bacteria in either an animal efficacy model or via an opsonophagocytic killing assay that demonstrates the antibodies kill the bacteria. Functional killing may not be demonstrated using an assay that just monitors the generation of antibodies alone, which is not indicative of the importance of high molecular weight conjugates in efficacy.

Table 20: Both LMW and HMW CP5 conjugates elicit opsonic antibodies

Antigen: 1µg CP5- CRM_{197} (25 kDa)		Antigen: 1 µg CP5- CRM_{197} (300 kDa)	
OPA titer wk0	OPA titer wk8	OPA titer wk0	OPA titer wk8
<100	400	<100	6400
<100	<100	<100	800
<100	400	<100	3200
<100	3200	<100	3200
<100	<100	<100	3200

Example 24: Opsonic Activity of Sera From Mice Immunized With Native and Chemically Modified CP8 Conjugates

[0294] Select mouse sera (n=5) with high CP8 titers from the study in Example 21 were compared for opsonic activity using PFESA0005 strain. The OPA results

(Table 21) show that only conjugates prepared by the conjugation of native CP8 elicited opsonic antibodies in mice. It is noteworthy that the de-OAc CP8 conjugate was immunogenic in mice but the antibodies elicited were not opsonic in this assay. OPA titers are reported as reciprocal of dilution at which 40% killing was observed. Antibodies need to be functional as measured by killing of bacteria in either an animal efficacy model or via opsonophagocytic killing assay that demonstrates the antibodies kill the bacteria. Functional killing may not be demonstrated using an assay that just monitors the generation of antibodies alone, which is not indicative of the importance of O-acetylation in efficacy.

Table 21. Opsonic Activity of Native CP8 vs. de-O-Ac CP8- CRM_{197}

De-O-Ac CP8- CRM_{197}		**CP8-** CRM_{197}	
OP titer Wk0 sera	OP titer Wk8 sera	OP titer Wk0 sera	OP titer Wk8 sera
<50	<50	50	150
<50	<50	<50	1350
<50	<50	<50	450
<50	<50	<50	1350
<50	<50	<50	4050

Example 25: Killing of Type 8 Strains by CP8 Conjugate Non-Human Primate Antisera is Inhibited by Addition of Native CP8

[0295] To confirm the specificity of the killing activity in the sera of non-human primates immunized with CP8-conjugate, an assay was performed in the presence of native CP8. The OP method II was used with the following modifications. Two fold serial dilutions of antibody samples (25 µl) were prepared and followed by addition of either 150 µl (Pn14 competitor) or 125 µl (CP8 competitor) of assay buffer to the antibody suspension. The competitor was purified CP8 polysaccharide (CP8 poly) and unrelated pneumococcal polysaccharide (Pn 14 poly) was used as a control. The polysaccharides were added (50 µg) to the antibody suspension and the plate incubated at 4°C for 30 minutes with end over end mixing. Following incubation with polysaccharides, bacteria were added (25 µl) to the plates and placed on a rotary shaker at 4 °C for 30 minutes followed by addition of 25 µl of human complement (1% final concentration). The results (Table 22) showed that the presence of native CP8 in reaction mixture inhibited

opsonophagocytic killing of *S. aureus* Type 8 These results confirm that opsonophagocytic killing by immune sera was mediated by capsule specific Abs.

Table 22. Addition of CP 8 Polysaccharide Inhibits Opsonophagocytic Killing Of *S. aureus* by Immune Sera.

Monkey	Sera Sample	OPA titer
02D133	Wk0	<50
	Wk 8	4050
	Wk0 + 20 µg CP8 poly	<50
	Wk8 + 20 µg CP8 poly	<50
	Wk0 + 20 µg Pn14 poly	<50
	Wk 8 + 20 µg Pn 14 poly	4050
A4N122	Wk 0	<50
	Wk 8	4050
	Wk0 + 20 µg CP8 poly	<50
	Wk8 + 20 µg CP8 poly	<50
	Wk0 + 20 µg Pn14 poly	<50
	Wk8 + 20 µg Pn 14 poly	1350

Example 26: Naturally Acquired Antibodies to ClfA Mediate Opsonophagocytic Killing of *S. Aureus*

[0296] Humans in the population are naturally exposed to *S. aureus* and thus have preexisting antibodies to that bacterium in their circulation. We affinity purified anti-ClfA antibodies from human serum and evaluated whether the antibodies could mediate opsonic killing. It has been shown that antibodies to ClfA are opsonic for *S. aureus* capsular polysaccharide (data not shown). Strain PFESA0266 was grown overnight in Columbia broth with 2% NaCl. Bacteria were opsonized with ClfA affinity purified human IgG or irrelevant antigen affinity purified human IgG (negative control, streptococcal SCP protein) and the opsonic activity tested. Differentiated HL-60 cells were used in the opsonophagocytic assay at an effector/target ratio of 100:1. As an additional control, a CP5 mAb was included in the experiment to demonstrate the presence of CP5 on the surface. The results are average of two independent experiments. ClfA and CP5 specific antibodies did mediate opsonic killing and SCP specific (negative control) antibodies had no activity in this assay.

Example 27: CP5-CRM$_{197}$ Conjugate Elicits Opsonic Antibodies in Non-Human Primates (NHP)

[0297] To compare the functionality of high vs. low molecular weight CP5-CRM$_{197}$ conjugates in NHP, groups of five monkeys were immunized with 2 and 20 μg doses of the conjugates with or without $AlPO_4$ adjuvant. The monkeys received the first and second vaccination on day 0 and 28, respectively. Bleeds from day 0, 14, 28 and 42 were tested for OP activity. Results are summarized in Table 23. The 20 μg HMW conjugate had the highest OP titers compared to other groups. Also, the frequency of OP positive monkeys was higher at both doses of the high MW groups than for the corresponding low MW groups. These results demonstrate that there is a trend for HMW CP5-CRM$_{197}$ conjugate to elicit better OP responses than LMW CP5 conjugate in NHP.

Table 23. OPA of NHP serum following immunization with CP5 conjugates.

		OPA Titer (40% Kill)			
Group	Monkey ID	Day 0	Day 14	Day 28	Day 42
20 μg CP5 (HMW) + 0.5mg/mL $AlPO_4$	A2N053	450	1350	4050	4050
	149N	<100	4050	4050	4050
	A4L069	<100	450	150	<100
	A1N097	<100	4050	1350	1350
	A4L014	<100	<100	<100	<100
2 μg CP5 (HMW) + 0.5mg/mL $AlPO_4$	02D125	<100	150	150	<100
	A4L081	<100	150	150	150
	A2N055	150	450	150	150
	A4N084	<100	<100	<100	<100
	A1N085	<100	150	450	4050
2 μg CP5 (HMW) no $AlPO_4$	A4L084	150	150	<100	<100
	97N004	150	450	450	450
	A4L055	<100	<100	<100	<100
	97N123	<100	<100	150	150
	225N	<100	<100	<100	<100
20 μg CP5 (LMW) + 0.5mg/mL $AlPO_4$	02D017	<100	<100	<100	<100
	A4N100	<100	150	150	4050
	257N	<100	<100	<100	<100
	A4L046	<100	<100	<100	<100
	A1N098	<100	150	<100	<100
2 μg CP5 (LMW) + 0.5mg/mL $AlPO_4$	96N022	150	150	450	150
	02D005	<100	1350	450	1350
	02D113	<100	150	150	<100
	A2N040	150	150	<100	<100
	A4L056	150	150	<100	<100

Example 28: Capsule Polysaccharide Conjugates Comprising High Molecular Weight Polysaccharides Show Enhanced Immunogenicity Compared To Conjugates Comprising Low Molecular Weight Polysaccharides.

[0298] Non human primate (NHP) studies were conducted to evaluate the immunogenicity of different capsule conjugate formulations. Two formulations were tested at two different dosage levels (2 and 20 μg). The first formulation was composed of a high molecular weight (HMW) polysaccharide (approximately 130 kDa) conjugated to CRM_{197}. The second formulation contained a low molecular weight (LMW) polysaccharide (approximately 25 kDa) conjugated to CRM_{197}. Groups of five primates were vaccinated with a single dose of either vaccine and immune titers were monitored prior to vaccination and two weeks post vaccination. OPA titers were defined as the dilution of serum required to kill 40% of *S. aureus* Strain PFESA0266 in an OPA assay. Antibody titers were also monitored by ELISA. Enhanced activity was seen for the HMW vaccine compared to the LMW formulation (Table 24), evidenced by a ten fold rise in antibody titers for the HMW vaccine compared to the LMW vaccine. The OPA responder rate for the NHPs that received the HMW vaccine were also higher (80% compared to 40%).

Table 24. Enhanced Immunogenicity is observed for HMW polysaccharide conjugate vaccines compared to LMW polysaccharide conjugate vaccine.

	CP5-CRM197 dose level (mcg) per animal	Geometric Mean of PD1*	OPA Responder Rate (%)±
HMW (125 kDa)	20	32	80
	2	21	80
LMW (25 kDa)	20	3	40
	2	8	40

* Fold rise calculated from CP5 ELISA titer 2 weeks post vaccination compared to pre vaccine titers. ± Responder rate calculated from monkeys generating a rise in OPA titer following a single dose of vaccine 2 weeks post vaccination. Each group contained 5 Rhesus maccaques and vaccines were formulated with $AlPO_4$ (250 mcg/dose)

Example 29: Bi-Antigen (CP5-CRM_{197} and ClfA) Formulation–Antibody Responses in Non-Human Primates

[0299] To evaluate the immune response to a single dose of two antigen immunogenic compositions (CP5-CRM_{197} and ClfA) in NHP, groups of five monkeys were immunized with different doses of the two antigens without the addition of $AlPO_4$. Bleeds from day 0, 14, and 28 were tested for opsnophagocytic (OP) activity and ELISA titers and the results are summarized in Table 24. Results showed that OP activity was consistently observed with CP5 immunized animals as compared to a CP5 sham group. Overall, the 100 µg group had the highest ELISA and OP titers compared to other groups. There was no OP killing activity observed with sera from the ClfA alone group. No interference was observed in the groups given ascending doses of ClfA or CP5. See Table 25.

Table 25: OPA Results From Bi-Valent Immunization Study In NHP

		OPA Titer (40% Killing)		
Group #	**ID Number**	**Week: 0**	**Week: 2**	**Week: 4**
180 µg ClfA + 20 µg 130 kDa CP5	A4R054	<100	150	<100
	A4R056	<100	150	150
	A4N087	<100	450	450
	97N152	<100	450	1350
	A4R027	<100	1350	1350
180 µg ClfA + 2 µg 130 kDa CP5	A4R062	<100	150	<100
	97N149	<100	150	<100
	A4R131	<100	450	150
	97N025	<100	450	450
	A4N064	<100	450	450
60 µg ClfA + 20 µg 130 kDa CP5	A4L005	<100	<100	<100
	A4R029	<100	1350	1350
	A3N015	<100	<100	<100
	98N021	150	4050	4050
	A4R137	<100	<100	<100
60 µg ClfA + 2 µg 130 kDa CP5	A1N040	<100	150	150
	A2N104	<100	1350	<100
	A4L033	<100	150	<100
	96N048	<100	<100	<100
	A4R032	<100	<100	<100
2 µg 130 kDa CP5	A4R135	<100	450	150
	A1N118	<100	150	150
	A4R061	<100	<100	1350
	A4R101	<100	4050	1350
	97N137	<100	1350	1350

		OPA Titer (40% Killing)		
Group #	ID Number	Week: 0	Week: 2	Week: 4
20 µg 130 kDa CP5	A4R135	<100	<100	<100
	A4N115	<100	150	150
	95N038	<100	<100	<100
	A4N120	<100	450	450
	96N004	<100	150	150
100 µg 130 kDa CP5	A4N116	<100	450	450
	A3N097	<100	450	450
	A4N108	<100	1350	1350
	98N034	<100	450	150
	99N034	<100	1350	4050
60 µg ClfA	97N057	<100	<100	<100
	A4R112	150	<100	150
	A4L022	<100	<100	<100
	97N100	<100	<100	<100
	99N041	150	150	150

Animal Models Demonstrate Potential of *S. aureus* CP5 and CP8 Capsule Polysaccharide Antigens

[0300] Both CP5-CRM_{197} and CP8-CRM_{197} conjugates induced capsular serotype specific antibody responses in mice, rats, rabbits and non-human primates (NHP). Conjugate induced antibodies were functional in the *in vitro* functional opsonophagocytosis killing assay. Data were generated to demonstrate that O-Acetylation is important for elicitation of protective antibodies for both CP5 and CP8, and that O-acetyl groups are part of an epitope recognized by OPA^+ mAbs against CP5. MAbs that recognize native CP5 which is O-acetylated are functional in OPA and mediate killing of the bacteria. CP8 conjugate induced functional antibodies in both mice and rabbits that mediated killing of Type 8 strain in OPA. The specificity of killing by polyclonal or monoclonal antibodies was confirmed by abolition of the killing after addition of the homologous native polysaccharide to the assay. The various active immunization models were used to show preclinical efficacy of both CP5- and CP8-CRM_{197} conjugates. The CP5 conjugate showed consistent efficacy in the murine pyelonephritis model and the rat endocarditis model. The importance of O-acetylation of CP5 was confirmed in the murine pyelonephritis model, where de-O-acetylated CP5 conjugated to CRM_{197} failed to protect animals against experimental infection.

[0301] The combination of the conjugates in a bi-antigen formulation induced antibodies to both capsules CP5 and CP8 and there was no interference to the specific antibody levels induced compared to single antigen immunizations. The combination of conjugates and ClfA in a tri-antigen formulation induced high CP5, CP8 and ClfA levels, and there was no interference to the antibody responses induced against any antigen present in the combination. The tri-antigen immunogenic compositions induced antibody (Ab) responses capable of being boosted to all three components in rabbits with high pre-immune titers.

[0302] These results suggest that CP5 and CP8 conjugated to CRM_{197} should be included as immunogenic formulation components of a protective *S. aureus* immunogenic composition.

Example 30: Requirement of Different Antigens to Protect from Multiple Possible *S. aureus* Diseases

[0303] *S. aureus* cause a wide array of infections ranging from relatively mild skin infections to more serious and invasive infections such as endocarditis, necrotizing fasciitis, osteomyelitis, septic arthritis and pneumonia. Each of these *in vivo* sites is unique and the bacteria likely respond to the differences in environmental stimuli by altering their antigen expression profiles to ones most suitable for the individual strain to colonize, grow and ultimately cause disease. As exemplified in Example 12, *S. aureus* strains show diversity of antigen expression *in vivo*. A multi-component immunogenic composition composed of different antigens is more likely to protect against the diverse disease manifestation caused by *S. aureus*.

[0304] ClfA was shown to protect in rodent endocarditis and sepsis models. ClfB has been reported to be important in nasal colonization of *S. aureus*. MntC protected mice in a murine bacteremia model. The CP5 conjugate protected in pyelonephritis and endocarditis, and the CP8 conjugate protected in rodent pyelonephritis and sepsis models. These results demonstrate that a multi-component vaccine containing these antigens will protect against multiple types of *S. aureus* disease.

[0305] *In vivo* animal models approximate the course of an actual infection and help to elucidate which antigens may be useful in protecting from a particular

disease. Table 26 summarizes results from numerous experiments performed in various *in vivo* models. The results are reported in each block as four numbers separated by a slash, for example ClfA in a sepsis model has the numbers 27/1/3/31. The first number represents the number of experiments where ClfA immunization produced a statistically significant positive result of protection. The second number represents the number of experiments where ClfA immunization produced a positive result of protection that trended toward significance but was not statistically significant. The third number represents the number of experiments where ClfA immunization produced a negative result, but was not statistically significant. The fourth number is the total number of experiments performed. The first three numbers should add up to equal the fourth number.

Table 26. Summary Of Protection In Animal Models For *S. aureus* Antigens

	ClfA	CP5	CP8	MntC[20]
Bacteremia	1/4/0/5	3/0/3/6	1/1/1/3	6/2/5/13
Sepsis	27/1/3/31	1/0/0/1	NT	NT
Pyelonephritis	0/4/2/6	13/1/0/14	NT	1/0/4/5[25]
Endocarditis	3/6/1/10	3/2/2/7	NT	NT

NT: Not Tested

Example 31: Testing of Various Multi-antigen Immunogenic Compositions *in vitro* and *in vivo*

[0306] Various multi-antigen staphylococcal immunogenic formulations containing either three, four or five antigens selected from the following polypeptides and/or polysaccharides are tested for immunogenicity and efficacy in various *in vivo* models: ClfA, ClfB, MntC, CP5- and CP8. The immunogenic compositions are as follows:

[0307] (1) an immunogenic composition comprising: an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated *S. aureus* capsular polysaccharide type 5 conjugated to CRM_{197}, and an isolated *S. aureus* capsular polysaccharide type 8 conjugated to CRM_{197};

[0308] (2) A second combination provides clumping factor A (ClfA), clumping factor B (ClfB), an isolated MntC, isolated staphylococcal capsular polysaccharide CP5 conjugated to CRM_{197}, and isolated staphylococcal capsular polysaccharide CP8 conjugated to CRM_{197};

[0309] (3) A third combination provides an immunogenic composition comprising: an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated *S. aureus* clumping factor B (ClfB) polypeptide, or an isolated *S. aureus* MntC protein, an isolated *S. aureus* capsular polysaccharide type 5 conjugated to CRM_{197}, and an isolated *S. aureus* capsular polysaccharide type 8 conjugated to CRM_{197}; isolated

[0310] (4) A fourth combination provides an immunogenic composition comprising: an isolated *S. aureus* clumping factor B (ClfB) polypeptide, an isolated *S. aureus* capsular polysaccharide type 5 conjugated to CRM_{197}, and an isolated *S. aureus* capsular polysaccharide type 8 conjugated to CRM_{197};

[0311] (5) A fifth combination provides an immunogenic composition comprising: an isolated *S. aureus* clumping factor B (ClfB) polypeptide, an isolated *S. aureus* MntC protein, an isolated *S. aureus* capsular polysaccharide type 5 conjugated to CRM_{197}, and an isolated *S. aureus* capsular polysaccharide type 8 conjugated to CRM_{197}; and

[0312] (6) A sixth combination provides an immunogenic composition comprising: an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated *S. aureus* clumping factor B (ClfB) polypeptide, and an isolated *S. aureus* MntC protein.

[0313] rClfA and rClfB are prepared and purified as described in Example 1. MntC is prepared and purified as described in Example 2. Isolated CP5 and CP8 are prepared and purified as described in Example 3 and are conjugated to CRM_{197} as described in Example 4.

[0314] More particularly, the procedures described in the previous Examples above are used to measure immunogenicity and efficacy. Studies are done to determine whether each of the three, four or five components, when delivered alone, or together, induce an immune response. These same studies are used to determine whether or not the presence of any one of the four or five components

interferes with the ability of any of the other three or four components to induce an immune response. Moreover, studies are done to determine whether the four or five components when tested alone, or when tested together, will confer protection in any one or more of the animal models described above. The four or five components are administered as a single dose or as multiple doses to an animal, *e.g.* mice, rats, rabbits or non-human primates, as noted in the previous examples above. The animals are bled and the serum collected and tested for the presence of antibodies to each of the four or five components. The presence of antigen specific antibodies is measured by any immunoassay known to those skilled in the art, for example, an ELISA (See Examples 11-29) or a Western blot (See Example 1) is used to assess the presence or absence of antigen-specific antibodies. In addition, an opsonophagocytic assay is used to determine whether the antigen specific antibodies are effective at mediating killing of the staphylococcal organisms by phagocytic cells (See Examples 11-29).

[0315] *In vivo* efficacy is also assessed using any one or more of the animal studies described above, such as, but not limited to, the in-dwelling tubing model; the murine bacteremia model; the wound infection model; the murine pyelonephritis model; the rat endocarditis model and the murine sepsis model (See Examples 11-30).

Example 32: Combinations of *S. Aureus* Antigens Generate Antibodies in Non-Human Primates That Enhance Killing of *S. Aureus* Strain Pfe5-1.

[0316] Enhanced efficacy, as measured using the OPA assay, was observed using combinations of antigens. A non-human primate study was conducted where groups of 3-10 monkeys were immunized with multi-component vaccines. Animals received a single dose of vaccine and OPA titers were monitored at day 0 and two weeks post vaccination. OPA titers were defined as the dilution of serum required to kill 50% of *S. aureus* Strain Pfe5-1 in an OPA assay. Enhanced activity was seen for a combination of 4 antigens compared to a 3-antigen vaccine formulation ($p=0.0272$; Figure 18).

Claims

1. An immunogenic polysaccharide-protein conjugate comprising a *Staphylococcus aureus* capsular polysaccharide conjugated to a carrier protein, wherein the polysaccharide has a molecular weight of between 50 kDa and 800 kDa or between 70 kDa and 300 kDa.

2. The immunogenic conjugate of claim 1, wherein the immunogenic conjugate has a molecular weight of between 200 kDa and 5000 kDa or between 500 kDa and 2500 kDa.

3. The immunogenic polysaccharide-protein conjugate of claim 1 or 2, wherein the capsular polysaccharide is a serotype 5 or serotype 8 capsular polysaccharide.

4. The immunogenic conjugate of any one of claims 1-3, wherein the polysaccharide has a degree of O-acetylation between 10-100%, between 50-100%, or between 75-100%.

5. The immunogenic conjugate of any one of claims 1-4, wherein the carrier protein is CRM_{197} or pneumolysin.

6. The immunogenic conjugate of claim 5, wherein the CRM_{197} is covalently linked to the polysaccharide through a carbamate linkage, an amide linkage, or both.

7. The immunogenic conjugate of claim 5 or 6, wherein the molar ratio of conjugated lysines to CRM_{197} is about 10:1 to about 25:1.

8. The immunogenic conjugate of claim 7, wherein at least one covalent linkage between CRM_{197} and polysaccharide occurs at least at every 5 to 10 saccharide repeat units of the polysaccharide or every 5 saccharide repeat units of the polysaccharide.

9. The immunogenic conjugate of any one of claims 5-8, wherein the CRM_{197} comprises 5 to 25, 5 to 20, or 10 to 25 lysines covalently linked to the polysaccharide.

10. An immunogenic composition comprising the immunogenic conjugate of any one of claims 1-9 and a pharmaceutically acceptable carrier.

11. An immunogenic composition comprising the immunogenic conjugate of any one of claims 1-9 and at least one component selected from the group consisting of an isolated *S. aureus* clumping factor A (ClfA) polypeptide, an isolated S. aureus clumping factor B (ClfB) polypeptide, and an isolated 5. *aureus* manganese transporter protein C (MntC).

12. The immunogenic composition of claim 11, wherein the at least one component is an isolated *S. aureus* ClfA polypeptide.

13. The immunogenic composition of claim 12, which further comprises an isolated *S. aureus* MntC protein.

14. The immunogenic composition of claim 11 or 13, wherein the MntC protein is a lipidated or a non-lipidated protein.

15. The immunogenic composition of any one of claims 11 - 14, wherein the ClfA polypeptide is a
polypeptide fragment selected from the group consisting of a fibrinogen binding domain; N1, N2 and N3 domains; and N2 and N3 domains of ClfA.

16. The immunogenic composition of any one of claims 11 - 15, wherein the ClfA polypeptide binds to fibrinogen at a reduced level compared to binding observed to fibrinogen with native ClfA.

17. The immunogenic composition of any one of claims 11 - 16, wherein the ClfA polypeptide has an amino acid substitution at one or more of Tyr338, Tyr256, Pro336, Lys389, Ala254, or Ile387.

18. The immunogenic composition of claim 17, wherein the amino acid substitution is to Ala or Ser.

19. The immunogenic composition of claim 18, wherein the Tyr338 is substituted to Ala.

20. The immunogenic composition of any one of claims 11 or 15 - 19, wherein the ClfB polypeptide is a polypeptide fragment selected from the group consisting of a fibrinogen binding domain; N1, N2 and N3 domains; and N2 and N3 domains of ClfB.

21. The immunogenic composition of any one of claims 10 - 20, wherein the immunogenic compositioncomprises less than 30% or less than 20% free type 5 or 8 polysaccharide compared to the total amount of type 5 or 8 polysaccharide.

22. The immunogenic composition of any one of claims 10 - 21, further comprising an antigen selected from the group consisting of Opp3a, DltD, HtsA, LtaS, IsdB, IsdC, SdrC, SdrD, SdrE, SdrF, SdrG, SdrH, SrtA, SpA, Sbi, FmtB, alpha-hemolysin (hla), beta-hemolysin, fibronectin-binding protein A (fnbA), fibronectin-binding protein B (fnbB), coagulase, ~~Fig, map,~~ PAnton-Valentine leukocidin (pvl), alpha-toxin and its variants, gamma toxin (hlg) and variants, ica, immunodominant ABC transporter, Mg2+ transporter, Ni ABC transporter, RAP, autolysin, laminin receptors, IsaA/PisA, IsaB/PisB, SPOlllE, SsaA, EbpS, SasA, SasF, SasH, EFB (FIB), SBI, Npase, EBP, bone sialo binding protein II, aureolysin precursor (AUR)/Sepp1, Cna, and fragments thereof such as M55, TSSST-1, mecA, poly-N-acetylglucosamine (PNAG/dPNAG) exopolysaccharide, GehD, EbhA, EbhB, SSP-1, SSP-2, HBP, vitronectin binding protein, HarA, EsxA, EsxB, Enterotoxin A, Enterotoxin B, and Enterotoxin C.

23. The immunogenic composition of any one of claims 10 – 22, further comprising an adjuvant.

24. The use of the immunogenic composition of any one of claims 10 – 23 in the manufacture of a medicament for inducing an immune response against *Staphylococcus aureus* in a subject.

25. The use of claim 24, wherein the immune response prevents or reduces an infection, disease, condition, or at least one symptom associated with a staphylococcal organism in a subject.

26. The use of claim 24, wherein the infection, disease, condition is selected from the group consisting of invasive *Staphylococcus aureus* disease, sepsis and carriage.

27. The use of any one of claims 24 - 26, wherein the immune response induced comprises the generation of antibodies having opsonophagocytic activity (OPA) against *S. aureus*.

SEQUENCE LISTING

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PAVLIAK, VILIAM
JANSEN, KATHRIN UTE
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BAKER, STEVEN MORRIS
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MURPHY, ELLEN
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gcatggttaa gtttagataa cggtattaaa tacgtaaaaa caattcaaca aacatttatc 480

gataacgaca aaaaacataa agcagattat gaaaagcaag gtaacaaata cattgctcaa 540

ttggaaaaat taaataatga cagtaaagac aaatttaatg acattccaaa agaacaacgt 600

gccatgatta caagtgaagg tgccttcaaa tacttctcaa aacaatacgg tattacacca 660

ggttatattt gggaaattaa cactgaaaaa caaggtacac cagaacaaat gagacaagct 720

attgagtttg ttaaaaaaca caaattaaaa cacttattag tagaaacaag tgttgataag 780

aaagcaatgg aaagtttatc tgaagaaacg aagaaagata tctttggtga agtgtacaca 840

gattcaatcg gtaaagaagg cactaaaggt gactcttact acaaaatgat gaaatcaaat 900

attgatactg tacacggaag catgaaa 927

<210> 8
<211> 309
<212> PRT
<213> Staphylococcus aureus

<400> 8

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Met Lys Lys Leu Val Pro Leu Leu Leu Ala Leu Leu Leu Leu Val Ala
1               5                  10                  15

Ala Cys Gly Thr Gly Gly Lys Gln Ser Ser Asp Lys Ser Asn Gly Lys
            20                  25                  30

Leu Lys Val Val Thr Thr Asn Ser Ile Leu Tyr Asp Met Ala Lys Asn
        35                  40                  45

Val Gly Gly Asp Asn Val Asp Ile His Ser Ile Val Pro Val Gly Gln
    50                  55                  60

Asp Pro His Glu Tyr Glu Val Lys Pro Lys Asp Ile Lys Lys Leu Thr
65                  70                  75                  80

Asp Ala Asp Val Ile Leu Tyr Asn Gly Leu Asn Leu Glu Thr Gly Asn
                85                  90                  95

Gly Trp Phe Glu Lys Ala Leu Glu Gln Ala Gly Lys Ser Leu Lys Asp
            100                 105                 110

Lys Lys Val Ile Ala Val Ser Lys Asp Val Lys Pro Ile Tyr Leu Asn
        115                 120                 125
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Gly Glu Glu Gly Asn Lys Asp Lys Gln Asp Pro His Ala Trp Leu Ser
130 135 140

Leu Asp Asn Gly Ile Lys Tyr Val Lys Thr Ile Gln Gln Thr Phe Ile
145 150 155 160

Asp Asn Asp Lys Lys His Lys Ala Asp Tyr Glu Lys Gln Gly Asn Lys
165 170 175

Tyr Ile Ala Gln Leu Glu Lys Leu Asn Asn Asp Ser Lys Asp Lys Phe
180 185 190

Asn Asp Ile Pro Lys Glu Gln Arg Ala Met Ile Thr Ser Glu Gly Ala
195 200 205

Phe Lys Tyr Phe Ser Lys Gln Tyr Gly Ile Thr Pro Gly Tyr Ile Trp
210 215 220

Glu Ile Asn Thr Glu Lys Gln Gly Thr Pro Glu Gln Met Arg Gln Ala
225 230 235 240

Ile Glu Phe Val Lys Lys His Lys Leu Lys His Leu Leu Val Glu Thr
245 250 255

Ser Val Asp Lys Lys Ala Met Glu Ser Leu Ser Glu Glu Thr Lys Lys
260 265 270

Asp Ile Phe Gly Glu Val Tyr Thr Asp Ser Ile Gly Lys Glu Gly Thr
275 280 285

Lys Gly Asp Ser Tyr Tyr Lys Met Met Lys Ser Asn Ile Asp Thr Val
290 295 300

His Gly Ser Met Lys
305

<210> 9
<211> 927
<212> DNA
<213> Staphylococcus aureus

<400> 9
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attttatatg atatggctaa aaatgttggt ggagacaacg tcgatattca tagtattgta 180

cctgttggtc aagatcctca tgaatatgaa gttaaaccta aagatattaa aaagttaact 240

gacgctgacg ttattttata caacggatta aatttagaga ctggtaacgg ttggtttgaa 300

aaagccttag aacaggctgg taaatcatta aaagataaaa aagttatcgc agtatcaaaa 360

gatgttaaac ctatctattt aaacggtgaa gaaggcaaca aagataaaca agatccacac 420

gcatggttaa gtttagataa cggtattaaa tacgtaaaaa caattcaaca aacatttatc 480

gataacgaca aaaaacataa agcagattat gaaaagcaag gtaacaaata cattgctcaa 540

ttggaaaaat taaataatga cagtaaagac aaatttaatg acattccaaa agaacaacgt 600

gccatgatta caagtgaagg tgccttcaag tacttctcaa aacaatacgg tattacacca 660

ggttatattt gggaaattaa cactgaaaaa caaggtacac ctgaacaaat gagacaagct 720

attgagtttg ttaaaaagca caaattaaaa cacttattag tagaaacaag tgttgataag 780

aaagcaatgg aaagtttatc tgaagaaacg aagaaagata tctttggtga agtgtacaca 840

gattcaatcg gtaaagaagg cactaaaggt gactcttact acaaaatgat gaaatcaaat 900

attgaaactg tacacggaag catgaaa 927

<210> 10
<211> 309
<212> PRT
<213> Staphylococcus aureus

<400> 10

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Met Lys Lys Leu Val Pro Leu Leu Leu Ala Leu Leu Leu Leu Val Ala
1               5                  10                  15

Ala Cys Gly Thr Asp Gly Lys Gln Ser Ser Asp Lys Ser Asn Gly Lys
            20                  25                  30

Leu Lys Val Val Thr Thr Asn Ser Ile Leu Tyr Asp Met Ala Lys Asn
        35                  40                  45

Val Gly Gly Asp Asn Val Asp Ile His Ser Ile Val Pro Val Gly Gln
    50                  55                  60

Asp Pro His Glu Tyr Glu Val Lys Pro Lys Asp Ile Lys Lys Leu Thr
65                  70                  75                  80

Asp Ala Asp Val Ile Leu Tyr Asn Gly Leu Asn Leu Glu Thr Gly Asn
                85                  90                  95

Gly Trp Phe Glu Lys Ala Leu Glu Gln Ala Gly Lys Ser Leu Lys Asp
            100                 105                 110

Lys Lys Val Ile Ala Val Ser Lys Asp Val Lys Pro Ile Tyr Leu Asn
        115                 120                 125

Gly Glu Glu Gly Asn Lys Asp Lys Gln Asp Pro His Ala Trp Leu Ser
    130                 135                 140

Leu Asp Asn Gly Ile Lys Tyr Val Lys Thr Ile Gln Gln Thr Phe Ile
145                 150                 155                 160

Asp Asn Asp Lys Lys His Lys Ala Asp Tyr Glu Lys Gln Gly Asn Lys
                165                 170                 175
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Tyr Ile Ala Gln Leu Glu Lys Leu Asn Asn Asp Ser Lys Asp Lys Phe
180 185 190

Asn Asp Ile Pro Lys Glu Gln Arg Ala Met Ile Thr Ser Glu Gly Ala
195 200 205

Phe Lys Tyr Phe Ser Lys Gln Tyr Gly Ile Thr Pro Gly Tyr Ile Trp
210 215 220

Glu Ile Asn Thr Glu Lys Gln Gly Thr Pro Glu Gln Met Arg Gln Ala
225 230 235 240

Ile Glu Phe Val Lys Lys His Lys Leu Lys His Leu Leu Val Glu Thr
245 250 255

Ser Val Asp Lys Lys Ala Met Glu Ser Leu Ser Glu Glu Thr Lys Lys
260 265 270

Asp Ile Phe Gly Glu Val Tyr Thr Asp Ser Ile Gly Lys Glu Gly Thr
275 280 285

Lys Gly Asp Ser Tyr Tyr Lys Met Met Lys Ser Asn Ile Glu Thr Val
290 295 300

His Gly Ser Met Lys
305

<210> 11
<211> 927
<212> DNA
<213> Staphylococcus aureus

<400> 11
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attttatatg atatggctaa aaatgttggt ggagacaacg tcgatattca tagtattgta 180

cctgttggtc aagatcctca tgaatatgaa gttaaaccta aagatattaa aaagttaact 240

gacgctgacg ttattttata caacggatta aatttagaga ctggtaacgg ttggtttgaa 300

aaagccttag aacaggctgg taaatcatta aaagataaaa aagttatcgc agtatcaaaa 360

gatgttaaac ctatctattt aaacggtgaa gaaggcaaca aagataaaca agatccacac 420

gcatggttaa gtttagataa cggtattaaa tacgtaaaaa caattcaaca aacatttatc 480

gataacgaca aaaaacataa agcatattat gaaaagcaag gtaacaaata cattgctcaa 540

ttggaaaaat taaataatga cagtaaagac aaatttaatg acattccaaa agaacaacgt 600

gccatgatta caagtgaagg tgccttcaag tacttctcaa aacaatacgg tattacacca 660

ggttatattt gggaaattaa cactgaaaaa caaggtacac ctgaacaaat gagacaagct 720

attgagtttg ttaaaaagca caaattaaaa cacttattag tagaaacaag tgttgataag 780

aaagcaatgg aaagtttatc tgaagaaacg aagaaagata tctttggtga agtgtacaca 840

gattcaatcg gtaaagaagg cactaaaggt gactcttact acaaaatgat gaaatcaaat 900

attgatactg tacacggaag catgaaa 927

<210> 12
<211> 309
<212> PRT
<213> Staphylococcus aureus

<400> 12

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Met Lys Lys Leu Val Pro Leu Leu Leu Ala Leu Leu Leu Leu Val Ala
1               5                  10                  15

Ala Cys Gly Thr Gly Gly Lys Gln Ser Ser Asp Lys Ser Asn Gly Lys
            20                  25                  30

Leu Lys Val Val Thr Thr Asn Ser Ile Leu Tyr Asp Met Ala Lys Asn
        35                  40                  45

Val Gly Gly Asp Asn Val Asp Ile His Ser Ile Val Pro Val Gly Gln
    50                  55                  60

Asp Pro His Glu Tyr Glu Val Lys Pro Lys Asp Ile Lys Lys Leu Thr
65                  70                  75                  80

Asp Ala Asp Val Ile Leu Tyr Asn Gly Leu Asn Leu Glu Thr Gly Asn
                85                  90                  95

Gly Trp Phe Glu Lys Ala Leu Glu Gln Ala Gly Lys Ser Leu Lys Asp
            100                 105                 110

Lys Lys Val Ile Ala Val Ser Lys Asp Val Lys Pro Ile Tyr Leu Asn
        115                 120                 125

Gly Glu Glu Gly Asn Lys Asp Lys Gln Asp Pro His Ala Trp Leu Ser
    130                 135                 140

Leu Asp Asn Gly Ile Lys Tyr Val Lys Thr Ile Gln Gln Thr Phe Ile
145                 150                 155                 160

Asp Asn Asp Lys Lys His Lys Ala Tyr Tyr Glu Lys Gln Gly Asn Lys
                165                 170                 175

Tyr Ile Ala Gln Leu Glu Lys Leu Asn Asn Asp Ser Lys Asp Lys Phe
            180                 185                 190

Asn Asp Ile Pro Lys Glu Gln Arg Ala Met Ile Thr Ser Glu Gly Ala
        195                 200                 205

Phe Lys Tyr Phe Ser Lys Gln Tyr Gly Ile Thr Pro Gly Tyr Ile Trp
    210                 215                 220
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Glu Ile Asn Thr Glu Lys Gln Gly Thr Pro Glu Gln Met Arg Gln Ala
225 230 235 240

Ile Glu Phe Val Lys Lys His Lys Leu Lys His Leu Leu Val Glu Thr
245 250 255

Ser Val Asp Lys Lys Ala Met Glu Ser Leu Ser Glu Glu Thr Lys Lys
260 265 270

Asp Ile Phe Gly Glu Val Tyr Thr Asp Ser Ile Gly Lys Glu Gly Thr
275 280 285

Lys Gly Asp Ser Tyr Tyr Lys Met Met Lys Ser Asn Ile Asp Thr Val
290 295 300

His Gly Ser Met Lys
305

<210> 13
<211> 927
<212> DNA
<213> Staphylococcus aureus

<400> 13
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ggtggtaaac aaagcagtga taagtcaaat ggcaaattaa aagtagtaac gacgaattca 120

attttatatg atatggctaa aaatgttggt ggagacaacg tcgatattca tagtattgta 180

cctgttggtc aagatcctca tgaatatgaa gttaaaccta aagatattaa aaagttaact 240

gacgctgacg ttattttata caacggatta aatttagaga ctggtaacgg ttggtttgaa 300

aaagccttag aacaggctgg taaatcatta aaagataaaa aagttatcgc agtatcaaaa 360

gatgttaaac ctatctattt aaacggtgaa gaaggcaaca aagataaaca agatccacac 420

gcatggttaa gtttagataa cggtattaaa tacgtaaaaa caattcaaca aacatttatc 480

gataacgaca aaaaacataa agcagattat gaaaagcaag gtaacaaata cattgctcaa 540

ttggaaaaat taaataatga cagtaaagac aaatttaatg acrttccaaa agaacaacgt 600

gccatgatta caagtgaagg tgccttcaag tacttctcaa aacaatacgg tattacacca 660

ggttatattt gggaaattaa cactgaaaaa caaggtacac ctgaacaaat gagacaagct 720

attgagtttg ttaaaaagca caaattaaaa cacttattag tagaaacaag tgttgataag 780

aaagcaatgg aaagtttatc tgaagaaacg aagaaagata tctttggtga agtgtacaca 840

gattcaatcg gtaaagaagg cactaaaggt gactcttact acaaaatgat gaaatcaaat 900

attgatactg tacacggaag catgaaa 927

<210> 14
<211> 309
<212> PRT

<213> Staphylococcus aureus

<220>
<221> MOD_RES
<222> (195)..(195)
<223> Any amino acid

<400> 14

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Met Lys Lys Leu Val Pro Leu Leu Leu Ala Leu Leu Leu Leu Val Ala
1               5                  10                  15

Ala Cys Gly Thr Gly Gly Lys Gln Ser Ser Asp Lys Ser Asn Gly Lys
            20                  25                  30

Leu Lys Val Val Thr Thr Asn Ser Ile Leu Tyr Asp Met Ala Lys Asn
        35                  40                  45

Val Gly Gly Asp Asn Val Asp Ile His Ser Ile Val Pro Val Gly Gln
    50                  55                  60

Asp Pro His Glu Tyr Glu Val Lys Pro Lys Asp Ile Lys Lys Leu Thr
65                  70                  75                  80

Asp Ala Asp Val Ile Leu Tyr Asn Gly Leu Asn Leu Glu Thr Gly Asn
                85                  90                  95

Gly Trp Phe Glu Lys Ala Leu Glu Gln Ala Gly Lys Ser Leu Lys Asp
            100                 105                 110

Lys Lys Val Ile Ala Val Ser Lys Asp Val Lys Pro Ile Tyr Leu Asn
        115                 120                 125

Gly Glu Glu Gly Asn Lys Asp Lys Gln Asp Pro His Ala Trp Leu Ser
    130                 135                 140

Leu Asp Asn Gly Ile Lys Tyr Val Lys Thr Ile Gln Gln Thr Phe Ile
145                 150                 155                 160

Asp Asn Asp Lys Lys His Lys Ala Asp Tyr Glu Lys Gln Gly Asn Lys
                165                 170                 175

Tyr Ile Ala Gln Leu Glu Lys Leu Asn Asn Asp Ser Lys Asp Lys Phe
            180                 185                 190

Asn Asp Xaa Pro Lys Glu Gln Arg Ala Met Ile Thr Ser Glu Gly Ala
        195                 200                 205

Phe Lys Tyr Phe Ser Lys Gln Tyr Gly Ile Thr Pro Gly Tyr Ile Trp
    210                 215                 220

Glu Ile Asn Thr Glu Lys Gln Gly Thr Pro Glu Gln Met Arg Gln Ala
225                 230                 235                 240
```

Ile Glu Phe Val Lys Lys His Lys Leu Lys His Leu Leu Val Glu Thr
245 250 255

Ser Val Asp Lys Lys Ala Met Glu Ser Leu Ser Glu Glu Thr Lys Lys
260 265 270

Asp Ile Phe Gly Glu Val Tyr Thr Asp Ser Ile Gly Lys Glu Gly Thr
275 280 285

Lys Gly Asp Ser Tyr Tyr Lys Met Met Lys Ser Asn Ile Asp Thr Val
290 295 300

His Gly Ser Met Lys
305

<210> 15
<211> 1626
<212> DNA
<213> Staphylococcus aureus

<400> 15
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caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt 180

gcagattccg aaaaaaacaa tacgatagaa acacctcaat taaatacaac ggctaatgat 240

acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacagc aaaaccaatg 300

tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcac 360

ccgacggcaa ttaaagatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420

gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaatagcat agcaacaaac 480

agtgagctta aaaatcctca aacattagat ttaccacaat catcaccaca aacgatttcc 540

aatgcgcaag gaactagtaa accaagtgtt agaacgagag ctgtacgtag tcttgcagtt 600

actgaacctg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatgg tcaagttacg 660

gcaagtgatt tcaagttaga aaagactaca tttgacccta accaaagtgg taacacattt 720

atggcggcaa attttaaagt ggcagggaaa gtgaaatcag gggattattt tacagcgaag 780

ttaccagata gtgtaactgg taatggagat gtggattact ctaactcgaa taatacgatg 840

ccaattgcag atattaaaag tacgaatggc gatgttgtag ctaaagcaac atatgatatc 900

ttgactaaga cgtatacatt tgtctttaca gattatgtaa atgataaaga aaatattaac 960

ggacaatttt cattaccatt atttacagac agagcaaagg cacctaaatc aggaacatat 1020

gatgcaaata ttaatattgc ggatgaaatg tttaataata aaattactta taactatagt 1080

tcaccaattg caggaattga taagccaaat ggcgcgaaca tttcttctca aattattggt 1140

gtagatacag cttcaggtca aaacacatac aagcaaacgg tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggttacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctac agatacaaaa ctgagaattt ttgaagtgaa tgatacatct 1320

aaattatcag atagctacta tgcagaccca aatgactcta accttaaaga agtaactgat 1380

caatttaaag ataaaatttc atacaaatac gataacgtag caagtattaa ttttggtgat 1440

ataaataaaa cgtatgtcgt tttagtcgaa ggtcattatg ataatactgg taaaaacttg 1500

aaaacacagg ttattcaaga aaatattgac ccagcgacag gtaaagatta cagtattttc 1560

ggttggaata atgagaatgt tgtacgttat ggaggcggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 16
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 16

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Leu Lys Lys Arg Ile Asp Tyr Leu Ser Asn Lys Gln Asn Lys Tyr Ser
1               5                  10                  15

Ile Arg Arg Phe Thr Val Gly Thr Thr Ser Val Ile Val Gly Ala Thr
            20                  25                  30

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
        35                  40                  45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
    50                  55                  60

Lys Asn Asn Thr Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65                  70                  75                  80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
                85                  90                  95

Ala Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
            100                 105                 110

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

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
    130                 135                 140

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

Ser Glu Leu Lys Asn Pro Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
                165                 170                 175

Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
            180                 185                 190
```

```
Arg Ala Val Arg Ser Leu Ala Val Thr Glu Pro Val Val Asn Ala Ala
        195                 200                 205

Asp Ala Lys Gly Thr Asn Val Asn Gly Gln Val Thr Ala Ser Asp Phe
    210                 215                 220

Lys Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225                 230                 235                 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Val Thr Gly Asn Gly Asp Val Asp
            260                 265                 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
        275                 280                 285

Asn Gly Asp Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
    290                 295                 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asp Lys Glu Asn Ile Asn
305                 310                 315                 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
                325                 330                 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
            340                 345                 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
        355                 360                 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
    370                 375                 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385                 390                 395                 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
                405                 410                 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
            420                 425                 430

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
        435                 440                 445

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asp Gln Phe Lys Asp
    450                 455                 460
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Lys Ile Ser Tyr Lys Tyr Asp Asn Val Ala Ser Ile Asn Phe Gly Asp
465 470 475 480

Ile Asn Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Ile Asp Pro Ala
500 505 510

Thr Gly Lys Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

<210> 17
<211> 1626
<212> DNA
<213> Staphylococcus aureus

<400> 17
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acagtaggta ccacatcagt aatagtaggg gcaactatac tatttgggat aggcaatcat 120
caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt 180
gcagattccg aaaaaaacaa tacgatagaa acacctcaat taaatacaac ggctaatgat 240
acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacagc aaaaacaatg 300
tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360
ccgacggcaa ttaaagatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420
gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaataacat agcaacaaac 480
agtgagctta aaaatcctca aacattagat ttaccacaat catcaccaca aacgatttcc 540
aatgcgcaag gaactagtaa accaagtgtt agaacgagag ctgtacgtag tcttgcagtt 600
gctgaacctg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatga taaagttacg 660
gcaagtgatt tcaagttaga aaagactgca tttgacccta accaaagtgg taacacattt 720
atggcggcaa attttaaagt gactggacaa gtgaaatcag gggattattt tacagcgaag 780
ttaccagata gtgtaactgg taatggagac gtggattact ctaattcaaa taatacgatg 840
ccaattgcag acattaaaag tacgaatggc gatgttgtag ctaaagcaac atatgatatc 900
ttgactaaga cgtatacatt tgtctttaca gattatgtaa atgataaaga aaatattaac 960
ggacaatttt cattaccttt atttacagac cgagcaaagg cacctaaatc aggaacatat 1020
gatgcaaata ttaatattgc ggatgaaatg tttgataata aaattactta taactatagt 1080
tcgccaattg caggaattga taagccaaat ggcgcgaaca tttcttctca aattattggt 1140
gtagatacag cttcaggtca aaacacatac aagcaaacgg tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggttacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctac agatacaaaa ctgagaattt ttgaagtgaa tgatacatct 1320

aaattatcag atagctacta tgcagaccca aatgactcta accttaaaga agtgactggt 1380

gagtttaaag ataaaatttc atacaaatac gataacgtag caagtattaa ttttggtgat 1440

ataaataaaa cgtatgttgt attagtggaa ggtcactatg ataatactgg taaaaacttg 1500

aaaacacagg ttattcaaga aaatattgac ccagcgacag gtaaagacta cagtattttc 1560

ggttggaata atgagaatgt tgtacgttat ggaggcggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 18
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 18

Leu Lys Lys Arg Ile Asp Tyr Leu Ser Asn Lys Gln Asn Lys Tyr Ser
1 5 10 15

Ile Arg Arg Phe Thr Val Gly Thr Thr Ser Val Ile Val Gly Ala Thr
20 25 30

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
35 40 45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
50 55 60

Lys Asn Asn Thr Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65 70 75 80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
85 90 95

Ala Lys Thr Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
100 105 110

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

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
130 135 140

Gln Val Asp Asn Lys Thr Thr Asn Asp Ala Asn Asn Ile Ala Thr Asn
145 150 155 160

Ser Glu Leu Lys Asn Pro Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
165 170 175

Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr

180 185 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
195 200 205

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Ser Asp Phe
210 215 220

Lys Leu Glu Lys Thr Ala Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225 230 235 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Val Thr Gly Asn Gly Asp Val Asp
260 265 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
275 280 285

Asn Gly Asp Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
290 295 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asp Lys Glu Asn Ile Asn
305 310 315 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
325 330 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asp
340 345 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
355 360 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
370 375 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385 390 395 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
405 410 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
420 425 430

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
435 440 445

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Gly Glu Phe Lys Asp

450 455 460

Lys Ile Ser Tyr Lys Tyr Asp Asn Val Ala Ser Ile Asn Phe Gly Asp
465 470 475 480

Ile Asn Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Ile Asp Pro Ala
500 505 510

Thr Gly Lys Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

<210> 19
<211> 1626
<212> DNA
<213> Staphylococcus aureus

<400> 19
ttgaaaaaaa gaattgatta tttgtcgaat aagcagaata agtattcgat tagacgtttt 60

acagtaggta ccacatcagt aatagtaggg gcaactatac tatttgggat aggcaatcat 120

caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt 180

gcagattccg aaaaaaacaa tacgatagaa acacctcaat taaatacaac ggctaatgat 240

acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacagc aaaaccaatg 300

tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360

ccgacggcaa ttaaagatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420

gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaatagcat agcgacaaac 480

agcgagctta aaaatcctca atcattagat ttaccacaat catcaccaca aacgatttcc 540

aatgcgcaag gaactagtaa accaagtgtt agaacgagag ctgtacgtag tcttgcagtt 600

gctgaacctg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatga taaagttacg 660

gcaaaagatt ttcaattaga aaagactaca tttgacccta accaaagtgg taatactttt 720

atggcggcaa actttacagt gactggacaa gtgaaatcag gggattattt tacagcgaag 780

ttaccagata gtgtaactgg taatggagac gtggattact ctaattcaaa taatacgatg 840

ccaattgcag atatagtaaa cgataaaaat gaagttgtag caaaagcgac atatgatatt 900

ttgactaaga catatacatt tgtctttaca gattatgtaa atgataagca aaatattaat 960

gggaaatttt cattaccatt atttacagac cgagcaaagg cacctaaatc aggaatatat 1020

gatgcgaata ttaatattgc ggatgaaatg tttaataata aaattactta taactatagt 1080

tcgccaattg caggaattga taagccaaat ggcgcgaaca tttcttctca aattattggt 1140

gtagatacag cttcaggtca aaatacatac aagcaaacgg tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggttacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctac agatacaaaa ctgagaattt ttgaagtgaa tgatacatct 1320

aaattatcag atagctacta tgcggaccca aatgactcta accttaaaga agtgactggt 1380

gagtttaata atagaatttt ttatgaacat ccaaacgtag caagtattaa ttttggtgat 1440

ataaataaaa cgtatgtcgt tttagttgaa ggtcactatg ataatactgg taaaaacttg 1500

aaaacacagg ttattcaaga aaatattgac ccagcgacag gtaaagacta cagtattttc 1560

ggatggaata atgagaatgt tgtacgttat ggtggtggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 20
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 20

Leu Lys Lys Arg Ile Asp Tyr Leu Ser Asn Lys Gln Asn Lys Tyr Ser
1 5 10 15

Ile Arg Arg Phe Thr Val Gly Thr Thr Ser Val Ile Val Gly Ala Thr
20 25 30

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
35 40 45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
50 55 60

Lys Asn Asn Thr Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65 70 75 80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
85 90 95

Ala Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
100 105 110

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

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
130 135 140

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

Ser Glu Leu Lys Asn Pro Gln Ser Leu Asp Leu Pro Gln Ser Ser Pro
165 170 175

```
Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
            180                 185                 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
        195                 200                 205

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Lys Asp Phe
    210                 215                 220

Gln Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225                 230                 235                 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Val Thr Gly Asn Gly Asp Val Asp
            260                 265                 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Val Asn Asp
        275                 280                 285

Lys Asn Glu Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
    290                 295                 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asp Lys Gln Asn Ile Asn
305                 310                 315                 320

Gly Lys Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
                325                 330                 335

Ser Gly Ile Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
            340                 345                 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
        355                 360                 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
    370                 375                 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385                 390                 395                 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
                405                 410                 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
            420                 425                 430

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
        435                 440                 445
```

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Gly Glu Phe Asn Asn
450 455 460

Arg Ile Phe Tyr Glu His Pro Asn Val Ala Ser Ile Asn Phe Gly Asp
465 470 475 480

Ile Asn Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Ile Asp Pro Ala
500 505 510

Thr Gly Lys Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

<210> 21
<211> 1626
<212> DNA
<213> Staphylococcus aureus

<400> 21
ttgaaaaaaa gaattgatta tttgtcgaat aagcagaata agtattcgat tagacgtttt 60

acagtaggta ccacatcagt aatagtaggg gcaactatac tatttgggat aggcaatcat 120

caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt 180

gcagattccg aaaaaaacaa tacgatagaa acacctcaat taaatacaac ggctaatgat 240

acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacagc aaaaccaatg 300

tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360

ccgacggcaa ttaaagatca agcaactgct gcaaaaatgc aagatcgaac tgttcctcaa 420

gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaatagcat aacaacaaac 480

agtgagctta aaaatcctca aacattagat ttaccacaat catcaccaca aacgatttcc 540

aatgcgcaag gaactagtaa accaagtgtt agaacgagag ctgtacgtag tcttgcagtt 600

gctgaacctg tagtaaatgc tgctgatgct aaaggcacaa atgtaaatga taaagttacg 660

gcaaaagatt ttcaattaga aaagactaca tttgacccta accaaagtgg taatactttt 720

atggcggcaa actttacagt gactggacaa gtgaaatcag gggattattt tacagcgaag 780

ttaccagaaa gtttaactgg taatggagac gtggattact ctaactcgaa taatacgatg 840

ccaattgcag atattaaaag tacgaatggc aatgttgtag ctaaagcaac atatgatatc 900

ttgactaaga cgtatacatt tgtctttaca gattatgtaa atgataaaga aaatattaac 960

ggacaatttt cattaccttt atttacagac cgagcaaagg cacctaaatc aggaacatat 1020

gatgcaaata ttaatattgc ggatgaaatg tttaacaata aaattactta taactatagt 1080

tcaccaattg caggaattga taagccaaat ggcgcgaaca tttcttctca aattattggt 1140

gtagatacag cttcaggtca aaacacatac aagcaaacgg tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggttacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctac agatacaaaa ctgagaattt ttgaagtgaa tgatacatct 1320

aaattatcag atagctacta tgcggaccca aatgactcta atcttaaaga agtaactgat 1380

caatttaagg ataaaatcac ttataaatac caaaatgtag caagtattaa ttttggtgat 1440

attactaaaa cgtatgttgt attagtggaa ggtcactatg ataatactgg taaaaacttg 1500

aaaacacagg ttattcaaga aaatattgac ccagcgacag gtaaagacta cagtattttc 1560

ggatggaata atgagaatgt tgtacgttat ggtggtggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 22
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 22

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Leu Lys Lys Arg Ile Asp Tyr Leu Ser Asn Lys Gln Asn Lys Tyr Ser
1               5                  10                  15

Ile Arg Arg Phe Thr Val Gly Thr Thr Ser Val Ile Val Gly Ala Thr
            20                  25                  30

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
        35                  40                  45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
    50                  55                  60

Lys Asn Asn Thr Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65                  70                  75                  80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
                85                  90                  95

Ala Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
            100                 105                 110

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

Thr Ala Ala Lys Met Gln Asp Arg Thr Val Pro Gln Glu Ala Asn Ser
    130                 135                 140

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

Ser Glu Leu Lys Asn Pro Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
                165                 170                 175
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Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
            180                 185                 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
        195                 200                 205

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Lys Asp Phe
    210                 215                 220

Gln Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225                 230                 235                 240

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

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

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
        275                 280                 285

Asn Gly Asn Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
    290                 295                 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asp Lys Glu Asn Ile Asn
305                 310                 315                 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
                325                 330                 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
            340                 345                 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
        355                 360                 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
    370                 375                 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385                 390                 395                 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
                405                 410                 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
            420                 425                 430

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
        435                 440                 445
```

```
Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asp Gln Phe Lys Asp
    450                 455                 460

Lys Ile Thr Tyr Lys Tyr Gln Asn Val Ala Ser Ile Asn Phe Gly Asp
465                 470                 475                 480

Ile Thr Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
                485                 490                 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Ile Asp Pro Ala
            500                 505                 510

Thr Gly Lys Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
        515                 520                 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
    530                 535                 540
```

<210> 23
<211> 1620
<212> DNA
<213> Staphylococcus aureus

<400> 23

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ttgaaaaaaa gaattgatta tttgtcgaat aagcagaata agtattcgat tagacgtttt     60
acagtaggta ccacatcagt aatagtaggg gcaactatac tatttgggat aggcaatcat    120
caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt    180
gcagattccg aaaaaaacaa tacgatagaa acacctcaat taaatactaa tgatacatct    240
gatattagtg caaacacaaa cagtgcgaat gtagatagca cagcaaaacc aatgtctaca    300
caaacgagca ataccactac aacagagcca gcttcaacaa atgaaacacc tcaaccgacg    360
gcaattaaag atcaagcaac tgctgcaaaa atgcaagatc gaactgttcc tcaagaagca    420
aattctcaag tagataataa aacaacgaat gatgctaata gcataacaac aaacagtgag    480
cttaaaaatc ctcaaacatt agatttacca caatcatcac cacaaacgat ttccaatgcg    540
caaggaacta gtaaaccaag tgttagaacg agagctgtac gtagtcttgc agttgctgaa    600
cctgtagtaa atgctgctga tgctaaaggc acaaatgtaa atgataaagt tacggcaaaa    660
gattttcaat tagaaaagac tacatttgac cctaaccaaa gtggtaatac ttttatggcg    720
gcaaacttta cagtgactgg acaagtgaaa tcaggggatt attttacagc gaagttacca    780
gaaagtttaa ctggtaatgg agacgtggat tactctaact cgaataatac gatgccaatt    840
gcagatatta aaagtacgaa tggcaatgtt gtagctaaag caacatatga tatcttgact    900
aagacgtata catttgtctt tacagattat gtaaatgata aagaaaatat taacggacaa    960
ttttcattac ctttatttac agaccgagca aaggcaccta aatcaggaac atatgatgca   1020
aatattaata ttgcggatga aatgtttaac aataaaatta cttataacta tagttcacca   1080
attgcaggaa ttgataagcc aaatggcgcg aacatttctt ctcaaattat tggtgtagat   1140
```

acagcttcag gtcaaaacac atacaagcaa acggtatttg ttaaccctaa gcaacgagtt 1200

ttaggtaata cgtgggtgta tattaaaggt taccaagata aaatcgaaga aagtagcggt 1260

aaagtaagtg ctacagatac aaaactgaga atttttgaag tgaatgatac atctaaatta 1320

tcagatagct actatgcgga cccaaatgac tctaatctta aagaagtaac tgatcaattt 1380

aaggataaaa tcacttataa ataccaaaat gtagcaagta ttaattttgg tgatattact 1440

aaaacgtatg ttgtattagt ggaaggtcac tatgataata ctggtaaaaa cttgaaaaca 1500

caggttattc aagaaaatat tgacccagcg acaggtaaag actacagtat tttcggatgg 1560

aataatgaga atgttgtacg ttatggtggt ggaagtgctg atggtgattc agcagtaaat 1620

<210> 24
<211> 540
<212> PRT
<213> Staphylococcus aureus

<400> 24

Leu Lys Lys Arg Ile Asp Tyr Leu Ser Asn Lys Gln Asn Lys Tyr Ser
1 5 10 15

Ile Arg Arg Phe Thr Val Gly Thr Thr Ser Val Ile Val Gly Ala Thr
20 25 30

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
35 40 45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
50 55 60

Lys Asn Asn Thr Ile Glu Thr Pro Gln Leu Asn Thr Asn Asp Thr Ser
65 70 75 80

Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr Ala Lys
85 90 95

Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro Ala Ser
100 105 110

Thr Asn Glu Thr Pro Gln Pro Thr Ala Ile Lys Asp Gln Ala Thr Ala
115 120 125

Ala Lys Met Gln Asp Arg Thr Val Pro Gln Glu Ala Asn Ser Gln Val
130 135 140

Asp Asn Lys Thr Thr Asn Asp Ala Asn Ser Ile Thr Thr Asn Ser Glu
145 150 155 160

Leu Lys Asn Pro Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro Gln Thr
165 170 175

```
Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr Arg Ala
            180                 185                 190

Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala Asp Ala
        195                 200                 205

Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Lys Asp Phe Gln Leu
    210                 215                 220

Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe Met Ala
225                 230                 235                 240

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

Ala Lys Leu Pro Glu Ser Leu Thr Gly Asn Gly Asp Val Asp Tyr Ser
            260                 265                 270

Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr Asn Gly
        275                 280                 285

Asn Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr Tyr Thr
    290                 295                 300

Phe Val Phe Thr Asp Tyr Val Asn Asp Lys Glu Asn Ile Asn Gly Gln
305                 310                 315                 320

Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys Ser Gly
                325                 330                 335

Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn Asn Lys
            340                 345                 350

Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys Pro Asn
        355                 360                 365

Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala Ser Gly
    370                 375                 380

Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln Arg Val
385                 390                 395                 400

Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys Ile Glu
                405                 410                 415

Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg Ile Phe
            420                 425                 430

Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala Asp Pro
        435                 440                 445
```

```
Asn Asp Ser Asn Leu Lys Glu Val Thr Asp Gln Phe Lys Asp Lys Ile
    450                 455                 460

Thr Tyr Lys Tyr Gln Asn Val Ala Ser Ile Asn Phe Gly Asp Ile Thr
465                 470                 475                 480

Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr Gly Lys
                485                 490                 495

Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Ile Asp Pro Ala Thr Gly
            500                 505                 510

Lys Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val Arg Tyr
        515                 520                 525

Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
    530                 535                 540
```

<210> 25
<211> 1626
<212> DNA
<213> Staphylococcus aureus

<400> 25

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ttgaaaaaaa gaattgatta tttgtcgaat aagcagaata agtattcgat tagacgtttt     60

acagtaggta ccacatcagt aatagtaggg gcaactatac tatttgggat aggcaatcat    120

caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt    180

gcagattccg aaaaaaacaa tatgatagaa acacctcaat taaatacaac ggctaatgat    240

acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacaac aaaaccaatg    300

tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa    360

ccgacggcaa ttaaaaatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa    420

gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaatagcat agcaacaaac    480

agtgagctta aaaattctca aacattagat ttaccacaat catcaccaca aacgatttcc    540

aatgcgcaag gaactagtaa accaagtgtt agaacgagag ctgtacgtag tttagctgtt    600

gctgaaccgg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatga taaagttacg    660

gcaagtaatt tcaagttaga aaagactaca tttgacccta atcaaagtgg taacacattt    720

atggcggcaa attttacagt gacagataaa gtgaaatcag gggattattt tacagcgaag    780

ttaccagata gtttaactgg taatggagac gtggattatt ctaattcaaa taatacgatg    840

ccaattgcag acattaaaag tacgaatggc gatgttgtag ctaaagcaac atatgatatc    900

ttgactaaga cgtatacatt tgtctttaca gattatgtaa ataataaaga aaatattaac    960

ggacaatttt cattaccttt atttacagac cgagcaaagg cacctaaatc aggaacatat   1020

gatgcgaata ttaatattgc ggatgaaatg tttaataata aaattactta taactatagt   1080

tcgccaattg caggaattga taaaccaaat ggcgcgaaca tttcttctca aattattggt   1140
```

gtagatacag cttcaggtca aaacacatac aagcaaacag tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggctacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctac agatacaaaa ctgagaattt ttgaagtgaa tgatacatct 1320

aaattatcag atagctacta tgcagatcca aatgactcta accttaaaga agtaacagac 1380

caatttaaaa atagaatcta ttatgagcat ccaaatgtag ctagtattaa atttggtgat 1440

attactaaaa catatgtagt attagtagaa gggcattacg acaatacagg taagaactta 1500

aaaactcagg ttattcaaga aaatgttgat cctgtaacaa atagagacta cagtattttc 1560

ggttggaata atgagaatgt tgtacgttat ggtggtggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 26
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 26

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Leu Lys Lys Arg Ile Asp Tyr Leu Ser Asn Lys Gln Asn Lys Tyr Ser
1               5                  10                  15

Ile Arg Arg Phe Thr Val Gly Thr Thr Ser Val Ile Val Gly Ala Thr
            20                  25                  30

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
        35                  40                  45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
    50                  55                  60

Lys Asn Asn Met Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65                  70                  75                  80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
                85                  90                  95

Thr Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
            100                 105                 110

Ala Ser Thr Asn Glu Thr Pro Gln Pro Thr Ala Ile Lys Asn Gln Ala
        115                 120                 125

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
    130                 135                 140

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

Ser Glu Leu Lys Asn Ser Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
                165                 170                 175
```

```
Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
            180                 185                 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
        195                 200                 205

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Ser Asn Phe
    210                 215                 220

Lys Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225                 230                 235                 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Leu Thr Gly Asn Gly Asp Val Asp
            260                 265                 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
        275                 280                 285

Asn Gly Asp Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
    290                 295                 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asn Lys Glu Asn Ile Asn
305                 310                 315                 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
                325                 330                 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
            340                 345                 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
        355                 360                 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
    370                 375                 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385                 390                 395                 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
                405                 410                 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
            420                 425                 430

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
        435                 440                 445
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Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asp Gln Phe Lys Asn
450 455 460

Arg Ile Tyr Tyr Glu His Pro Asn Val Ala Ser Ile Lys Phe Gly Asp
465 470 475 480

Ile Thr Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Val Asp Pro Val
500 505 510

Thr Asn Arg Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
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<212> DNA
<213> Staphylococcus aureus

<400> 27
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gcagattccg aaaaaaacaa tatgatagaa acacctcaat taaatacaac ggctaatgat 240

acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacaac aaaaccaatg 300

tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360

ccgacggcaa ttaaaaatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420

gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaatagcat agcaacaaac 480

agtgagctta aaaattctca aacattagat ttaccacaat catcaccaca aacgatttcc 540

aatgcgcaag gaactagtaa accaagtgtt agaacgagag ctgtacgtag tttagctgtt 600

gctgaaccgg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatga taaagttacg 660

gcaagtaatt tcaagttaga aaagactaca tttgacccta atcaaagtgg taacacattt 720

atggcggcaa attttacagt gacagataaa gtgaaatcag gggattattt tacagcgaag 780

ttaccagata gtttaactgg taatggagac gtggattatt ctaattcaaa taatacgatg 840

ccaattgcag acattaaaag tacgaatggc gatgttgtag ctaaagcaac atatgatatc 900

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gatgcgaata ttaatattgc ggatgaaatg tttaataata aaattactta taactatagt 1080

tcgccaattg caggaattga taaaccaaat ggcgcgaaca tttcttctca aattattggt 1140

gtagatacag cttcaggtca aaacacatac aagcaaacag tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggctacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctac agatacaaaa ctgagaattt ttgaagtgaa tgatatatct 1320

aaattatcag atagctacta tgcagatcca aatgactcta accttaaaga agtaacagac 1380

caatttaaaa atagaatcta ttatgagcat ccaaatgtag ctagtattaa atttggtgat 1440

attactaaaa catatgtagt attagtagaa gggcattacg acaatacagg taagaactta 1500

aaaactcagg ttattcaaga aaatgttgat cctgtaacaa atagagacta cagtattttc 1560

ggttggaata atgagaatgt tgtacgttat ggtggtggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 28
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 28

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Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
35 40 45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
50 55 60

Lys Asn Asn Met Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65 70 75 80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
85 90 95

Thr Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
100 105 110

Ala Ser Thr Asn Glu Thr Pro Gln Pro Thr Ala Ile Lys Asn Gln Ala
115 120 125

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
130 135 140

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

Ser Glu Leu Lys Asn Ser Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
165 170 175

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Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
            180                 185                 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
        195                 200                 205

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Ser Asn Phe
    210                 215                 220

Lys Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225                 230                 235                 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Leu Thr Gly Asn Gly Asp Val Asp
            260                 265                 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
        275                 280                 285

Asn Gly Asp Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
    290                 295                 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asn Lys Glu Asn Ile Asn
305                 310                 315                 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
                325                 330                 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
            340                 345                 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
        355                 360                 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
    370                 375                 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385                 390                 395                 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
                405                 410                 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
            420                 425                 430

Ile Phe Glu Val Asn Asp Ile Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
        435                 440                 445
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Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asp Gln Phe Lys Asn
450 455 460

Arg Ile Tyr Tyr Glu His Pro Asn Val Ala Ser Ile Lys Phe Gly Asp
465 470 475 480

Ile Thr Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Val Asp Pro Val
500 505 510

Thr Asn Arg Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

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<211> 1626
<212> DNA
<213> Staphylococcus aureus

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gcagattccg aaaaaaacaa tatgatagaa acacctcaat taaatacaac ggctaatgat 240
acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacagc aaaaccaatg 300
tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360
ccgacggcaa ttaaagatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420
gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaatagcat agcgacaaac 480
agtgagctta aaaatcctca aacattagat ttaccacaat catcaccaca aacgatttcc 540
aatgcgcaaa gaactagtaa accaagtgtt agaacgagag ctgtacgtag tttagctgtt 600
gctgaaccgg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatgg tcaagttacg 660
gcaagtgatt tcaagttaga aaagactaca tttgacccta accaaagtgg taacacattt 720
atggcggtaa attttaaagt ggcagggaaa gtgaaatcag gggattatta tacagcgaag 780
ttaccagata gtttaactgg taatggagac gtggattact ctaattcaaa taatacgatg 840
ccaattgcag atattaaaag tacgaatggc gatgttgtag ctaaagcaac atatgatatc 900
ttgactaaga cgtatacatt tgtctttaca gattatgtaa atgataaaga aaatattaac 960
ggacaatttt cattaccttt atttacagac cgagcaaagg cacctaaatc aggaacatac 1020
gatgcaaata ttaatattgc ggatgaaatg tttaataata aaattactta taactatagt 1080

tcgccaattg caggaattga taagccaaat ggcgcgaaca tttcttctca aattattggt 1140

gtagatacag cttcaggtca aaacacatac aagcaaacgg tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggttacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctac agatacaaaa ctgagaattt ttgaagtgaa tgatacatct 1320

aaattatcag atagctacta tgcagatcca aatgactcta accttaaaga agtaacgaat 1380

gagtttaagg ataaaatcac ttataaatac caaaatgtag caagtattaa ttttggcgat 1440

attactaaaa cgtatgttgt attagtggaa ggtcactatg ataatactgg taaaaacttg 1500

aaaacacagg ttattcaaga aaatattgac ccagcgacag gtaaagacta cagtattttc 1560

ggttggaata atgagaatgt tgtacgttat ggtggtggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 30
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 30

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

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
35 40 45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
50 55 60

Lys Asn Asn Met Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65 70 75 80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
85 90 95

Ala Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
100 105 110

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

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
130 135 140

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

Ser Glu Leu Lys Asn Pro Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro

165 170 175

Gln Thr Ile Ser Asn Ala Gln Arg Thr Ser Lys Pro Ser Val Arg Thr
180 185 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
195 200 205

Asp Ala Lys Gly Thr Asn Val Asn Gly Gln Val Thr Ala Ser Asp Phe
210 215 220

Lys Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225 230 235 240

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

Tyr Thr Ala Lys Leu Pro Asp Ser Leu Thr Gly Asn Gly Asp Val Asp
260 265 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
275 280 285

Asn Gly Asp Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
290 295 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asp Lys Glu Asn Ile Asn
305 310 315 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
325 330 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
340 345 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
355 360 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
370 375 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385 390 395 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
405 410 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
420 425 430

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala

435 440 445

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asn Glu Phe Lys Asp
450 455 460

Lys Ile Thr Tyr Lys Tyr Gln Asn Val Ala Ser Ile Asn Phe Gly Asp
465 470 475 480

Ile Thr Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Ile Asp Pro Ala
500 505 510

Thr Gly Lys Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

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<212> DNA
<213> Staphylococcus aureus

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caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt 180

gcagattccg aaaaaaacaa tatgatagaa acacctcaat taaatacaac ggctaatgat 240

acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacagc aaaaccaatg 300

tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360

ctgacggcaa ttaaagatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420

gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaatagcat agcgacaaac 480

agtgagctta aaaatcctca aacattagat ttaccacaat catcaccaca aacaatttcc 540

aatgcgcaag gaactagtaa accaagtgtt agaacgagag ctgtacgtag tcttgcagtt 600

gctgaacctg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatga taaagttacg 660

gcaaaagatt ttcaattaga aaagactaca tttgacccta accaaagtgg taatactttt 720

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ttaccagata gtgtaactgg taatggagac gtggattact ctaattcgaa taatacgatg 840

ccaattgcag atatagtaaa cgataaaaat gaagttgtag caaaagcgac atatgatatt 900

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tcgccaattg caggaattga taagccaaat ggcgcgaaca tttcttctca aattattggt 1140

gtagatacag cttcaggtca aaatacatac aagcaaacgg tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggttacc aagataaaat cgaagaaagt 1260

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caatttaagg ataaaatcac ttataaatac caaaatgtag caagtattaa ttttggtgat 1440

ataaataaaa cgtatgtcgt tttagtcgaa ggtcattatg ataaaacagg taaaaacttg 1500

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gtaaat 1626

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<211> 542
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<213> Staphylococcus aureus

<400> 32

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            20                  25                  30

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
        35                  40                  45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
    50                  55                  60

Lys Asn Asn Met Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65                  70                  75                  80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
                85                  90                  95

Ala Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
            100                 105                 110

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

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
    130                 135                 140

Gln Val Asp Asn Lys Thr Thr Asn Asp Ala Asn Ser Ile Ala Thr Asn
145                 150                 155                 160
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Ser Glu Leu Lys Asn Pro Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
                165                 170                 175

Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
            180                 185                 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
        195                 200                 205

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Lys Asp Phe
    210                 215                 220

Gln Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225                 230                 235                 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Val Thr Gly Asn Gly Asp Val Asp
            260                 265                 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Val Asn Asp
        275                 280                 285

Lys Asn Glu Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
    290                 295                 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asp Lys Gln Asn Ile Asn
305                 310                 315                 320

Gly Lys Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
                325                 330                 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
            340                 345                 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
        355                 360                 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
    370                 375                 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385                 390                 395                 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
                405                 410                 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
            420                 425                 430
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Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
435 440 445

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asp Gln Phe Lys Asp
450 455 460

Lys Ile Thr Tyr Lys Tyr Gln Asn Val Ala Ser Ile Asn Phe Gly Asp
465 470 475 480

Ile Asn Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Lys Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Val Asp Pro Ala
500 505 510

Thr Gly Lys Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

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<211> 1626
<212> DNA
<213> Staphylococcus aureus

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caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt 180

gcagattccg aaaaaaacaa tatgatagaa acacctcaat taaatacaac ggctaatgat 240

acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacagc aaaaccaatg 300

tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360

ctgacggcaa ttaaagatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420

gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaatagcat agcgacaaac 480

agtgagctta aaaatcctca aacattagat ttaccacaat catcaccaca aacaatttcc 540

aatgcgcaag gaactagtaa accaagtgtt agaacgagag ctgtacgtag tcttgcagtt 600

gctgaacctg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatga taaagttacg 660

gcaaaagatt ttcaattaga aaagactaca tttgacccta accaaagtgg taatactttt 720

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gaatttaagg ataaaatcac ttataaatac caaaatgtag caagtattaa ttttggcgat 1440

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gtaaat 1626

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<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 34

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Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
35 40 45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
50 55 60

Lys Asn Asn Met Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65 70 75 80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
85 90 95

Ala Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
100 105 110

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

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
130 135 140

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

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Ser Glu Leu Lys Asn Pro Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
                165                 170                 175

Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
            180                 185                 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
        195                 200                 205

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Lys Asp Phe
    210                 215                 220

Gln Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225                 230                 235                 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Val Thr Gly Asn Gly Asp Val Asp
            260                 265                 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
        275                 280                 285

Asn Gly Asp Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
    290                 295                 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Glu Lys Glu Asn Ile Asn
305                 310                 315                 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
                325                 330                 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asp
            340                 345                 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
        355                 360                 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
    370                 375                 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385                 390                 395                 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
                405                 410                 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
            420                 425                 430
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Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
435 440 445

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asn Glu Phe Lys Asp
450 455 460

Lys Ile Thr Tyr Lys Tyr Gln Asn Val Ala Ser Ile Asn Phe Gly Asp
465 470 475 480

Ile Thr Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Ile Asp Pro Ala
500 505 510

Thr Gly Lys Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

<210> 35
<211> 1626
<212> DNA
<213> Staphylococcus aureus

<400> 35
ttgaaaaaaa gaattgatta tttgtcgaat aagcagaata agtattcgat tagacgtttt 60

acagtaggta ccacatcagt aatagtaggg gcaactatac tatttgggat aggcaatcat 120

caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt 180

gcagattccg aaaaaaataa tatgatagaa acacctcaat taaatacaac ggctaatgat 240

acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacagc aaaaccaatg 300

tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360

ccgacggcaa ttaaagatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420

gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaatagcat agcaacaaac 480

agtgaactta aaaatcctca aacattagat ttaccacaat catcaccaca aacgatttcc 540

aatgcgcaag gaactagtaa accaagtgtt agaacgagag ctgtacgtag tcttgcagtt 600

gctgaacctg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatga taaagttacg 660

gcaagtaatc tacagttgca aaagactaca tttgacccta accaaagtgg aaatacattt 720

atggcggcaa attttacagt gacagataaa gtgaaatcag gggattattt tacagcgaag 780

ttaccagata gtttaactgg taatggagac gtggattact ctaattcaaa taatacgatg 840

ccaattgcag atattaaaag tacgaatggc gatgttgtag ctaaagcaac atatgatatc 900

ttgactaaga cgtatacatt tgtctttaca gattatgtaa atgataaaga aaatattaac 960

gggcaatttt cattaccttt atttacagac cgagcaaagg cacctaaatc aggaacatat 1020

gatgcaaata ttaatattgc ggatgaaatg tttaataata aaattactta taactatagt 1080

tcgccaattg caggaattga taagccaaat ggcgcgaaca tttcttctca aattattggt 1140

gtagatacag cttcaggtca aaacacatac aagcaaacgg tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggttacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctac agatacaaaa ctgagaattt ttgaagtgaa tgatacatct 1320

aaattatcag atagctacta tgcagaccca aatgactcta accttaaaga agtaactgat 1380

caatttaagg ataaaatcac ttataaatac caaaacgtag caagtattaa ttttggtgat 1440

ataaataaaa cgtatgtcgt tttagttgaa ggtcactatg ataatactgg aaaaaacttg 1500

aaaacacagg ttattcaaga aaatattgac ccagcgacag gtaaagacta cagtattttc 1560

ggatggaata atgagaatgt tgtacgttat ggtggtggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 36
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 36

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Leu Lys Lys Arg Ile Asp Tyr Leu Ser Asn Lys Gln Asn Lys Tyr Ser
1               5                   10                  15

Ile Arg Arg Phe Thr Val Gly Thr Thr Ser Val Ile Val Gly Ala Thr
            20                  25                  30

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
        35                  40                  45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
    50                  55                  60

Lys Asn Asn Met Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65                  70                  75                  80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
                85                  90                  95

Ala Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
            100                 105                 110

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

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
    130                 135                 140

Gln Val Asp Asn Lys Thr Thr Asn Asp Ala Asn Ser Ile Ala Thr Asn
145                 150                 155                 160
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Ser Glu Leu Lys Asn Pro Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
                165                 170                 175

Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
            180                 185                 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
        195                 200                 205

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Ser Asn Leu
    210                 215                 220

Gln Leu Gln Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225                 230                 235                 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Leu Thr Gly Asn Gly Asp Val Asp
            260                 265                 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
        275                 280                 285

Asn Gly Asp Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
    290                 295                 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asp Lys Glu Asn Ile Asn
305                 310                 315                 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
                325                 330                 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
            340                 345                 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
        355                 360                 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
    370                 375                 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385                 390                 395                 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
                405                 410                 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
            420                 425                 430
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Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
435 440 445

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asp Gln Phe Lys Asp
450 455 460

Lys Ile Thr Tyr Lys Tyr Gln Asn Val Ala Ser Ile Asn Phe Gly Asp
465 470 475 480

Ile Asn Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Ile Asp Pro Ala
500 505 510

Thr Gly Lys Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

<210> 37
<211> 1626
<212> DNA
<213> Staphylococcus aureus

<400> 37
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caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt 180
gcagattccg aaaaaaacaa tatgatagaa acacctcaat taaatacaac ggctaatgat 240
acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacaac aaaaccaatg 300
tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360
ccgacggcaa ttaaagatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420
gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaatagcat agcgacaaac 480
agtgagctta aaaatcctca aacattagat ttaccacaat catcaccaca aacaatttcc 540
aatgcgcaag gaactagtaa accaagtgtt agaacgagag ctgtacgtag tcttgcagtt 600
gctgaacctg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatga taaagttacg 660
gcaaaagatt ttcaattaga aaagactaca tttgacccta accaaagtgg taatactttt 720
atggcggcaa actttacagt gactggacaa gtgaaatcag gggattattt tacagcgaag 780
ttaccagata gtgtaactgg taatggagac gtggattact ctaattcgaa taatacgatg 840
ccaattgcag atattaaaag cacgaatggt gatgttgtag ctaaagcaac atatgatatc 900
ttgactaaga catatacatt tgtctttaca gattatgtaa atgaaaaaga aaatattaac 960

ggacaatttt cattaccttt atttacagac agagcaaagg cacctaaatc aggaacatac 1020

gatgcaaata ttaatattgc ggatgaaatg tttgataata aaattactta taactatagt 1080

tcgcctattg caggaattga taaaccaaat ggcgcaaata tttcttctca aattattggt 1140

gtagatacag cttcaggtca aaacacatac aagcaaacag tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggttacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctac agatacaaaa ctgagaattt ttgaagtgaa tgatacatct 1320

aaattatcag atagctacta tgcggaccca aatgactcta accttaaaga agtaacgaat 1380

gaatttaagg ataaaatcac ttataaatac caaaatgtag caagtattaa ttttggcgat 1440

attactaaaa cgtatgttgt attagtggaa ggtcactatg ataatactgg taaaaacttg 1500

aaaacacagg ttattcaaga aaatattgac ccagcgacag gtaaagacta cagtattttc 1560

ggttggaata atgagaatgt tgtacgttat ggtggtggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 38
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 38

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

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
35 40 45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
50 55 60

Lys Asn Asn Met Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65 70 75 80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
85 90 95

Thr Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
100 105 110

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

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
130 135 140

Gln Val Asp Asn Lys Thr Thr Asn Asp Ala Asn Ser Ile Ala Thr Asn

145 150 155 160

Ser Glu Leu Lys Asn Pro Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
165 170 175

Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
180 185 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
195 200 205

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Lys Asp Phe
210 215 220

Gln Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225 230 235 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Val Thr Gly Asn Gly Asp Val Asp
260 265 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
275 280 285

Asn Gly Asp Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
290 295 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Glu Lys Glu Asn Ile Asn
305 310 315 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
325 330 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asp
340 345 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
355 360 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
370 375 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385 390 395 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
405 410 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg

420 425 430

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
435 440 445

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asn Glu Phe Lys Asp
450 455 460

Lys Ile Thr Tyr Lys Tyr Gln Asn Val Ala Ser Ile Asn Phe Gly Asp
465 470 475 480

Ile Thr Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Ile Asp Pro Ala
500 505 510

Thr Gly Lys Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

<210> 39
<211> 1626
<212> DNA
<213> Staphylococcus aureus

<400> 39
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caagcacaag cttcagaaca atcgaacgat acaacacaat cttcgaaaaa taatgcaagt 180

gcagattccg aaaaaaacaa tatgatagaa acacctcaat taaatacaac ggctaatgat 240

acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacagc aaaaccaatg 300

tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360

ccgacggcaa ttaaagatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420

gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaatagcat agcaacaaac 480

agtgagctta aaaatcctca aacattagat ttaccacaat catcaccaca aacgatttcc 540

aatgcgcaag gaactagtaa accgagtgtt agaacgagag ctgtacgtag tcttgcagtt 600

gctgaacctg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatgg tcaagttacg 660

gcaagtgatt tcaagttaga aaagactaca tttgacccta accaaagtgg taacacattt 720

atggcggcaa aatttacagt gactggacaa gtgaaagcag gggattattt tacagcgaag 780

ttaccagata gtgtaaatgg taatggagat gtggattact ctaattcaaa taatacgatg 840

ccaattgcag atattaaaag tacgaatggc gatgttgtag ctaaagcaac atatgatatc 900

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gatgcgaata ttaatattgc ggatgaaatg tttaataata aaattactta taactatagt 1080

tcgccaattg caggaattga taaaccaaat ggcgcgaaca tttcttctca aattattggt 1140

gtagatacag cttcaggtca aaacacatac aagcaaacag tatatgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggttacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctac agatacaaaa ctgagaattt ttgaagtgaa tgatacatct 1320

aaattatcag atagctacta tgcagaccca aatgattcga atcttaaaga agtaacgaat 1380

gagtttaagg ataaaatcac ttataaatac caaaatgtag caagtattaa ttttggcgat 1440

attactaaaa cgtatgttgt attagtggaa ggtcactatg ataatactgg taaaaacttg 1500

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ggttggaata atgagaatgt tgtacgttat ggtggtggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 40
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 40

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1               5                  10                  15

Ile Arg Arg Phe Thr Val Gly Thr Thr Ser Val Ile Val Gly Ala Thr
            20                  25                  30

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
        35                  40                  45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
    50                  55                  60

Lys Asn Asn Met Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65                  70                  75                  80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
                85                  90                  95

Ala Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
            100                 105                 110

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

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
    130                 135                 140
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Gln Val Asp Asn Lys Thr Thr Asn Asp Ala Asn Ser Ile Ala Thr Asn
145 150 155 160

Ser Glu Leu Lys Asn Pro Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
165 170 175

Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
180 185 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
195 200 205

Asp Ala Lys Gly Thr Asn Val Asn Gly Gln Val Thr Ala Ser Asp Phe
210 215 220

Lys Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225 230 235 240

Met Ala Ala Lys Phe Thr Val Thr Gly Gln Val Lys Ala Gly Asp Tyr
245 250 255

Phe Thr Ala Lys Leu Pro Asp Ser Val Asn Gly Asn Gly Asp Val Asp
260 265 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
275 280 285

Asn Gly Asp Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
290 295 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asn Lys Glu Asn Ile Asn
305 310 315 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
325 330 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
340 345 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
355 360 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
370 375 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Tyr Val Asn Pro Lys Gln
385 390 395 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
405 410 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
420 425 430

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
435 440 445

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asn Glu Phe Lys Asp
450 455 460

Lys Ile Thr Tyr Lys Tyr Gln Asn Val Ala Ser Ile Asn Phe Gly Asp
465 470 475 480

Ile Thr Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Ile Asp Pro Ala
500 505 510

Thr Gly Lys Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

<210> 41
<211> 1626
<212> DNA
<213> Staphylococcus aureus

<400> 41
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caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt 180

gcagattccg aaaaaaacaa tatgatagaa acacctcaat taaatacaac ggctaatgat 240

acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacaac aaaaccaatg 300

tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360

ccgacggcaa ttaaaaatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420

gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaatagcat agcaacaaac 480

agtgagctta aaaattctca aacattagat ttaccacaat catcaccaca aacgatttcc 540

aatgcgcaag gaactagtaa accaagtgtt agaacgagag ctgtacgtag tttagctgtt 600

gctgaaccgg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatga taaagttacg 660

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ccaattgcag acattaaaag tacgaatggc gatgttgtag ctaaagcaac atatgatatc 900

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gtagatacag cttcaggtca aaacacatac aagcaaacag tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggctacc aagataaaat cgaagaaagt 1260

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aaattatcag atagctacta tgcagatcca aatgactcta accttaaaga agtaacagac 1380

caatttaaaa atagaatcta ttatgagcat ccaaatgtag ctagtattaa atttggtgat 1440

attactaaaa catatgtagt attagtagaa gggcattacg acaatacagg taagaactta 1500

aaaactcagg ttattcaaga aaatgttgat cctgtaacaa atagagacta cagtattttc 1560

ggttggaata atgagaatgt tgtacgttat ggtggtggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 42
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 42

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Leu Lys Lys Arg Ile Asp Tyr Leu Ser Asn Arg Gln Asn Lys Tyr Ser
1               5                   10                  15

Ile Arg Arg Phe Thr Val Gly Thr Thr Ser Val Ile Val Gly Ala Thr
            20                  25                  30

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
        35                  40                  45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
    50                  55                  60

Lys Asn Asn Met Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65                  70                  75                  80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
                85                  90                  95

Thr Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
            100                 105                 110

Ala Ser Thr Asn Glu Thr Pro Gln Pro Thr Ala Ile Lys Asn Gln Ala
        115                 120                 125

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
    130                 135                 140
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Gln Val Asp Asn Lys Thr Thr Asn Asp Ala Asn Ser Ile Ala Thr Asn
145                 150                 155                 160

Ser Glu Leu Lys Asn Ser Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
                165                 170                 175

Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
            180                 185                 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
        195                 200                 205

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Ser Asn Phe
    210                 215                 220

Lys Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225                 230                 235                 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Leu Thr Gly Asn Gly Asp Val Asp
            260                 265                 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
        275                 280                 285

Asn Gly Asp Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
    290                 295                 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asn Lys Glu Asn Ile Asn
305                 310                 315                 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
                325                 330                 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
            340                 345                 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
        355                 360                 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
    370                 375                 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385                 390                 395                 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
                405                 410                 415
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Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
420 425 430

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
435 440 445

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asp Gln Phe Lys Asn
450 455 460

Arg Ile Tyr Tyr Glu His Pro Asn Val Ala Ser Ile Lys Phe Gly Asp
465 470 475 480

Ile Thr Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Val Asp Pro Val
500 505 510

Thr Asn Arg Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

<210> 43
<211> 1626
<212> DNA
<213> Staphylococcus aureus

<400> 43
ttgaaaaaaa gaattgatta tttgtcgaat aagcagaata agtattcgat tagacgtttt 60

acagtaggta ccacatcagt aatagtaggg gcaactatac tatttgggat aggcaatcat 120

caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt 180

gcagattccg aaaaaaacaa tatgatagaa acacctcaat taaatacaac ggctaatgat 240

acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacaac aaaaccaatg 300

tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360

ccgacggcaa ttaaaaatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420

gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaatagcat agcaacaacc 480

agtgagctta aaaattctca aacattagat ttaccacaat catcaccaca aacgatttcc 540

aatgcgcaag gaactagtaa accaagtgtt agaacgagag ctgtacgtag tttagctgtt 600

gctgaaccgg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatga taaagttacg 660

gcaagtaatt tcaagttaga aaagactaca tttgacccta atcaaagtgg taacacattt 720

atggcggcaa attttacagt gacagataaa gtgaaatcag gggattattt tacagcgaag 780

ttaccagata gtttaactgg taatggagac gtggattatt ctaattcaaa taatacgatg 840

ccaattgcag acattaaaag tacgaatggc gatgttgtag ctaaagcaac atatgatatc 900

ttgactaaga cgtatacatt tgtctttaca gattatgtaa ataataaaga aaatattaac 960

ggacaatttt cattaccttt atttacagac cgagcaaagg cacctaaatc aggaacatat 1020

gatgcgaata ttaatattgc ggatgaaatg tttaataata aaattactta taactatagt 1080

tcgccaattg caggaattga taaaccaaat ggcgcgaaca tttcttctca aattattggt 1140

gtagatacag cttcaggtca aaacacatac aagcaaacag tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggctacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctac agatacaaaa ctgagaattt ttgaagtgaa tgatacatct 1320

aaattatcag atagctacta tgcagatcca aatgactcta accttaaaga agtaacagac 1380

caatttaaaa atagaatcta ttatgagcat ccaaatgtag ctagtattaa atttggtgat 1440

attactaaaa catatgtagt attagtagaa gggcattacg acaatacagg taagaactta 1500

aaaactcagg ttattcaaga aaatgttgat cctgtaacaa atagagacta cagtattttc 1560

ggttggaata atgagaatgt tgtacgttat ggtggtggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 44
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 44

Leu Lys Lys Arg Ile Asp Tyr Leu Ser Asn Lys Gln Asn Lys Tyr Ser
1 5 10 15

Ile Arg Arg Phe Thr Val Gly Thr Thr Ser Val Ile Val Gly Ala Thr
20 25 30

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
35 40 45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
50 55 60

Lys Asn Asn Met Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65 70 75 80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
85 90 95

Thr Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
100 105 110

Ala Ser Thr Asn Glu Thr Pro Gln Pro Thr Ala Ile Lys Asn Gln Ala
115 120 125

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
130 135 140

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

Ser Glu Leu Lys Asn Ser Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
                165                 170                 175

Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
            180                 185                 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
        195                 200                 205

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Ser Asn Phe
    210                 215                 220

Lys Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225                 230                 235                 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Leu Thr Gly Asn Gly Asp Val Asp
            260                 265                 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
        275                 280                 285

Asn Gly Asp Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
    290                 295                 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asn Lys Glu Asn Ile Asn
305                 310                 315                 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
                325                 330                 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
            340                 345                 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
        355                 360                 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
    370                 375                 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385                 390                 395                 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
                405                 410                 415
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Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
420 425 430

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
435 440 445

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asp Gln Phe Lys Asn
450 455 460

Arg Ile Tyr Tyr Glu His Pro Asn Val Ala Ser Ile Lys Phe Gly Asp
465 470 475 480

Ile Thr Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Val Asp Pro Val
500 505 510

Thr Asn Arg Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

<210> 45
<211> 1626
<212> DNA
<213> Staphylococcus aureus

<400> 45
ttgaaaaaaa gaattgatta tttgtcgaat aagcagaata agtattcgat tagacgtttt 60

acagtaggta ccacatcagt aatagtaggg gcaactatac tatttgggat aggcaatcat 120

caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt 180

gcagattccg aaaaaaacaa tatgatagaa acacctcaat taaatacaac ggctaatgat 240

acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacagc aaaaccaatg 300

tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360

ccgacggcaa ttaaagatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420

gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaatagcat agcgacaaac 480

tgtgagctta aaaatcctca aacattagat ttaccacaat catcaccaca aacaatttcc 540

aatgcgcaag gaactagtaa accaagtgtt agaacgagag ctgtacgtag tcttgcagtt 600

gctgaacctg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatga taaagttacg 660

gcaaaagatt ttcaattaga aaagaccaca tttgacccta accaaagtgg taatactttt 720

atggcggcaa actttacagt gactggacaa gtgaaatcag gggattattt tacagcgaag 780

ttaccagata gtgtaactgg taatggagac gtggattact ctaattcgaa taatacgatg 840

ccaattgcag atattaaaag tacgaatggc gatgttgtag ctaaagcaac atatgatatc 900

ttgactaaga cgtatacatt tgtctttaca gattatgtaa ataataaaga aaatattaac 960

ggacaatttt cattaccttt atttacagac cgagcaaagg cacctaaatc aggaacatat 1020

gatgcgaata ttaatattgc ggatgaaatg tttaataata aaattactta taactatagt 1080

tcgccaattg caggaattga taaaccaaat ggcgcgaaca tttcttctca aattattggt 1140

gtagatacag cttcaggtca aaacacatac aagcaaacag tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggttacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctac agatacaaaa ctgagaattt ttgaagtgaa tgatacatct 1320

aaattatcag atagctacta tgcggaccca aatgactcta accttaaaga agtaacgaat 1380

gagtttaagg ataaaatcac ttataaatac caaaatgtag caagtattaa ttttggcgat 1440

attactaaaa cgtatgttgt attagtggaa ggtcactatg ataatactgg taaaaacttg 1500

aaaacacagg ttattcaaga aaatattgac ccagcgacag gtaaagacta cagtattttc 1560

ggttggaata atgagaatgt tgtacgttat ggtggtggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 46
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 46

Leu Lys Lys Arg Ile Asp Tyr Leu Ser Asn Lys Gln Asn Lys Tyr Ser
1 5 10 15

Ile Arg Arg Phe Thr Val Gly Thr Thr Ser Val Ile Val Gly Ala Thr
20 25 30

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
35 40 45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
50 55 60

Lys Asn Asn Met Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65 70 75 80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
85 90 95

Ala Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
100 105 110

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

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser

130 135 140

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

Cys Glu Leu Lys Asn Pro Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
165 170 175

Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
180 185 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
195 200 205

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Lys Asp Phe
210 215 220

Gln Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225 230 235 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Val Thr Gly Asn Gly Asp Val Asp
260 265 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
275 280 285

Asn Gly Asp Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
290 295 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asn Lys Glu Asn Ile Asn
305 310 315 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
325 330 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
340 345 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
355 360 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
370 375 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385 390 395 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys

405 410 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
420 425 430

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
435 440 445

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asn Glu Phe Lys Asp
450 455 460

Lys Ile Thr Tyr Lys Tyr Gln Asn Val Ala Ser Ile Asn Phe Gly Asp
465 470 475 480

Ile Thr Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Ile Asp Pro Ala
500 505 510

Thr Gly Lys Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

<210> 47
<211> 1626
<212> DNA
<213> Staphylococcus aureus

<400> 47
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acagtaggta ccacatcagt aatagtaggg gcaactatac tatttgggat aggcaatcat 120

caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt 180

gcagattccg aaaaaaacaa tacgatagaa acacctcaat taaatacaac ggctaatgat 240

acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacagc aaaaccaatg 300

tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360

ccgacggcaa ttaaagatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420

gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaatagcat agcgacaaac 480

agcgagctta aaaatcctca gacattagat ttaccacaat catcaccaca aacgatttcc 540

aatgcgcaag gaactagtga accaagtgtt agaacgagag ctgtacgtag tcttgcagtt 600

gctgaacctg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatga taaagttacg 660

gcaagtgatt tcaagttaga aaagactaca tttgacccta accaaagtgg taacacattt 720

atggcggcaa attttaaagt ggcagggaaa gtgaaatcag gggattattt tacagcgaag 780

ttaccagata gtgtaactgg taatggagac gtggattact ctaattcaaa taatacgatg 840

ccaattgcag atatagtgaa tgataaaaaa gaagttgtag ctaaagcaac atatgatatc 900

ttgactaaga cgtatacatt tgtctttaca gattatgtaa atgataaaga aaatattaac 960

ggacaatttt cattaccttt atttacagac cgagcaaagg cacctaaatc aggaacatat 1020

gatgcaaata ttaatattgc ggatgaaatg tttaacaatc aaattactta taactatagt 1080

tcaccaattg caggaattga taagccaaat ggcgcgaaca tttcttctca aattattggt 1140

gtagatacag cttcaggtca aaacacatac aagcaaacgg tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggttacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctac agatacaaaa ctgagaattt ttgaagtgaa tgatacatct 1320

aaattatcag atagctacta tgcagaccca aatgactcta accttaaaga agtaactaat 1380

gagtttaagg ataaaatcac ttataaatac caaaacgtag caagtattaa ttttggtgat 1440

ataaataaaa cgtatgtcgt tttagtcgaa ggtcattatg ataatactgg taaaaacttg 1500

aaaacacagg ttattcaaga aaatattgac ccagcgacag gtaaagatta cagtattttc 1560

ggttggaata atgagaatgt tgtacgttat ggaggcggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 48
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 48

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Leu Lys Lys Arg Ile Asp Tyr Leu Ser Asn Lys Gln Asn Lys Tyr Ser
1               5                   10                  15

Ile Arg Arg Phe Thr Val Gly Thr Thr Ser Val Ile Val Gly Ala Thr
            20                  25                  30

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
        35                  40                  45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
    50                  55                  60

Lys Asn Asn Thr Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65                  70                  75                  80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
                85                  90                  95

Ala Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
            100                 105                 110

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

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Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
    130                 135                 140

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

Ser Glu Leu Lys Asn Pro Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
                165                 170                 175

Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Glu Pro Ser Val Arg Thr
            180                 185                 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
        195                 200                 205

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Ser Asp Phe
    210                 215                 220

Lys Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225                 230                 235                 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Val Thr Gly Asn Gly Asp Val Asp
            260                 265                 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Val Asn Asp
        275                 280                 285

Lys Lys Glu Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
    290                 295                 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asp Lys Glu Asn Ile Asn
305                 310                 315                 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
                325                 330                 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
            340                 345                 350

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

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
    370                 375                 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385                 390                 395                 400
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Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
405 410 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
420 425 430

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
435 440 445

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asn Glu Phe Lys Asp
450 455 460

Lys Ile Thr Tyr Lys Tyr Gln Asn Val Ala Ser Ile Asn Phe Gly Asp
465 470 475 480

Ile Asn Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Ile Asp Pro Ala
500 505 510

Thr Gly Lys Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

<210> 49
<211> 1626
<212> DNA
<213> Staphylococcus aureus

<400> 49
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acagtaggta ccacatcagt aatagtaggg gcaactatac tatttgggat aggcaatcat 120

caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt 180

gcagattccg aaaaaaacaa tatgatagaa acacctcaat taaatacaac ggctaatgat 240

acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacagc aaaaccaatg 300

tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360

ccgacggcaa ttaaagatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420

gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaatagcat agcgacaaac 480

agtgagctta aaaatcctca aacattagat ttaccacaat catcaccaca aacgatttcc 540

aatgcgcaaa gaactagtaa accaagtgtt agaaccagag ctgtacgtag tttagctgtt 600

gctgaaccgg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatga taaagttacg 660

gcaagtaatc tacagttgca aaagactacg tttgacccta accaaagtgg taacacattt 720

atggcggcaa attttacagt gacagataaa gtgaaatcag gagattattt tacagcgaag 780

ttaccagata gtttaactgg taatggagac gtggattact ctaattcaaa taatacgatg 840

ccaattgcag atattaaaag tacgaatggc gatgttgtag ctaaagcaac atatgatatc 900

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ggacaatttt cattaccttt atttacagac cgagcaaagg cacctaaatc aggaacatac 1020

gatgcaaata ttaatattgc ggatgaaatg tttaataata aaattactta taactatagt 1080

tcgccaattg caggaattga taagccaaat ggcgcgaaca tttcttctca gattattggt 1140

gtagatacag cttcaggtca aaacacatac aagcaaacgg tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggctacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctaa agatacaaaa ctgagaattt ttgaagtgaa tgatacatct 1320

aaattatcag atagctacta tgcagaccca aatgattcga atcttaaaga agtaacagac 1380

caatttaaaa atagaatcta ttatgagcat ccaaatgtag ctagtattaa ttttggcgat 1440

attactaaaa cgtatgttgt attagtggaa ggtcactatg ataatactgg taaaaacttg 1500

aaaacacagg ttattcaaga aaatattgac ccagcgacag gtaaagacta cagtattttc 1560

ggttggaata atgagaatgt tgtacgttat ggtggtggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 50
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 50

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Leu Lys Lys Arg Ile Asp Tyr Leu Ser Asn Lys Gln Asn Lys Tyr Ser
1               5                   10                  15

Ile Arg Arg Phe Thr Val Gly Thr Thr Ser Val Ile Val Gly Ala Thr
            20                  25                  30

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
        35                  40                  45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
    50                  55                  60

Lys Asn Asn Met Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65                  70                  75                  80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
                85                  90                  95

Ala Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
            100                 105                 110

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

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Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
    130                 135                 140

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

Ser Glu Leu Lys Asn Pro Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
                165                 170                 175

Gln Thr Ile Ser Asn Ala Gln Arg Thr Ser Lys Pro Ser Val Arg Thr
            180                 185                 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
        195                 200                 205

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Ser Asn Leu
    210                 215                 220

Gln Leu Gln Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225                 230                 235                 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Leu Thr Gly Asn Gly Asp Val Asp
            260                 265                 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
        275                 280                 285

Asn Gly Asp Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
    290                 295                 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asp Lys Glu Asn Ile Asn
305                 310                 315                 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
                325                 330                 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
            340                 345                 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
        355                 360                 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
    370                 375                 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385                 390                 395                 400
```

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
405 410 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Lys Asp Thr Lys Leu Arg
420 425 430

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
435 440 445

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asp Gln Phe Lys Asn
450 455 460

Arg Ile Tyr Tyr Glu His Pro Asn Val Ala Ser Ile Asn Phe Gly Asp
465 470 475 480

Ile Thr Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Ile Asp Pro Ala
500 505 510

Thr Gly Lys Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

<210> 51
<211> 1626
<212> DNA
<213> Staphylococcus aureus

<400> 51
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caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt 180

gcagattccg aaaaaaacaa tatgatagaa acacctcaat taaatacaac ggctaatgat 240

acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacagc aaaaccaatg 300

tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360

ccgacggcaa ttaaagatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420

gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaataacat agcaacaaac 480

agtgggctta aaaatcctca aacattagat ttaccacaat catcaccaca aacgatttcc 540

aatgcgcaag gaactagtaa accaagtgtt agaacgagag ctgtacgtag tcttgcagtt 600

gctgaacctg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatga taaagttacg 660

gcaagtgatt tcaagttaga aaagactaca ttcgacccta accaaagtgg taacacattt 720

atggcggcaa attttacagt gacagataaa gtgaaatcag gggattattt tacagcgaag 780

ttaccagata gtttaactgg taatggagac gtggattact ctaattcaaa taatacgatg 840

ccaattgcag acattaaaag tacgaatggt gatgttgtag cgacagcgac ttataatatc 900

ttgactaaga cgtatacatt tgtctttaca gattatgtaa atgataaaga aaatattaac 960

ggacaatttt cattaccttt atttacagac cgagcaaagg cacctaaatc aggaacatat 1020

gatgcaaata ttaatattgc ggatgaaatg tttaataata aaattactta taactatagt 1080

tcgccaattg caggaattga taagccaaat ggcgcgaaca tttcttctca aattattggt 1140

gtagatacag cttcaggcca aaacacatac aagcaaacgg tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggctacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctac agatacaaaa ctgagaattt ttgaagtgaa tgatacatct 1320

aaattatcag atagctacta tgcggaccca aatgactcta atcttaaaga agtaacgaat 1380

gagtttaagg ataaaatcac ttataaatac caaaatgtag caagtattaa ttttggcgat 1440

attactaaaa cgtatgttgt attagtggaa ggtcactatg ataatactgg taaaaacttg 1500

aaaacacagg ttattcaaga aaatattgac ccagcgacag gtaaagatta cagtattttc 1560

ggttggaata atgagaatgt tgtacgttat ggaggcggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 52
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 52

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

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
35 40 45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
50 55 60

Lys Asn Asn Met Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65 70 75 80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
85 90 95

Ala Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
100 105 110

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

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Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
    130                 135                 140

Gln Val Asp Asn Lys Thr Thr Asn Asp Ala Asn Asn Ile Ala Thr Asn
145                 150                 155                 160

Ser Gly Leu Lys Asn Pro Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
                165                 170                 175

Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
            180                 185                 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
        195                 200                 205

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Ser Asp Phe
    210                 215                 220

Lys Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225                 230                 235                 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Leu Thr Gly Asn Gly Asp Val Asp
            260                 265                 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
        275                 280                 285

Asn Gly Asp Val Val Ala Thr Ala Thr Tyr Asn Ile Leu Thr Lys Thr
    290                 295                 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asp Lys Glu Asn Ile Asn
305                 310                 315                 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
                325                 330                 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
            340                 345                 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
        355                 360                 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
    370                 375                 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385                 390                 395                 400
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Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
405 410 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
420 425 430

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
435 440 445

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asn Glu Phe Lys Asp
450 455 460

Lys Ile Thr Tyr Lys Tyr Gln Asn Val Ala Ser Ile Asn Phe Gly Asp
465 470 475 480

Ile Thr Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Ile Asp Pro Ala
500 505 510

Thr Gly Lys Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

<210> 53
<211> 1626
<212> DNA
<213> Staphylococcus aureus

<400> 53
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caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt 180

gcagattccg aaaaaaacaa tatgatagaa acacctcaat taaatacaac ggctaatgat 240

acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacagc aaaaccaatg 300

tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360

ccgacggcaa ttaaagatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420

gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaataacat agcaacaaac 480

agtgagctta aaaatcctca aacattagat ttaccacaat catcaccaca aacgatttcc 540

aatgcgcaag gaactagtaa accaagtgtt agaacgagag ctgtacgtag tcttgcagtt 600

gctgaacctg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatga taaagttacg 660

gcaagtgatt tcaagttaga aaagactaca ttcgacccta accaaagtgg taacacattt 720

atggcggcaa attttacagt gacagataaa gtgaaatcag gggattattt tacagcgaag 780

ttaccagata gtttaactgg taatggagac gtggattact ctaattcaaa taatacgatg 840

ccaattgcag acattaaaag tacgaatggt gatgttgtag cgacagcgac ttataatatc 900

ttgactaaga cgtatacatt tgtctttaca gattatgtaa atgataaaga aaatattaac 960

ggacaatttt cattaccttt atttacagac cgagcaaagg cacctaaatc aggaacatat 1020

gatgcaaata ttaatattgc ggatgaaatg tttaataata aaattactta taactatagt 1080

tcgccaattg caggaattga taagccaaat ggcgcgaaca tttcttctca aattattggt 1140

gtagatacag cttcaggcca aaacacatac aagcaaacgg tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggctacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctac agatacaaaa ctgagaattt ttgaagtgaa tgatacatct 1320

aaattatcag atagctacta tgcggaccca aatgactcta atcttaaaga agtaacgaat 1380

gagtttaagg ataaaatcac ttataaatac caaaatgtag caagtattaa ttttggcgat 1440

attactaaaa cgtatgttgt attagtggaa ggtcactatg ataatactgg taaaaacttg 1500

aaaacacagg ttattcaaga aaatattgac ccagcgacag gtaaagatta cagtattttc 1560

ggttggaata atgagaatgt tgtacgttat ggaggcggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 54
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 54

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

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
35 40 45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
50 55 60

Lys Asn Asn Met Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65 70 75 80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
85 90 95

Ala Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
100 105 110

Ala Ser Thr Asn Glu Thr Pro Gln Pro Thr Ala Ile Lys Asp Gln Ala

115 120 125

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
130 135 140

Gln Val Asp Asn Lys Thr Thr Asn Asp Ala Asn Asn Ile Ala Thr Asn
145 150 155 160

Ser Glu Leu Lys Asn Pro Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
165 170 175

Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
180 185 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
195 200 205

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Ser Asp Phe
210 215 220

Lys Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225 230 235 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Leu Thr Gly Asn Gly Asp Val Asp
260 265 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
275 280 285

Asn Gly Asp Val Val Ala Thr Ala Thr Tyr Asn Ile Leu Thr Lys Thr
290 295 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asp Lys Glu Asn Ile Asn
305 310 315 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
325 330 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
340 345 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
355 360 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
370 375 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln

385 390 395 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
405 410 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
420 425 430

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
435 440 445

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asn Glu Phe Lys Asp
450 455 460

Lys Ile Thr Tyr Lys Tyr Gln Asn Val Ala Ser Ile Asn Phe Gly Asp
465 470 475 480

Ile Thr Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Ile Asp Pro Ala
500 505 510

Thr Gly Lys Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

<210> 55
<211> 1626
<212> DNA
<213> Staphylococcus aureus

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caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt 180

gcagattccg aaaaaaacaa tatgatagaa acacctcaat taaatacaac ggctaatgat 240

acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacagc aaaaccaatg 300

tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360

ccgacggcaa ttaaagatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420

gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaatagcat agcgacaaac 480

agtgagctta aaaatcctca aacattagat ttaccacaat catcaccaca aacaatttcc 540

aatgcgcaag gaactagtaa accaagtgtt agaacgagag ctgtacgtag tcttgcagtt 600

gctgaacctg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatga taaagttacg 660

gcaaaagatt ttcaattaga aaagaccaca tttgacccta accaaagtgg taatactttt 720

atggcggcaa actttacagt gactggacaa gtgaaatcag gggattattt tacagcgaag 780

ttaccagata gtgtaactgg taatggagac gtggattact ctaattcgaa taatacgatg 840

ccaattgcag atattaaaag tacgaatggc gatgttgtag ctaaagcaac atatgatatc 900

ttgactaaga cgtatacatt tgtctttaca gattatgtaa ataataaaga aaatattaac 960

ggacaatttt cattaccttt atttacagac cgagcaaagg cacctaaatc aggaacatat 1020

gatgcgaata ttaatattgc ggatgaaatg tttaataata aaattactta taactatagt 1080

tcgccaattg caggaattga taaaccaaat ggcgcgaaca tttcttctca aattattggt 1140

gtagatacag cttcaggtca aaacacatac aagcaaacag tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggttacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctac agatacaaaa ctgagaattt ttgaagtgaa tgatacatct 1320

aaattatcag atagctacta tgcggaccca aatgactcta accttaaaga agtaacgaat 1380

gagtttaagg ataaaatcac ttataaatac caaaatgtag caagtattaa ttttggcgat 1440

attactaaaa cgtatgttgt attagtggaa ggtcactatg ataatactgg taaaaacttg 1500

aaaacacagg ttattcaaga aaatattgac ccagcgacag gtaaagacta cagtattttc 1560

ggttggaata atgagaatgt tgtacgttat ggtggtggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 56
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 56

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

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
35 40 45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
50 55 60

Lys Asn Asn Met Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65 70 75 80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
85 90 95

Ala Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
100 105 110

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

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
130 135 140

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

Ser Glu Leu Lys Asn Pro Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
165 170 175

Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
180 185 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
195 200 205

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Lys Asp Phe
210 215 220

Gln Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225 230 235 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Val Thr Gly Asn Gly Asp Val Asp
260 265 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
275 280 285

Asn Gly Asp Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
290 295 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asn Lys Glu Asn Ile Asn
305 310 315 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
325 330 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
340 345 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
355 360 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
370 375 380

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385 390 395 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
405 410 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
420 425 430

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
435 440 445

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asn Glu Phe Lys Asp
450 455 460

Lys Ile Thr Tyr Lys Tyr Gln Asn Val Ala Ser Ile Asn Phe Gly Asp
465 470 475 480

Ile Thr Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Ile Asp Pro Ala
500 505 510

Thr Gly Lys Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

<210> 57
<211> 1626
<212> DNA
<213> Staphylococcus aureus

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caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt 180

gcagattccg aaaaaaacaa tacgatagaa acacctcaat taaatacaac ggctaatgat 240

acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacagc aaaaacaatg 300

tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa 360

ccgacggcaa ttaaagatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa 420

gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaataacat agcaacaaac 480

agtgagctta aaaatcctca aacattagat ttaccacaat catcaccaca aacgatttcc 540

aatgcgcaag gaactagtaa accaagtgtt agaacgagag ctgtacgtag tcttgcagtt 600

gctgaacctg tagtaaatgc tgctgatgct aaaggtacaa atgtaaatga taaagttacg 660

gcaagtgatc tcaagttaga aaagactgca tttgacccta accaaagtgg taacacattt 720

atggcggcaa attttaaagt gactggacaa gtgaaatcag gggattattt tacagcgaag 780

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ccaattgcag acattaaaag tacgaatggc gatgttgtag ctaaagcaac atatgatatc 900

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gatgcaaata ttaatattgc ggatgaaatg tttgataata aaattactta taactatagt 1080

tcgccaattg caggaattga taagccaaat ggcgcgaaca tttcttctca aattattggt 1140

gtagatacag cttcaggtca aaacacatac aagcaaacgg tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtatatt aaaggttacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctac agatacaaaa ctgagaattt ttgaagtgaa tgatacatct 1320

aaattatcag atagctacta tgcagaccca aatgactcta accttaaaga agtgactggt 1380

gagtttaaag ataaaatttc atacaaatac gataacgtag caagtattaa ttttggtgat 1440

ataaataaaa cgtatgttgt attagtggaa ggtcactatg ataatactgg taaaaacttg 1500

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ggttggaata atgagaatgt tgtacgttat ggaggcggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 58
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 58

Leu Lys Lys Arg Ile Asp Tyr Leu Ser Asn Lys Gln Asn Lys Tyr Ser
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Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
35 40 45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
50 55 60

Lys Asn Asn Thr Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65 70 75 80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
85 90 95

Ala Lys Thr Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
100 105 110

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

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
    130                 135                 140

Gln Val Asp Asn Lys Thr Thr Asn Asp Ala Asn Asn Ile Ala Thr Asn
145                 150                 155                 160

Ser Glu Leu Lys Asn Pro Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
                165                 170                 175

Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
            180                 185                 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
        195                 200                 205

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Ser Asp Leu
    210                 215                 220

Lys Leu Glu Lys Thr Ala Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225                 230                 235                 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Val Thr Gly Asn Gly Asp Val Asp
            260                 265                 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
        275                 280                 285

Asn Gly Asp Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
    290                 295                 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asp Lys Glu Asn Ile Asn
305                 310                 315                 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
                325                 330                 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asp
            340                 345                 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
        355                 360                 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
    370                 375                 380
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Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385                 390                 395                 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
                405                 410                 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
            420                 425                 430

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
        435                 440                 445

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Gly Glu Phe Lys Asp
    450                 455                 460

Lys Ile Ser Tyr Lys Tyr Asp Asn Val Ala Ser Ile Asn Phe Gly Asp
465                 470                 475                 480

Ile Asn Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
                485                 490                 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Ile Asp Ser Ala
            500                 505                 510

Thr Gly Lys Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
        515                 520                 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
    530                 535                 540
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<210> 59
<211> 1626
<212> DNA
<213> Staphylococcus aureus

<400> 59

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caagcacaag cttcagaaca atcgaacgat acaacgcaat cttcgaaaaa taatgcaagt    180
gcagattccg aaaaaaacaa tatgatagaa acacctcaat taaatacaac ggctaatgat    240
acatctgata ttagtgcaaa cacaaacagt gcgaatgtag atagcacaac aaaaccaatg    300
tctacacaaa cgagcaatac cactacaaca gagccagctt caacaaatga aacacctcaa    360
ccgacggcaa ttaaaaatca agcaactgct gcaaaaatgc aagatcaaac tgttcctcaa    420
gaagcaaatt ctcaagtaga taataaaaca acgaatgatg ctaatagcat agcaacaaac    480
agtgagctta aaaattctca aacattagat ttaccacaat catcaccaca aacgatttcc    540
aatgcgcaag gaactagtaa accaagtgtt agaacgagag ctgtacgtag tttagctgtt    600
gctgaaccgg tagtaaatgc tgctgatgct aaagatacaa atgtaaatga taaagttacg    660
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gcaagtaatt tcaagttaga aaagactaca tttgacccta atcaaagtgg taacacattt 720

atggcggcaa attttacagt gacagataaa gtgaaatcag gggattattt tacagcgaag 780

ttaccagata gtttaactgg taatggagac gtggattatt ctaattcaaa taatacgatg 840

ccaattgcag acattaaaag tacgaatggc gatgttgtag ctaaagcaac atatgatatc 900

ttgactaaga cgtatacatt tgtctttaca gattatgtaa ataataaaga aaatattaac 960

ggacaatttt cattaccttt atttacagac cgagcaaagg cacctaaatc aggaacatat 1020

gatgcgaata ttaatattgc ggatgaaatg tttaataata aaattactta taactatagt 1080

tcgccaattg caggaattga taaaccaaat ggcgcgaaca tttcttctca aattattggt 1140

gtagatacag cttcaggtca aaacacatac aagcaaacag tatttgttaa ccctaagcaa 1200

cgagttttag gtaatacgtg ggtgtataat aaaggctacc aagataaaat cgaagaaagt 1260

agcggtaaag taagtgctac agatacaaaa ctgagaattt ttgaagtgaa tgatacatct 1320

aaattatcag atagctacta tgcagatcca aatgactcta accttaaaga agtaacagac 1380

caatttaaaa atagaatcta ttatgagcat ccaaatgtag ctagtattaa atttggtgat 1440

attactaaaa catatgtagt attagtagaa gggcattacg acaatacagg taagaactta 1500

aaaactcagg ttattcaaga aaatgttgat cctgtaacaa atagagacta cagtattttc 1560

ggttggaata atgagaatgt tgtacgttat ggtggtggaa gtgctgatgg tgattcagca 1620

gtaaat 1626

<210> 60
<211> 542
<212> PRT
<213> Staphylococcus aureus

<400> 60

Leu Lys Lys Arg Ile Asp Tyr Leu Ser Asn Lys Gln Asn Lys Tyr Ser
1 5 10 15

Ile Arg Arg Phe Thr Val Gly Thr Thr Ser Val Ile Val Gly Ala Thr
20 25 30

Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
35 40 45

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
50 55 60

Lys Asn Asn Met Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65 70 75 80

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
85 90 95

Thr Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
100 105 110

```
Ala Ser Thr Asn Glu Thr Pro Gln Pro Thr Ala Ile Lys Asn Gln Ala
        115                 120                 125

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
    130                 135                 140

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

Ser Glu Leu Lys Asn Ser Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
                165                 170                 175

Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
            180                 185                 190

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
        195                 200                 205

Asp Ala Lys Asp Thr Asn Val Asn Asp Lys Val Thr Ala Ser Asn Phe
    210                 215                 220

Lys Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225                 230                 235                 240

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

Phe Thr Ala Lys Leu Pro Asp Ser Leu Thr Gly Asn Gly Asp Val Asp
            260                 265                 270

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
        275                 280                 285

Asn Gly Asp Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
    290                 295                 300

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asn Lys Glu Asn Ile Asn
305                 310                 315                 320

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
                325                 330                 335

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
            340                 345                 350

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
        355                 360                 365

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
    370                 375                 380
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Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385 390 395 400

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
405 410 415

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
420 425 430

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
435 440 445

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asp Gln Phe Lys Asn
450 455 460

Arg Ile Tyr Tyr Glu His Pro Asn Val Ala Ser Ile Lys Phe Gly Asp
465 470 475 480

Ile Thr Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485 490 495

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Val Asp Pro Val
500 505 510

Thr Asn Arg Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515 520 525

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
530 535 540

<210> 61
<211> 1677
<212> DNA
<213> Staphylococcus aureus

<400> 61
atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt 180

agcgttagtg ctgcacctaa aacagacgac acaaacgtga gtgatactaa aacatcgtca 240

aacactaata atggcgaaac gagtgtggcg caaaatccag cacaacagga aacgacacaa 300

tcatcatcaa caaatgcaac tacggaagaa acgccggtaa ctggtgaagc tactactacg 360

acaacgaatc aagctaatac accggcaaca actcaatcaa gcaatacaaa tgcggaggaa 420

ttagtgaatc aaacaagtaa tgaaacgact tctaatgata ctaatacagt atcatctgta 480

aattcacctc aaaattctac aaatgcggaa aatgtttcaa caacgcaaga tacttcaact 540

gaagcaacac cttcaaacaa tgaatcagct ccacagagta cagatgcaag taataaagat 600

gtagttaatc aagcggttaa tacaagtgcg cctagaatga gagcatttag tttagcggca 660

gtagctgcag atgcaccggc agctggcaca gatattacga atcagttgac gaatgtgaca 720

gttggtattg actctggtac gactgtgtat ccgcaccaag caggttatgt caaactgaat 780

tatggttttt cagtgcctaa ttctgctgtt aaaggtgaca cattcaaaat aactgtacct 840

aaagaattaa acttaaatgg tgtaacttca actgctaaag tgccaccaat tatggctgga 900

gatcaagtat tggcaaatgg tgtaatcgat agtgatggta atgttattta tacatttaca 960

gactatgtaa atactaaaga tgatgtaaaa gcaactttga ccatgcccgc ttatattgac 1020

cctgaaaatg ttaaaaagac aggtaatgtg acattggcta ctggcatagg tagtacaaca 1080

gcaaacaaaa cagtattagt agattatgaa aaatatggta agttttataa cttatctatt 1140

aaaggtacaa ttgaccaaat cgataaaaca aataatacgt atcgtcagac aatttatgtc 1200

aatccaagtg gagataacgt tattgcgccg gttttaacag gtaatttaaa accaaatacg 1260

gatagtaatg cattaataga tcagcaaaat acaagtatta aagtatataa agtagataat 1320

gcagctgatt tatctgaaag ttactttgtg aatccagaaa actttgagga tgtcactaat 1380

agtgtgaata ttacattccc aaatccaaat caatataaag tagagtttaa tacgcctgat 1440

gatcaaatta caacaccgta tatagtagtt gttaatggtc atattgatcc gaatagcaaa 1500

ggtgatttag ctttacgttc aactttatat gggtataact cgaatataat ttggcgctct 1560

atgtcatggg acaacgaagt agcatttaat aacggatcag gttctggtga cggtatcgat 1620

aaaccagttg ttcctgaaca acctgatgag cctggtgaaa ttgaaccaat tccagag 1677

<210> 62
<211> 559
<212> PRT
<213> Staphylococcus aureus

<400> 62

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Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1               5                  10                  15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
            20                  25                  30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
        35                  40                  45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Ser Ala
    50                  55                  60

Ala Pro Lys Thr Asp Asp Thr Asn Val Ser Asp Thr Lys Thr Ser Ser
65                  70                  75                  80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
                85                  90                  95

Glu Thr Thr Gln Ser Ser Ser Thr Asn Ala Thr Thr Glu Glu Thr Pro
```

100 105 110

Val Thr Gly Glu Ala Thr Thr Thr Thr Asn Gln Ala Asn Thr Pro
115 120 125

Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln
130 135 140

Thr Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val
145 150 155 160

Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln
165 170 175

Asp Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln
180 185 190

Ser Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr
195 200 205

Ser Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
210 215 220

Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asn Val Thr
225 230 235 240

Val Gly Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr
245 250 255

Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly
260 265 270

Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
275 280 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
290 295 300

Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305 310 315 320

Asp Tyr Val Asn Thr Lys Asp Asp Val Lys Ala Thr Leu Thr Met Pro
325 330 335

Ala Tyr Ile Asp Pro Glu Asn Val Lys Lys Thr Gly Asn Val Thr Leu
340 345 350

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

Tyr Glu Lys Tyr Gly Lys Phe Tyr Asn Leu Ser Ile Lys Gly Thr Ile

370 375 380

Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385 390 395 400

Asn Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu Thr Gly Asn Leu
405 410 415

Lys Pro Asn Thr Asp Ser Asn Ala Leu Ile Asp Gln Gln Asn Thr Ser
420 425 430

Ile Lys Val Tyr Lys Val Asp Asn Ala Ala Asp Leu Ser Glu Ser Tyr
435 440 445

Phe Val Asn Pro Glu Asn Phe Glu Asp Val Thr Asn Ser Val Asn Ile
450 455 460

Thr Phe Pro Asn Pro Asn Gln Tyr Lys Val Glu Phe Asn Thr Pro Asp
465 470 475 480

Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp
485 490 495

Pro Asn Ser Lys Gly Asp Leu Ala Leu Arg Ser Thr Leu Tyr Gly Tyr
500 505 510

Asn Ser Asn Ile Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala
515 520 525

Phe Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val
530 535 540

Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 63
<211> 1677
<212> DNA
<213> Staphylococcus aureus

<400> 63
atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt 180

agcgttagtg ctgcacctaa aacagacgac acaaacgtga gtgatactaa aacatcgtca 240

aacactaata atggcgaaac gagtgtggcg caaaatccag cacaacagga aacgacacaa 300

tcatcatcaa caaatgcaac tacggaagaa acgccggtaa ctggtgaagc tactactacg 360

acaacgaatc aagctaatac accggcaaca actcaatcaa gcaatacaaa tgcggaggaa 420

ttagtgaatc aaacaagtaa tgaaacgact tctaatgata ctaatacagt atcatctgta 480

aattcacctc aaaattctac aaatgcggaa aatgtttcaa caacgcaaga tacttcaact 540

gaagcaacac cttcaaacaa tgaatcagct ccacagaata cagatgcaag taataaagat 600

gtagttagtc aagcggttaa tccaagtacg cctagaatga gagcatttag tttagcggca 660

gtagctgcag atgcaccggc agctggcaca gatattacga atcagttgac agatgtgaaa 720

gttactattg actctggtac gactgtgtat ccgcaccaag caggttatgt caaactgaat 780

tatggttttt cagtgcctaa ttctgctgtt aaaggtgaca cattcaaaat aactgtacct 840

aaagaattaa acttaaatgg tgtaacttca actgctaaag tgccaccaat tatggctgga 900

gatcaagtat tggcaaatgg tgtaatcgat agtgatggta atgttattta tacatttaca 960

gactatgttg ataataaaga aaatgtaaca gctaatatta ctatgccagc ttatattgac 1020

cctgaaaatg ttacaaagac aggtaatgtg acattgacaa ctggcatagg aaccaatact 1080

gctagtaaga cagtattaat cgactatgag aaatatggac aattccataa tttatcaatt 1140

aaaggtacga ttgatcaaat cgataaaaca aataatacgt atcgccaaac aatttatgtc 1200

aatccaagcg gagataacgt tgtgttacct gccttaacag gtaatttaat tcctaataca 1260

aagagtaatg cgttaataga tgcaaaaaac actgatatta aagtttatag agtcgataat 1320

gctaatgatt tatctgaaag ttattatgtg aatcctagcg attttgaaga tgtaactaat 1380

caagttagaa tttcatttcc aaatgctaat caatacaaag tagaatttcc tacggacgat 1440

gaccaaatta caacaccgta tattgtagtt gttaatggcc atattgatcc tgctagtaca 1500

ggtgatttag cactacgttc gacattttat ggttatgatt ctaattttat atggagatct 1560

atgtcatggg acaacgaagt agcatttaat aacggatcag gttctggtga cggtatcgat 1620

aaaccagttg ttcctgaaca acctgatgag cctggtgaaa ttgaaccaat tccagag 1677

<210> 64
<211> 559
<212> PRT
<213> Staphylococcus aureus

<400> 64

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Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1               5                  10                  15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
            20                  25                  30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
        35                  40                  45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Ser Ala
    50                  55                  60

Ala Pro Lys Thr Asp Asp Thr Asn Val Ser Asp Thr Lys Thr Ser Ser
65                  70                  75                  80
```

```
Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
                85                  90                  95

Glu Thr Thr Gln Ser Ser Ser Thr Asn Ala Thr Thr Glu Glu Thr Pro
            100                 105                 110

Val Thr Gly Glu Ala Thr Thr Thr Thr Thr Asn Gln Ala Asn Thr Pro
        115                 120                 125

Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln
    130                 135                 140

Thr Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val
145                 150                 155                 160

Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln
                165                 170                 175

Asp Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln
            180                 185                 190

Asn Thr Asp Ala Ser Asn Lys Asp Val Val Ser Gln Ala Val Asn Pro
        195                 200                 205

Ser Thr Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
    210                 215                 220

Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asp Val Lys
225                 230                 235                 240

Val Thr Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr
                245                 250                 255

Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly
            260                 265                 270

Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
        275                 280                 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
    290                 295                 300

Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305                 310                 315                 320

Asp Tyr Val Asp Asn Lys Glu Asn Val Thr Ala Asn Ile Thr Met Pro
                325                 330                 335

Ala Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu
            340                 345                 350
```

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

Tyr Glu Lys Tyr Gly Gln Phe His Asn Leu Ser Ile Lys Gly Thr Ile
370 375 380

Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385 390 395 400

Asn Pro Ser Gly Asp Asn Val Val Leu Pro Ala Leu Thr Gly Asn Leu
405 410 415

Ile Pro Asn Thr Lys Ser Asn Ala Leu Ile Asp Ala Lys Asn Thr Asp
420 425 430

Ile Lys Val Tyr Arg Val Asp Asn Ala Asn Asp Leu Ser Glu Ser Tyr
435 440 445

Tyr Val Asn Pro Ser Asp Phe Glu Asp Val Thr Asn Gln Val Arg Ile
450 455 460

Ser Phe Pro Asn Ala Asn Gln Tyr Lys Val Glu Phe Pro Thr Asp Asp
465 470 475 480

Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp
485 490 495

Pro Ala Ser Thr Gly Asp Leu Ala Leu Arg Ser Thr Phe Tyr Gly Tyr
500 505 510

Asp Ser Asn Phe Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala
515 520 525

Phe Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val
530 535 540

Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 65
<211> 1677
<212> DNA
<213> Staphylococcus aureus

<400> 65
atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt 180

agcgttagtg ctgcacctaa aacagacgac acaaacgtga gtgatactaa aacatcgtca 240

aacactaata atggcgaaac gagtgtggcg caaaatccag cacaacagga aacgacacaa 300

tcatcatcaa caaatgcaac tacggaagaa acgccggtaa ctggtgaagc tactactacg 360

acaacgaatc aagctaatac accggcaaca actcaatcaa gcaatacaaa tgcggaggaa 420

ttagtgaatc aaacaagtaa tgaaacgact tctaatgata ctaatacagt atcatctgta 480

aattcacctc aaaattctac aaatgcggaa aatgtttcaa caacgcaaga tacttcaact 540

gaagcaacac cttcaaacaa tgaatcagct ccacagagta cagatgcaag taataaagat 600

gtagttaatc aagcggttaa tacaagtgcg cctagaatga gagcatttag tttagcggca 660

gtagctgcag atgcaccggc agctggcaca gatattacga atcagttgac gaatgtgaca 720

gttggtattg actctggtac gactgtgtat ccgcaccaag caggttatgt caaactgaat 780

tatggttttt cagtgcctaa ttctgctgtt aaaggtgaca cattcaaaat aactgtacct 840

aaagaattaa acttaaatgg tgtaacttca actgctaaag tgccaccaat tatggctgga 900

gatcaagtat tggcaaatgg tgtaatcgat agtgatggta atgttattta tacatttaca 960

gactatgtaa atactaaaga tgatgtaaaa gcaactttga ccatgcccgc ttatattaac 1020

cctgaaaatg ttaaaaagac aggtaatgtg acattggcta ctggcatagg tagtacaaca 1080

gcaaacaaaa cagtattagt agattatgaa aaatatggta agttttataa cttatctatt 1140

aaaggtacaa ttgaccaaat cgataaaaca aataatacgt atcgtcagac aatttatgtc 1200

aatccaagtg gagataacgt tattgcgccg gttttaacag gtaatttaaa accaaatacg 1260

gatagtaatg cattaataga tcagcaaaat acaagtatta aagtatataa agtagataat 1320

gcagctgatt tatctgaaag ttactttgtg aatccagaaa actttgagga tgtcactaat 1380

agtgtgaata ttacattccc aaatccaaat caatataaag tagagtttaa tacgcctgat 1440

gatcaaatta caacaccgta tatagtagtt gttaatggtc atattgatcc gaatagcaaa 1500

ggtgatttag ctttacgttc aactttatat gggtataact cgaatataat ttggcgctct 1560

atgtcatggg acaacgaagt agcatttaat aacggatcag gttctggtga cggtatcgat 1620

aaaccagttg ttcctgaaca acctgatgag cctggtgaaa ttgaaccaat tccagag 1677

<210> 66
<211> 559
<212> PRT
<213> Staphylococcus aureus

<400> 66

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Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1               5                  10                  15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
            20                  25                  30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
        35                  40                  45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Ser Ala
    50                  55                  60
```

```
Ala Pro Lys Thr Asp Asp Thr Asn Val Ser Asp Thr Lys Thr Ser Ser
65                  70                  75                  80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
                85                  90                  95

Glu Thr Thr Gln Ser Ser Ser Thr Asn Ala Thr Thr Glu Glu Thr Pro
            100                 105                 110

Val Thr Gly Glu Ala Thr Thr Thr Thr Thr Asn Gln Ala Asn Thr Pro
        115                 120                 125

Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln
    130                 135                 140

Thr Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val
145                 150                 155                 160

Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln
                165                 170                 175

Asp Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln
            180                 185                 190

Ser Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr
        195                 200                 205

Ser Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
    210                 215                 220

Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asn Val Thr
225                 230                 235                 240

Val Gly Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr
                245                 250                 255

Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly
            260                 265                 270

Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
        275                 280                 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
    290                 295                 300

Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305                 310                 315                 320

Asp Tyr Val Asn Thr Lys Asp Asp Val Lys Ala Thr Leu Thr Met Pro
                325                 330                 335
```

```
Ala Tyr Ile Asn Pro Glu Asn Val Lys Lys Thr Gly Asn Val Thr Leu
            340                 345                 350

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

Tyr Glu Lys Tyr Gly Lys Phe Tyr Asn Leu Ser Ile Lys Gly Thr Ile
    370                 375                 380

Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385                 390                 395                 400

Asn Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu Thr Gly Asn Leu
                405                 410                 415

Lys Pro Asn Thr Asp Ser Asn Ala Leu Ile Asp Gln Gln Asn Thr Ser
            420                 425                 430

Ile Lys Val Tyr Lys Val Asp Asn Ala Ala Asp Leu Ser Glu Ser Tyr
        435                 440                 445

Phe Val Asn Pro Glu Asn Phe Glu Asp Val Thr Asn Ser Val Asn Ile
    450                 455                 460

Thr Phe Pro Asn Pro Asn Gln Tyr Lys Val Glu Phe Asn Thr Pro Asp
465                 470                 475                 480

Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp
                485                 490                 495

Pro Asn Ser Lys Gly Asp Leu Ala Leu Arg Ser Thr Leu Tyr Gly Tyr
            500                 505                 510

Asn Ser Asn Ile Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala
        515                 520                 525

Phe Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val
    530                 535                 540

Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545                 550                 555


<210> 67
<211> 1677
<212> DNA
<213> Staphylococcus aureus

<400> 67
atgaatatga agaaacaaga aaaacacgca attcgtaaaa aatcgattgg cgtggcttca     60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt    120

gaaaatagta tgacacaaac ggaaaatacg agtaatgaga gcaaaagtaa tgatccaagt    180
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agcgttaatg ctgcacctaa aacagacaac acaaacgtga gtgattctaa tacaacgaca 240

aacactaata gtgacgaaac gaatgtagcg caaaatccag cacaacagga aacgacacaa 300

tcagcatcaa caaatgcaac tacagaagaa acaccggtaa ctggtgaagt tactactacg 360

gcaacgaatc aagctaatac accggcaaca actcaatcaa gcaatacaaa tgcggaagaa 420

tcagtgaatc aaacaagtaa tgaaacgact tctaatgata ctaatacagt atcatctgta 480

aattcacctc aaaattctac aaatgcggaa aatgtttcaa caacgcaaga catttcaact 540

gaagcaacac cttcaaacaa tgaatcagct ccacagagta cagatgcaag taataaagat 600

gtagttaatc aagcggttaa tacaagtgcg cctagaatga gagcatttag tttagcggct 660

gtagctgcag atgcaccggc tgctggcaaa gatattacga atcagttgac gaatgtgaca 720

gttggtattg actctggaga tacagtttat ccgcaccaag caggctatgt caaactgaat 780

tatgggttct cagtaccaaa tgaggctgtt caaggtgaca cattcaaaat aactgtgccc 840

aaagaattaa acttaaatgg tgtaacttca actgctaaag tgccaccaat tatggccgga 900

gatcaagtat tggcaaatgg tgtaatcgat agtgatggta atgttattta tacatttaca 960

gactatgtaa atactaaaga tgatgttaaa gcaactttga ccatgcccgc ttatattgac 1020

cctgaaaatg ttacaaagac aggtaatgtg acattggcta ctggcatagg tagtacaaca 1080

gcaaacaaaa cagtattagt agattatgaa aaatatggta agttttataa cttatctatt 1140

aaaggtacaa ttgaccaaat cgataaaaca aataatacgt atcgtcagac aatttatgtc 1200

aatccaagtg gagataacgt tattgcgccg gttttaacag gtaatttaaa accaaatacg 1260

gatagtaatg cattaataga tgcacaaaat actagtatta aagtatataa agttgataat 1320

gcatcagact tgtctgaaag ttattatgtg aatccagata actttgaaga tgtcactgat 1380

agtgtgaata ttacattccc aaatccaaat caatataaag tagagttcaa tacgcctgat 1440

gatcaaataa caacaccata tattgtagtt gttaatgggc atattgatcc taatagtaaa 1500

ggtgatttag ctttacgttc aactttatat ggatataatt cgaatataat ttggcgatca 1560

atgtcatggg ataatgaagt agcatttaat aacggatcag gttctggtga cggtatcgat 1620

aaacctgttg ttcctgaaca acctgatgag ccgggtgaaa ttgaaccaat tccagag 1677

<210> 68
<211> 559
<212> PRT
<213> Staphylococcus aureus

<400> 68
Met Asn Met Lys Lys Gln Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1 5 10 15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
20 25 30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Met Thr Gln Thr Glu
35 40 45

```
Asn Thr Ser Asn Glu Ser Lys Ser Asn Asp Pro Ser Ser Val Asn Ala
    50                  55                  60

Ala Pro Lys Thr Asp Asn Thr Asn Val Ser Asp Ser Asn Thr Thr Thr
65                  70                  75                  80

Asn Thr Asn Ser Asp Glu Thr Asn Val Ala Gln Asn Pro Ala Gln Gln
                85                  90                  95

Glu Thr Thr Gln Ser Ala Ser Thr Asn Ala Thr Thr Glu Glu Thr Pro
            100                 105                 110

Val Thr Gly Glu Val Thr Thr Thr Ala Thr Asn Gln Ala Asn Thr Pro
        115                 120                 125

Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Ser Val Asn Gln
    130                 135                 140

Thr Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val
145                 150                 155                 160

Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln
                165                 170                 175

Asp Ile Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln
            180                 185                 190

Ser Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr
        195                 200                 205

Ser Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
    210                 215                 220

Ala Pro Ala Ala Gly Lys Asp Ile Thr Asn Gln Leu Thr Asn Val Thr
225                 230                 235                 240

Val Gly Ile Asp Ser Gly Asp Thr Val Tyr Pro His Gln Ala Gly Tyr
                245                 250                 255

Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Glu Ala Val Gln Gly
            260                 265                 270

Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
        275                 280                 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
    290                 295                 300

Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305                 310                 315                 320
```

Asp Tyr Val Asn Thr Lys Asp Asp Val Lys Ala Thr Leu Thr Met Pro
325 330 335

Ala Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu
340 345 350

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

Tyr Glu Lys Tyr Gly Lys Phe Tyr Asn Leu Ser Ile Lys Gly Thr Ile
370 375 380

Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385 390 395 400

Asn Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu Thr Gly Asn Leu
405 410 415

Lys Pro Asn Thr Asp Ser Asn Ala Leu Ile Asp Ala Gln Asn Thr Ser
420 425 430

Ile Lys Val Tyr Lys Val Asp Asn Ala Ser Asp Leu Ser Glu Ser Tyr
435 440 445

Tyr Val Asn Pro Asp Asn Phe Glu Asp Val Thr Asp Ser Val Asn Ile
450 455 460

Thr Phe Pro Asn Pro Asn Gln Tyr Lys Val Glu Phe Asn Thr Pro Asp
465 470 475 480

Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp
485 490 495

Pro Asn Ser Lys Gly Asp Leu Ala Leu Arg Ser Thr Leu Tyr Gly Tyr
500 505 510

Asn Ser Asn Ile Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala
515 520 525

Phe Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val
530 535 540

Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 69
<211> 1677
<212> DNA
<213> Staphylococcus aureus

<400> 69

atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt 180

agcattaatg ctgcacctaa aacagacaac acaaacgtga gtgatactaa accaacgtca 240

aacactaata atggcgaaac gagtgtggcg caaaatccag cacaacagga aacgacacaa 300

tcagcatcaa caaatgcaac tacggaagaa acgccggtaa ctggtgaagc tactactacg 360

acaacgaatc aagctaatac accggcaaca actcaatcaa gcaatacaaa tgcggaggaa 420

ttagtgaatc aaacaagtaa tgaaacgact tctaatgata ctaatacagt atcatctgta 480

aattcacctc aaaattctac aaatgcggaa aatgtttcaa caacgcaaga tacttcaact 540

gaagcaacac cttcaaacaa tgaatcagct ccacagagta cagatgcaag taataaagat 600

gtagttaatc aagcggttaa tacaagtgcg cctagaaaga gagcatttag tttagcggct 660

gtagctgcag atgcaccggc agctggcaca gatattacga atcagttgac agatgtgaaa 720

gttactattg actctggtac gactgtgtat ccgcaccaag caggttatgt caaactgaat 780

tatggttttt cagtgcctaa ttctgctgtt aaaggtgaca cattcaaaat aactgtacct 840

aaagaattaa acttaaatgg tgtaacttca actgctaaag tgccaccaat tatggctgga 900

gatcaagtat tggcaaatgg tgtaatcgat agtgatggta atgttattta tacatttaca 960

gactatgttg ataataaaga aaatgtaaca gctaatatta ctatgccagc ttatattgac 1020

cctgaaaatg ttacaaagac aggtaatgtg acattgacaa ctggcatagg aaccaatact 1080

gctagtaaga cagtattaat cgactatgag aaatatggac aattccataa tttatcaatt 1140

aaaggtacga ttgatcaaat cgataaaaca aataatacgt atcgccaaac aatttatgtc 1200

aatccaagcg gagataacgt tgtgttacct gccttaacag gtaatttaat tcctaataca 1260

aagagtaatg cgttaataga tgcaaaaaac actgatatta aagtttatag agtcgataat 1320

gctaatgatt tatctgaaag ttattatgtg aatcctagcg attttgaaga tgtaactaat 1380

caagttagaa tttcatttcc aaatgctaat caatacaaag tagaatttcc tacggacgat 1440

gaccaaatta caacaccgta tattgtagtt gttaatggcc atattgatcc tgctagtaca 1500

ggtgatttag cactacgttc gacattttat ggttatgatt ctaattttat atggagatct 1560

atgtcatggg acaacgaagt agcatttaat aacggatcag gttctggtga cggtatcgat 1620

aaaccagttg ttcctgaaca acctgatgag cctggtgaaa ttgaaccaat tccagag 1677

<210> 70
<211> 559
<212> PRT
<213> Staphylococcus aureus

<400> 70
Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1 5 10 15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu

```
            20                  25                  30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
        35                  40                  45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Ile Asn Ala
    50                  55                  60

Ala Pro Lys Thr Asp Asn Thr Asn Val Ser Asp Thr Lys Pro Thr Ser
65                  70                  75                  80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
                85                  90                  95

Glu Thr Thr Gln Ser Ala Ser Thr Asn Ala Thr Thr Glu Glu Thr Pro
            100                 105                 110

Val Thr Gly Glu Ala Thr Thr Thr Thr Thr Asn Gln Ala Asn Thr Pro
        115                 120                 125

Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln
    130                 135                 140

Thr Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val
145                 150                 155                 160

Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln
                165                 170                 175

Asp Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln
            180                 185                 190

Ser Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr
        195                 200                 205

Ser Ala Pro Arg Lys Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
    210                 215                 220

Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asp Val Lys
225                 230                 235                 240

Val Thr Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr
                245                 250                 255

Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly
            260                 265                 270

Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
        275                 280                 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
```

290 295 300

Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305 310 315 320

Asp Tyr Val Asp Asn Lys Glu Asn Val Thr Ala Asn Ile Thr Met Pro
325 330 335

Ala Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu
340 345 350

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

Tyr Glu Lys Tyr Gly Gln Phe His Asn Leu Ser Ile Lys Gly Thr Ile
370 375 380

Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385 390 395 400

Asn Pro Ser Gly Asp Asn Val Val Leu Pro Ala Leu Thr Gly Asn Leu
405 410 415

Ile Pro Asn Thr Lys Ser Asn Ala Leu Ile Asp Ala Lys Asn Thr Asp
420 425 430

Ile Lys Val Tyr Arg Val Asp Asn Ala Asn Asp Leu Ser Glu Ser Tyr
435 440 445

Tyr Val Asn Pro Ser Asp Phe Glu Asp Val Thr Asn Gln Val Arg Ile
450 455 460

Ser Phe Pro Asn Ala Asn Gln Tyr Lys Val Glu Phe Pro Thr Asp Asp
465 470 475 480

Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp
485 490 495

Pro Ala Ser Thr Gly Asp Leu Ala Leu Arg Ser Thr Phe Tyr Gly Tyr
500 505 510

Asp Ser Asn Phe Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala
515 520 525

Phe Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val
530 535 540

Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 71

<211> 1677
<212> DNA
<213> Staphylococcus aureus

<400> 71
atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt 180

agcgttagtg ctgcacctaa aacagacgac acaaacgtga gtgatactaa aacatcgtca 240

aacactaata atggcgaaac gagtgtggcg caaaatccag cacaacagga aacgacacaa 300

tcatcatcaa caaatgcaac tacggaagaa acgccggtaa ctggtgaagc tactactacg 360

acaacgaatc aagctaatac accggcaaca actcaatcaa gcaatacaaa tgcggaggaa 420

ttagtgaatc aaacaagtaa tgaaacgact tctaatgata ctaatacagt atcatctgta 480

aattcacctc aaaattctac aaatgcggaa aatgtttcaa caacgcaaga tacttcaact 540

gaagcaacac cttcaaacaa tgaatcagct ccacagaata cagatgcaag taataaagat 600

gtagttagtc aagcggttaa tccaagtacg cctagaatga gagcatttag tttagcggca 660

gtagctgcag atgcaccggc agctggcaca gatattacga atcagttgac agatgtgaaa 720

gttactattg actctggtac gactgtgtat ccgcaccaag caggttatgt caaactgaat 780

tatggttttt cagtgcctaa ttctcctgtt aaaggtgaca cattcaaaat aactgtacct 840

aaagaattaa acttaaatgg tgtaacttca actgctaaag tgccaccaat tatggctgga 900

gatcaagtat tggcaaatgg tgtaatcgat agtgatggta atgttattta tacatttaca 960

gactatgttg ataataaaga aaatgtaaca gctaatatta ctatgccagc ttatattgac 1020

cctgaaaatg ttacaaagac aggtaatgtg acattgacaa ctggcatagg aaccaatact 1080

gctagtaaga cagtattaat cgactatgag aaatatggac aattccataa tttatcaatt 1140

aaaggtacga ttgatcaaat cgataaaaca aataatacgt atcgccaaac aatttatgtc 1200

aatccaagcg gagataacgt tgtgttacct gccttaacag gtaatttaat tcctaataca 1260

aagagtaatg cgttaataga tgcaaaaaac actgatatta aagtttatag agtcgataat 1320

gctaatgatt tatctgaaag ttattatgtg aatcctagcg attttgaaga tgtaactaat 1380

caagttagaa tttcatttcc aaatgctaat caatacaaag tagaatttcc tacggacgat 1440

gaccaaatta caacaccgta tattgtagtt gttaatggcc atattgatcc tgctagtaca 1500

ggtgatttag cactacgttc gacattttat ggttatgatt ctaattttat atggagatct 1560

atgtcatggg acaacgaagt agcatttaat aacggatcag gttctggtga cggtatcgat 1620

aaaccagttg ttcctgaaca acctgatgag cctggtgaaa ttgaaccaat tccagag 1677

<210> 72
<211> 559
<212> PRT
<213> Staphylococcus aureus

<400> 72

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Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1               5                  10                  15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
            20                  25                  30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
        35                  40                  45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Ser Ala
    50                  55                  60

Ala Pro Lys Thr Asp Asp Thr Asn Val Ser Asp Thr Lys Thr Ser Ser
65                  70                  75                  80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
                85                  90                  95

Glu Thr Thr Gln Ser Ser Ser Thr Asn Ala Thr Thr Glu Glu Thr Pro
            100                 105                 110

Val Thr Gly Glu Ala Thr Thr Thr Thr Thr Asn Gln Ala Asn Thr Pro
        115                 120                 125

Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln
    130                 135                 140

Thr Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val
145                 150                 155                 160

Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln
                165                 170                 175

Asp Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln
            180                 185                 190

Asn Thr Asp Ala Ser Asn Lys Asp Val Val Ser Gln Ala Val Asn Pro
        195                 200                 205

Ser Thr Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
    210                 215                 220

Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asp Val Lys
225                 230                 235                 240

Val Thr Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr
                245                 250                 255

Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Pro Val Lys Gly
            260                 265                 270
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Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
        275                 280                 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
    290                 295                 300

Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305                 310                 315                 320

Asp Tyr Val Asp Asn Lys Glu Asn Val Thr Ala Asn Ile Thr Met Pro
                325                 330                 335

Ala Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu
            340                 345                 350

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

Tyr Glu Lys Tyr Gly Gln Phe His Asn Leu Ser Ile Lys Gly Thr Ile
    370                 375                 380

Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385                 390                 395                 400

Asn Pro Ser Gly Asp Asn Val Val Leu Pro Ala Leu Thr Gly Asn Leu
                405                 410                 415

Ile Pro Asn Thr Lys Ser Asn Ala Leu Ile Asp Ala Lys Asn Thr Asp
            420                 425                 430

Ile Lys Val Tyr Arg Val Asp Asn Ala Asn Asp Leu Ser Glu Ser Tyr
        435                 440                 445

Tyr Val Asn Pro Ser Asp Phe Glu Asp Val Thr Asn Gln Val Arg Ile
    450                 455                 460

Ser Phe Pro Asn Ala Asn Gln Tyr Lys Val Glu Phe Pro Thr Asp Asp
465                 470                 475                 480

Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp
                485                 490                 495

Pro Ala Ser Thr Gly Asp Leu Ala Leu Arg Ser Thr Phe Tyr Gly Tyr
            500                 505                 510

Asp Ser Asn Phe Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala
        515                 520                 525

Phe Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val
    530                 535                 540
```

Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 73
<211> 1677
<212> DNA
<213> Staphylococcus aureus

<400> 73
atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt 180

agcattaatg ctgcacctaa aacagacaac acaaacgtga gtgatactaa aacaacgtca 240

aacactaata atggcgaaac gagtgtggcg caaaatccag cacaacagga aacgacacaa 300

tcagcatcaa caaatgcaac tacggaagaa acgccggtaa ctggtgaaac tactactacg 360

gcaacgaatc aagctaatac accggcaaca actcaatcaa gcaatacaaa tgcggaggaa 420

ttagtgaatc aaacaagtaa tgaaacgact tctaatgata ctaatacagt atcatctgta 480

aattcacctc aaaattctac aaatgcggaa aatgtttcaa caacgcaaga tacttcaact 540

gaagcaacac cttcaaacaa tgaatcagct ccacagagta cagatgcaag taataaagat 600

gtagttaatc aagcggttaa tacaagtgcg cctagaatga gagcatttag tttagcggca 660

gtagctgcag atgcaccggc agctggcaca gatattacga atcagttgac agatgtgaaa 720

gttactattg actctggtac gactgtgtat ccgcaccaag caggttatgt caaactgaat 780

tatggttttt cagtgcctaa ttctgctgtt aaaggtgaca cattcaaaat aactgtacct 840

aaagaattaa acttaaatgg tgtaacttca actgctaaag tgccaccaat tatggctgga 900

gatcaagtat tggcaaatgg tgtaatcgat agtgatggta atgttattta tacatttaca 960

gactatgttg ataataaaga aaatgtaaca gctaatatta ctatgccagc ttatattgac 1020

cctgaaaatg ttacaaagac aggtaatgtg acattgacaa ctggcatagg aaccaatact 1080

gctagtaaga cagtattaat cgactatgag aaatatggac aattccataa tttatcaatt 1140

aaaggtacga ttgatcaaat cgataaaaca aataatacgt atcgccaaac aatttatgtc 1200

aatccaagcg gagataacgt tgtgttacct gccttaacag gtaatttaat tcctaataca 1260

aagagtaatg cgttaataga tgcaaaaaac actgatatta aagtttatag agtcgataat 1320

gctaatgatt tatctgaaag ttattatgtg aatcctagcg attttgaaga tgtaactaat 1380

caagttagaa tttcatttcc aaatgctaat caatacaaag tagaatttcc tacggacgat 1440

gaccaaatta caacaccgta tattgtagtt gttaatggcc atattgatcc tgctagtaca 1500

ggtgatttag cactacgttc gacattttat ggttatgatt ctaattttat atggagatct 1560

atgtcatggg acaacgaagt agcatttaat aacggatcag gttctggtga cggtatcgat 1620

aaaccagttg ttcctgaaca acctgatgag cctggtgaaa ttgaaccaat tccagag 1677

<210> 74

<211> 559
<212> PRT
<213> Staphylococcus aureus

<400> 74

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Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1               5                  10                  15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
            20                  25                  30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
        35                  40                  45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Ile Asn Ala
    50                  55                  60

Ala Pro Lys Thr Asp Asn Thr Asn Val Ser Asp Thr Lys Thr Thr Ser
65                  70                  75                  80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
                85                  90                  95

Glu Thr Thr Gln Ser Ala Ser Thr Asn Ala Thr Thr Glu Glu Thr Pro
            100                 105                 110

Val Thr Gly Glu Thr Thr Thr Thr Ala Thr Asn Gln Ala Asn Thr Pro
        115                 120                 125

Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln
    130                 135                 140

Thr Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val
145                 150                 155                 160

Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln
                165                 170                 175

Asp Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln
            180                 185                 190

Ser Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr
        195                 200                 205

Ser Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
    210                 215                 220

Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asp Val Lys
225                 230                 235                 240

Val Thr Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr
                245                 250                 255
```

Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly
260 265 270

Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
275 280 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
290 295 300

Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305 310 315 320

Asp Tyr Val Asp Asn Lys Glu Asn Val Thr Ala Asn Ile Thr Met Pro
325 330 335

Ala Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu
340 345 350

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

Tyr Glu Lys Tyr Gly Gln Phe His Asn Leu Ser Ile Lys Gly Thr Ile
370 375 380

Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385 390 395 400

Asn Pro Ser Gly Asp Asn Val Val Leu Pro Ala Leu Thr Gly Asn Leu
405 410 415

Ile Pro Asn Thr Lys Ser Asn Ala Leu Ile Asp Ala Lys Asn Thr Asp
420 425 430

Ile Lys Val Tyr Arg Val Asp Asn Ala Asn Asp Leu Ser Glu Ser Tyr
435 440 445

Tyr Val Asn Pro Ser Asp Phe Glu Asp Val Thr Asn Gln Val Arg Ile
450 455 460

Ser Phe Pro Asn Ala Asn Gln Tyr Lys Val Glu Phe Pro Thr Asp Asp
465 470 475 480

Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Asn Gly His Ile Asp
485 490 495

Pro Ala Ser Thr Gly Asp Leu Ala Leu Arg Ser Thr Phe Tyr Gly Tyr
500 505 510

Asp Ser Asn Phe Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala
515 520 525

Phe Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val
530 535 540

Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 75
<211> 1677
<212> DNA
<213> Staphylococcus aureus

<400> 75
atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggtttcgga ttacttagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt 180

agcgttaatg ctgcacctaa aacagacaac acaaacgtga gtgatactaa aacaacgtca 240

aacactaata atggcgaaac gagtgtggcg caaaatccag cacaacagga aacgatacaa 300

tcagcatcaa caaatgcaac tacggaagaa acaccggtaa ctggtgaagc tactactacg 360

gcaacgaagc aagctaatac accggcaaca actcaatcaa gcaatacaaa tgcggaggaa 420

ttagtgaatc aaacaagtaa tgaaacgact tctaatgata ctaatacagt atcatctgta 480

aattcacctc aaaattctac aaatgcggaa aatgtttcaa caacgcaaga tacttcaact 540

gaagcaacac cttcaaacaa tgaatcagct ccacagagta cagatgcaag taataaagat 600

gtagttaatc aagcggttaa tacaagtgcg cctagaatga gagcatttag tttagcggct 660

gtagctgcag atgcaccggc tgctggcaca gatattacga atcagttgac agatgtgaaa 720

gttactattg actctggtac gactgtgtat ccgcaccaag caggttatgt caaactgaat 780

tatggttttt cagtgcctaa ttctgctgtt aaaggtgaca cattcaaaat aactgtacct 840

aaagaattaa acttaaatgg tgtaacttca actgctaaag tgccaccaat tatggccgga 900

gatcaagtat tggcaaatgg tgtaatcgat agtgatggta atgttattta tacatttaca 960

gactatgtaa atactaaaga tgatgttaaa gcaactttga ccatgcccgc ttatattgac 1020

cctgaaaatg ttacaaagac aggtaatgtg acattggcta ctggcatagg tagtacaaca 1080

gcaaacaaaa cagtattagt agattatgaa aaatatggta agttttataa cttatctatt 1140

aaaggtacaa ttgaccaaat cgataaaaca aataatacgt atcgtcagac aatttatgtc 1200

aatccaagtg gagataacgt tattgcgccg gttttaacag gtaatttaaa accaaatacg 1260

gatagtaatg cattaataga tcagcaaaat acaagtatta aagtatataa agtagataat 1320

gcagctgatt tatctgaaag ttactttgtg aatccagaaa actttgagga tgtcactaat 1380

agtgtgaata ttacattccc aaatccaaat caatataaag tagagtttaa tacgcctgat 1440

gatcaaatta caacaccgta tattgtagtt gttaatggtc atattgatcc gaatagcaaa 1500

ggtgatttag ctttacgttc aactttatat gggtatgact caaggtttgt atggagatct 1560

atgtcatggg acaacgaagt agcatttaat aacggatcag gttctggtga cggtatcgat 1620

aaaccagttg ttcctgaaca acctgatgag cctggtgaaa ttgaaccaat tccagag 1677

<210> 76
<211> 559
<212> PRT
<213> Staphylococcus aureus

<400> 76
Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1 5 10 15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
20 25 30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
35 40 45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Asn Ala
50 55 60

Ala Pro Lys Thr Asp Asn Thr Asn Val Ser Asp Thr Lys Thr Thr Ser
65 70 75 80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
85 90 95

Glu Thr Ile Gln Ser Ala Ser Thr Asn Ala Thr Thr Glu Glu Thr Pro
100 105 110

Val Thr Gly Glu Ala Thr Thr Thr Ala Thr Lys Gln Ala Asn Thr Pro
115 120 125

Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln
130 135 140

Thr Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val
145 150 155 160

Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln
165 170 175

Asp Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln
180 185 190

Ser Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr
195 200 205

Ser Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
210 215 220

Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asp Val Lys
225 230 235 240

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Val Thr Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr
                245                 250                 255

Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly
            260                 265                 270

Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
        275                 280                 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
    290                 295                 300

Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305                 310                 315                 320

Asp Tyr Val Asn Thr Lys Asp Asp Val Lys Ala Thr Leu Thr Met Pro
                325                 330                 335

Ala Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu
            340                 345                 350

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

Tyr Glu Lys Tyr Gly Lys Phe Tyr Asn Leu Ser Ile Lys Gly Thr Ile
    370                 375                 380

Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385                 390                 395                 400

Asn Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu Thr Gly Asn Leu
                405                 410                 415

Lys Pro Asn Thr Asp Ser Asn Ala Leu Ile Asp Gln Gln Asn Thr Ser
            420                 425                 430

Ile Lys Val Tyr Lys Val Asp Asn Ala Ala Asp Leu Ser Glu Ser Tyr
        435                 440                 445

Phe Val Asn Pro Glu Asn Phe Glu Asp Val Thr Asn Ser Val Asn Ile
    450                 455                 460

Thr Phe Pro Asn Pro Asn Gln Tyr Lys Val Glu Phe Asn Thr Pro Asp
465                 470                 475                 480

Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp
                485                 490                 495

Pro Asn Ser Lys Gly Asp Leu Ala Leu Arg Ser Thr Leu Tyr Gly Tyr
            500                 505                 510
```

Asp Ser Arg Phe Val Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala
515 520 525

Phe Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val
530 535 540

Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 77
<211> 1677
<212> DNA
<213> Staphylococcus aureus

<400> 77
atgaatatga agaaacaaga aaaacacgca attcgtaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaaac ggaaaatacg agtaatgaga gcaaaagtaa tgattcgagt 180

agcgttaatg ctgcacctaa aacagacaac acaaacgtga gtgattctaa tacaacgaca 240

aacactaata gtgacgaaac gaatgtagcg caaaatccag cacaacagga aacgacacaa 300

tcagcatcaa caaatgcaac tacagaagaa acaccggtaa ctggtgaagt tactactacg 360

gcaacgaatc aagctaatac accggcaaca actcaatcaa gcaatacaaa tgcggaaaaa 420

tcagtgaatc aaacaagtaa tgaaacgact tctaatgata ctaatacagt atcatctgta 480

aattcacctc aaaattctac aaatgcggaa aatgtttcaa caacgcaaga tacttcaact 540

gaagcaaaac cttcaaacaa tgaatcagct ccacagagta cagatgcaag taataaagat 600

gtagttaatc aagcggttaa tacaagtgcg cctagaatga gagcatttag tttagcggct 660

gtagctgcag atgcaccggc tgctggcaca gatattacga atcagttgac gaatgtgaca 720

gttggtattg actctggaga tacagtttat ccgcaccaag caggctatgt caaactgaat 780

tatgggttct cagtacccaa ttctgcggtt caaggtgaca catttaaaat aactgtacct 840

aaagaattaa acttaaatgg tgtaacctca actgctaaag tgccaccaat tatggccgga 900

gatcaagtat tggcaaatgg tgtaatcgat agtgatggta atgttattta tacatttaca 960

gactatgtaa atactaaaga tgatgttaaa gcaacattaa ctgtgccggc ttatattgac 1020

cctgaatatg ttacacatac tggtaatgtg acattggcta ctggcatagg aaatacaaca 1080

gcaaacaaaa cagtattagt agattatgaa aaatatggta agttttataa cttatctatt 1140

aaaggtacaa ttgaccaaat cgataaaaca aataatacgt atcgtcagac aatttatgtc 1200

aatccaagtg gagataacgt tattgcaccg gttttaacag gtaatttaaa accaaatacg 1260

gaaagtaatg cattaataga tcagcaaaat acaagtatta aagtatataa agtagataat 1320

gcagctgatt tatctgaaag ttactttgtg aatccagaaa actttgagga tgtcactaat 1380

agtgtaaata ttacattccc aaatccaaat caatataaag tagagtttaa tacgcctgat 1440

gatcaaataa caacaccata tattgtagtt gttaatgggc atattgatcc taatagtaaa 1500

ggtgatttag ctttacgttc aactttatat ggatataatt cgaatataat ttggagatct 1560

atgtcatggg acaacgaagt agcatttaat aacggatcag gttctggtga cggtatcgat 1620

aaacctgttg ttcctgaaca acctgatgag cctggtgaaa ttgaaccaat tccagag 1677

<210> 78
<211> 559
<212> PRT
<213> Staphylococcus aureus

<400> 78

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Met Asn Met Lys Lys Gln Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1               5                  10                  15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
            20                  25                  30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Thr Glu
        35                  40                  45

Asn Thr Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Asn Ala
    50                  55                  60

Ala Pro Lys Thr Asp Asn Thr Asn Val Ser Asp Ser Asn Thr Thr Thr
65                  70                  75                  80

Asn Thr Asn Ser Asp Glu Thr Asn Val Ala Gln Asn Pro Ala Gln Gln
                85                  90                  95

Glu Thr Thr Gln Ser Ala Ser Thr Asn Ala Thr Thr Glu Glu Thr Pro
            100                 105                 110

Val Thr Gly Glu Val Thr Thr Thr Ala Thr Asn Gln Ala Asn Thr Pro
        115                 120                 125

Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Lys Ser Val Asn Gln
    130                 135                 140

Thr Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val
145                 150                 155                 160

Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln
                165                 170                 175

Asp Thr Ser Thr Glu Ala Lys Pro Ser Asn Asn Glu Ser Ala Pro Gln
            180                 185                 190

Ser Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr
        195                 200                 205

Ser Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
```

210 215 220

Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asn Val Thr
225 230 235 240

Val Gly Ile Asp Ser Gly Asp Thr Val Tyr Pro His Gln Ala Gly Tyr
245 250 255

Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Gln Gly
260 265 270

Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
275 280 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
290 295 300

Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305 310 315 320

Asp Tyr Val Asn Thr Lys Asp Asp Val Lys Ala Thr Leu Thr Val Pro
325 330 335

Ala Tyr Ile Asp Pro Glu Tyr Val Thr His Thr Gly Asn Val Thr Leu
340 345 350

Ala Thr Gly Ile Gly Asn Thr Thr Ala Asn Lys Thr Val Leu Val Asp
355 360 365

Tyr Glu Lys Tyr Gly Lys Phe Tyr Asn Leu Ser Ile Lys Gly Thr Ile
370 375 380

Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385 390 395 400

Asn Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu Thr Gly Asn Leu
405 410 415

Lys Pro Asn Thr Glu Ser Asn Ala Leu Ile Asp Gln Gln Asn Thr Ser
420 425 430

Ile Lys Val Tyr Lys Val Asp Asn Ala Ala Asp Leu Ser Glu Ser Tyr
435 440 445

Phe Val Asn Pro Glu Asn Phe Glu Asp Val Thr Asn Ser Val Asn Ile
450 455 460

Thr Phe Pro Asn Pro Asn Gln Tyr Lys Val Glu Phe Asn Thr Pro Asp
465 470 475 480

Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp

485 490 495

Pro Asn Ser Lys Gly Asp Leu Ala Leu Arg Ser Thr Leu Tyr Gly Tyr
500 505 510

Asn Ser Asn Ile Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala
515 520 525

Phe Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val
530 535 540

Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 79
<211> 1677
<212> DNA
<213> Staphylococcus aureus

<400> 79
atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt 180

agcgttagtg ctgcacctaa aacagacgac acaaacgtga gtgatactaa aacatcgtca 240

aacactaata atggcgaaac gagtgtggcg caaaatccag cacaacagga aacgacacaa 300

tcatcatcaa caaatgcaac tacggaagaa acgccggtaa ctggtgaagc tactactacg 360

acaacgaatc aagctaatac accggcaaca actcaatcaa gcaatacaaa tgcggaggaa 420

ttagtgaatc aaacaagtaa tgaaacgact tctaatgata ctaatacagt atcatctgta 480

aattcacctc aaaattctac aaatgcggaa aatgtttcaa caacgcaaga tacttcaact 540

gaagcaacac cttcaaacaa tgaatcagct ccacagagta cagatgcaag taataaagat 600

gtagttaatc aagcggttaa tacaagtgcg cctagaatga gagcatttag tttagcggca 660

gtagctgcag atgcaccggt agctggcaca gatattacga atcagttgac gaatgtgaca 720

gttggtattg actctggtac gactgtgtat ccgcaccaag caggttatgt caaactgaat 780

tatggttttt cagtgcctaa ttctgctgtt aaaggtgaca cattcaaaat aactgtacct 840

aaagaattaa acttaaatgg tgtaacttca actgctaaag tgccaccaat tatggctgga 900

gatcaagtat tggcaaatgg tgtaatcgat agtgatggta atgttattta tacatttaca 960

gactatgtaa atactaaaga tgatgtaaaa gcaactttga ccatgcccgc ttatattgac 1020

cctgaaaatg ttaaaaagac aggtaatgtg acattggcta ctggcatagg tagtacaaca 1080

gcaaacaaaa cagtattagt agattatgaa aaatatggta agttttataa cttatctatt 1140

aaaggtacaa ttgaccaaat cgataaaaca aataatacgt atcgtcagac aatttatgtc 1200

aatccaagtg gagataacgt tattgcgccg gttttaacag gtaatttaaa accaaatacg 1260

gatagtaatg cattaataga tcagcaaaat acaagtatta aagtatataa agtagataat 1320

gcagctgatt tatctgaaag ttactttgtg aatccagaaa actttgagga tgtcactaat 1380

agtgtgaata ttacattccc aaatccaaat caatataaag tagagtttaa tacgcctgat 1440

gatcaaatta caacaccgta tatagtagtt gttaatggtc atattgatcc gaatagcaaa 1500

ggtgatttag ctttacgttc aactttatat gggtataact cgaatataat ttggcgctct 1560

atgtcatggg acaacgaagt agcatttaat aacggatcag gttctggtga cggtatcgat 1620

aaaccagttg ttcctgaaca acctgatgag cctggtgaaa ttgaaccaat tccagag 1677

<210> 80
<211> 559
<212> PRT
<213> Staphylococcus aureus

<400> 80

Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1 5 10 15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
20 25 30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
35 40 45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Ser Ala
50 55 60

Ala Pro Lys Thr Asp Asp Thr Asn Val Ser Asp Thr Lys Thr Ser Ser
65 70 75 80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
85 90 95

Glu Thr Thr Gln Ser Ser Ser Thr Asn Ala Thr Thr Glu Glu Thr Pro
100 105 110

Val Thr Gly Glu Ala Thr Thr Thr Thr Thr Asn Gln Ala Asn Thr Pro
115 120 125

Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln
130 135 140

Thr Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val
145 150 155 160

Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln
165 170 175

Asp Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln
180 185 190

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Ser Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr
        195                 200                 205

Ser Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
    210                 215                 220

Ala Pro Val Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asn Val Thr
225                 230                 235                 240

Val Gly Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr
                245                 250                 255

Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly
            260                 265                 270

Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
        275                 280                 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
    290                 295                 300

Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305                 310                 315                 320

Asp Tyr Val Asn Thr Lys Asp Asp Val Lys Ala Thr Leu Thr Met Pro
                325                 330                 335

Ala Tyr Ile Asp Pro Glu Asn Val Lys Lys Thr Gly Asn Val Thr Leu
            340                 345                 350

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

Tyr Glu Lys Tyr Gly Lys Phe Tyr Asn Leu Ser Ile Lys Gly Thr Ile
    370                 375                 380

Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385                 390                 395                 400

Asn Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu Thr Gly Asn Leu
                405                 410                 415

Lys Pro Asn Thr Asp Ser Asn Ala Leu Ile Asp Gln Gln Asn Thr Ser
            420                 425                 430

Ile Lys Val Tyr Lys Val Asp Asn Ala Ala Asp Leu Ser Glu Ser Tyr
        435                 440                 445

Phe Val Asn Pro Glu Asn Phe Glu Asp Val Thr Asn Ser Val Asn Ile
    450                 455                 460
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```
Thr Phe Pro Asn Pro Asn Gln Tyr Lys Val Glu Phe Asn Thr Pro Asp
465                 470                 475                 480

Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp
                485                 490                 495

Pro Asn Ser Lys Gly Asp Leu Ala Leu Arg Ser Thr Leu Tyr Gly Tyr
            500                 505                 510

Asn Ser Asn Ile Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala
        515                 520                 525

Phe Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val
    530                 535                 540

Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545                 550                 555
```

<210> 81
<211> 1677
<212> DNA
<213> Staphylococcus aureus

<400> 81

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atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca     60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt    120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt    180

agcgttagtg ctgcacctaa aacagacgac acaaacgtga gtgatactaa aacatcgtca    240

aacactaata atggcgaaac gagtgtggcg caaaatccag cacaacagga aacgacacaa    300

tcatcatcaa caaatgcaac tacggaagaa acgccggtaa ctggtgaagc tactactacg    360

acaacgaatc aagctaatac accggcaaca actcaatcaa gcaatacaaa tgcggaggaa    420

ttagtgaatc aaacaagtaa tgaaacgact tttaatgata ctaatacagt atcatctgta    480

aattcacctc aaaattctac aaatgcggaa aatgtttcaa caacgcaaga tacttcaact    540

gaagcaacac cttcaaacaa tgaatcagct ccacagagta cagatgcaag taataaagat    600

gtagttaatc aagcggttaa tacaagtgcg cctagaatga gagcatttag tttagcggca    660

gtagctgcag atgcaccggc agctggcaca gatattacga atcagttgac gaatgtgaca    720

gttggtattg actctggtac gactgtgtat ccgcaccaag caggttatgt caaactgaat    780

tatggttttt cagtgcctaa ttctgctgtt aaaggtgaca cattcaaaat aactgtacct    840

aaagaattaa acttaaatgg tgtaacttca actgctaaag tgccaccaat tatggctgga    900

gatcaagtat tggcaaatgg tgtaatcgat agtgatggta atgttattta tacatttaca    960

gactatgtaa atactaaaga tgatgtaaaa gcaactttga ccatgcccgc ttatattgac   1020

cctgaaaatg ttaaaaagac aggtaatgtg acattggcta ctggcatagg tagtacaaca   1080

gcaaacaaaa cagtattagt agattatgaa aaatatggta agttttataa cttatctatt   1140
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aaaggtacaa ttgaccaaat cgataaaaca aataatacgt atcgtcagac aatttatgtc 1200

aatccaagtg gagataacgt tattgcgccg gttttaacag gtaatttaaa accaaatacg 1260

gatagtaatg cattaataga tcagcaaaat acaagtatta aagtatataa agtagataat 1320

gcagctgatt tatctgaaag ttactttgtg aatccagaaa actttgagga tgtcactaat 1380

agtgtgaata ttacattccc aaatccaaat caatataaag tagagtttaa tacgcctgat 1440

gatcaaatta caacaccgta tatagtagtt gttaatggtc atattgatcc gaatagcaaa 1500

ggtgatttag ctttacgttc aactttatat gggtataact cgaatataat ttggcgctct 1560

atgtcatggg acaacgaagt agcatttaat aacggatcag gttctggtga cggtatcgat 1620

aaaccagttg ttcctgaaca acctgatgag cctggtgaaa ttgaaccaat tccagag 1677

<210> 82
<211> 559
<212> PRT
<213> Staphylococcus aureus

<400> 82

Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1 5 10 15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
20 25 30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
35 40 45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Ser Ala
50 55 60

Ala Pro Lys Thr Asp Asp Thr Asn Val Ser Asp Thr Lys Thr Ser Ser
65 70 75 80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
85 90 95

Glu Thr Thr Gln Ser Ser Ser Thr Asn Ala Thr Thr Glu Glu Thr Pro
100 105 110

Val Thr Gly Glu Ala Thr Thr Thr Thr Thr Asn Gln Ala Asn Thr Pro
115 120 125

Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln
130 135 140

Thr Ser Asn Glu Thr Thr Phe Asn Asp Thr Asn Thr Val Ser Ser Val
145 150 155 160

Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln
165 170 175

```
Asp Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln
            180                 185                 190

Ser Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr
        195                 200                 205

Ser Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
    210                 215                 220

Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asn Val Thr
225                 230                 235                 240

Val Gly Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr
                245                 250                 255

Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly
            260                 265                 270

Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
        275                 280                 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
    290                 295                 300

Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305                 310                 315                 320

Asp Tyr Val Asn Thr Lys Asp Asp Val Lys Ala Thr Leu Thr Met Pro
                325                 330                 335

Ala Tyr Ile Asp Pro Glu Asn Val Lys Lys Thr Gly Asn Val Thr Leu
            340                 345                 350

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

Tyr Glu Lys Tyr Gly Lys Phe Tyr Asn Leu Ser Ile Lys Gly Thr Ile
    370                 375                 380

Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385                 390                 395                 400

Asn Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu Thr Gly Asn Leu
                405                 410                 415

Lys Pro Asn Thr Asp Ser Asn Ala Leu Ile Asp Gln Gln Asn Thr Ser
            420                 425                 430

Ile Lys Val Tyr Lys Val Asp Asn Ala Ala Asp Leu Ser Glu Ser Tyr
        435                 440                 445
```

Phe Val Asn Pro Glu Asn Phe Glu Asp Val Thr Asn Ser Val Asn Ile
450 455 460

Thr Phe Pro Asn Pro Asn Gln Tyr Lys Val Glu Phe Asn Thr Pro Asp
465 470 475 480

Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp
485 490 495

Pro Asn Ser Lys Gly Asp Leu Ala Leu Arg Ser Thr Leu Tyr Gly Tyr
500 505 510

Asn Ser Asn Ile Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala
515 520 525

Phe Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val
530 535 540

Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 83
<211> 1674
<212> DNA
<213> Staphylococcus aureus

<400> 83
atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt 180

agcgttagtg ctgcacctaa aacagacgac acaaacgtga gtgatactaa aacatcgtca 240

aacactaata atggcgaaac gagtgtggcg caaaatccag cacaacagga aacgacacaa 300

tcagcattaa caaatgcaac tacggaagaa actccggtaa ctggtgaagc tactacggca 360

acgaatcaag ctaatacacc ggcaacaact caatcaagca atacaaatgc ggaggaatta 420

gtgaatcaaa caagtaatga aacgacttct aatgatacta atacagtatc atctgtaaat 480

tcacctcaaa attctacaaa tgcggaaaat gtttcaacaa cgcaagatac ttcaactgaa 540

gcaacacctt caaacaatga atcagctcca cagagtacag atgcaagtaa taaagatgta 600

gttaatcaag cggttaatac aagtgcgcct agaatgagag catttagttt atcggcagta 660

gctgcagatg caccggcagc tggcaaagat attacgaatc agttgacgaa tgtgacagtt 720

ggtattgact ctggagatac agtttatccg caccaagcag gctatgtcaa actgaattat 780

ggtttttcag tgcctaattc tgctgttaaa ggtgacacat tcaaaataac tgtacctaaa 840

gaattaaact taaatggtgt aacttcaact gctaaagtgc ctccaattat ggccggagat 900

caagtattgg caaatggtgt aatcgatagt gatggtaatg ttatttatac atttacagac 960

tatgttgata ctaaagaaaa tgtaacagct aatattacta tgccagctta tattgaccct 1020

gaaaatgtta caaagacagg taatgtaaca ttgacaactg gcataggtag tacaacagca 1080

aacaaaacag tattagtaga ttatgaaaaa tatggtaagt tttataactt atctattaaa 1140

ggtacaattg accaaatcga taaaacaaat aatacgtatc gtcagacaat ttatgtcaat 1200

ccaagtggag ataatgttat tgcgccggtt ttaacaggta atttaaaacc aaatacggat 1260

agtaatgcat taatagatca gcaaaataca agtattaaag tatataaagt agataatgca 1320

gctgatttat ctgaaagtta ctttgtgaat ccagaaaact ttgaggatgt cactaatagt 1380

gtgaatatta cattcccaaa tccaaatcaa tataaagtag agtttaatac gcctgatgat 1440

caaattacaa caccgtatat tgtagttgtt aatggtcata ttgatccgaa tagcaaaggt 1500

gatttagctt tacgttcaac tttatatgga tatgactcaa ggtttgtatg gagatctatg 1560

tcatgggaca acgaagtagc atttaataac ggatcaggtt ctggtgacgg tatcgataaa 1620

ccagttgttc ctgaacaacc tgatgagcct ggtgaaattg aaccaattcc agag 1674

<210> 84
<211> 558
<212> PRT
<213> Staphylococcus aureus

<400> 84

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Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1               5                  10                  15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
            20                  25                  30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
        35                  40                  45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Ser Ala
    50                  55                  60

Ala Pro Lys Thr Asp Asp Thr Asn Val Ser Asp Thr Lys Thr Ser Ser
65                  70                  75                  80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
                85                  90                  95

Glu Thr Thr Gln Ser Ala Leu Thr Asn Ala Thr Thr Glu Glu Thr Pro
            100                 105                 110

Val Thr Gly Glu Ala Thr Thr Ala Thr Asn Gln Ala Asn Thr Pro Ala
        115                 120                 125

Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln Thr
    130                 135                 140

Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val Asn
145                 150                 155                 160
```

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Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln Asp
                165                 170                 175

Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln Ser
            180                 185                 190

Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr Ser
        195                 200                 205

Ala Pro Arg Met Arg Ala Phe Ser Leu Ser Ala Val Ala Ala Asp Ala
    210                 215                 220

Pro Ala Ala Gly Lys Asp Ile Thr Asn Gln Leu Thr Asn Val Thr Val
225                 230                 235                 240

Gly Ile Asp Ser Gly Asp Thr Val Tyr Pro His Gln Ala Gly Tyr Val
                245                 250                 255

Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly Asp
            260                 265                 270

Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val Thr
        275                 280                 285

Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu Ala
    290                 295                 300

Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr Asp
305                 310                 315                 320

Tyr Val Asp Thr Lys Glu Asn Val Thr Ala Asn Ile Thr Met Pro Ala
                325                 330                 335

Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu Thr
            340                 345                 350

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

Glu Lys Tyr Gly Lys Phe Tyr Asn Leu Ser Ile Lys Gly Thr Ile Asp
    370                 375                 380

Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val Asn
385                 390                 395                 400

Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu Thr Gly Asn Leu Lys
                405                 410                 415

Pro Asn Thr Asp Ser Asn Ala Leu Ile Asp Gln Gln Asn Thr Ser Ile
            420                 425                 430
```

Lys Val Tyr Lys Val Asp Asn Ala Ala Asp Leu Ser Glu Ser Tyr Phe
435 440 445

Val Asn Pro Glu Asn Phe Glu Asp Val Thr Asn Ser Val Asn Ile Thr
450 455 460

Phe Pro Asn Pro Asn Gln Tyr Lys Val Glu Phe Asn Thr Pro Asp Asp
465 470 475 480

Gln Ile Thr Thr Pro Tyr Ile Val Val Asn Gly His Ile Asp Pro
485 490 495

Asn Ser Lys Gly Asp Leu Ala Leu Arg Ser Thr Leu Tyr Gly Tyr Asp
500 505 510

Ser Arg Phe Val Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala Phe
515 520 525

Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val Pro
530 535 540

Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 85
<211> 1674
<212> DNA
<213> Staphylococcus aureus

<400> 85
atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt 180

agcgttagtg ctgcacctaa aacagacgac acaaacgtga gtgatactaa aacatcgtca 240

aacactaata atggcgaaac gagtgtggcg caaaatccag cacaacagga aacgacacaa 300

tcagcattaa caaatgcaac tacggaagaa actccgttaa ctggtgaagc tactacggca 360

acgaatcaag ctaatacacc ggcaacaact caatcaagca atacaaatgc ggaggaatta 420

gtgaatcaaa caagtaatga aacgacttct aatgatacta atacagtatc atctgtaaat 480

tcacctcaaa attctacaaa tgcggaaaat gtttcaacaa cgcaagatac ttcaactgaa 540

gcaacacctt caaacaatga atcagctcca cagagtacag atgcaagtaa taaagatgta 600

gttaatcaag cggttaatac aagtgcgcct agaatgagag catttagttt agcggcagta 660

gctgcagatg caccggcagc tggcacagat attacgaatc agttgacaga tgtgaaagtt 720

actattgact ctggtacgac tgtgtatccg caccaagcag gttatgtcaa actgaattat 780

ggtttttcag tgcctaattc tgctgttaaa ggtgacacat tcaaaataac tgtacctaaa 840

gaattaaact taaatggtgt aacttcaact gctaaagtgc ctccaattat ggccggagat 900

caagtattgg caaatggtgt aatcgatagt gatggtaatg ttatttatac atttacagac 960

tatgttgata ctaaaaatga tgttaaagca acactaactg tgcctgcata cattgatcca 1020

gaaaatgtta caaagacggg taatgtaaca ttgaaaactg gcataggaac caatactgat 1080

agtaagacag ttttaatcga ctatgagaaa tatggacaat tccataattt atcaattaaa 1140

ggtacgattg atcaaatcga taaaacaaat aatacgtatc gtcaaacaat ttatgtcaat 1200

ccaagcggag ataacgttgt gttacctgcc ttaacaggta atttaattcc taatacaaag 1260

agtaatgcgt taatagatgc aaaaaacact gatattaaag tttatagagt agataatgct 1320

aatgatttat ctgaaagtta ttatgtgaat cctagcgatt ttgaagatgt aactaatcaa 1380

gttagaattt catttccaaa tgctaatcaa tacaaagtag aatttcctac ggacgatgat 1440

caaattacaa caccgtatat tgtagttgtt aatggccata ttgatcctgc tagcacaggt 1500

gatttagcac tacgttcgac attttatggt tatgattcta attttatatg gagatctatg 1560

tcatgggaca acgaagtagc atttaataac ggatcaggtt caggtgacgg tatcgataaa 1620

cctgttgttc ctgaacaacc tgatgagcct ggtgaaattg aaccaattcc agag 1674

<210> 86
<211> 558
<212> PRT
<213> Staphylococcus aureus

<400> 86

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Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1               5                  10                  15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
            20                  25                  30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
        35                  40                  45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Ser Ala
    50                  55                  60

Ala Pro Lys Thr Asp Asp Thr Asn Val Ser Asp Thr Lys Thr Ser Ser
65                  70                  75                  80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
                85                  90                  95

Glu Thr Thr Gln Ser Ala Leu Thr Asn Ala Thr Thr Glu Glu Thr Pro
            100                 105                 110

Leu Thr Gly Glu Ala Thr Thr Ala Thr Asn Gln Ala Asn Thr Pro Ala
        115                 120                 125

Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln Thr
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130 135 140

Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val Asn
145 150 155 160

Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln Asp
165 170 175

Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln Ser
180 185 190

Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr Ser
195 200 205

Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp Ala
210 215 220

Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asp Val Lys Val
225 230 235 240

Thr Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr Val
245 250 255

Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly Asp
260 265 270

Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val Thr
275 280 285

Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu Ala
290 295 300

Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr Asp
305 310 315 320

Tyr Val Asp Thr Lys Asn Asp Val Lys Ala Thr Leu Thr Val Pro Ala
325 330 335

Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu Lys
340 345 350

Thr Gly Ile Gly Thr Asn Thr Asp Ser Lys Thr Val Leu Ile Asp Tyr
355 360 365

Glu Lys Tyr Gly Gln Phe His Asn Leu Ser Ile Lys Gly Thr Ile Asp
370 375 380

Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val Asn
385 390 395 400

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

405 410 415

Pro Asn Thr Lys Ser Asn Ala Leu Ile Asp Ala Lys Asn Thr Asp Ile
420 425 430

Lys Val Tyr Arg Val Asp Asn Ala Asn Asp Leu Ser Glu Ser Tyr Tyr
435 440 445

Val Asn Pro Ser Asp Phe Glu Asp Val Thr Asn Gln Val Arg Ile Ser
450 455 460

Phe Pro Asn Ala Asn Gln Tyr Lys Val Glu Phe Pro Thr Asp Asp Asp
465 470 475 480

Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp Pro
485 490 495

Ala Ser Thr Gly Asp Leu Ala Leu Arg Ser Thr Phe Tyr Gly Tyr Asp
500 505 510

Ser Asn Phe Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala Phe
515 520 525

Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val Pro
530 535 540

Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 87
<211> 1674
<212> DNA
<213> Staphylococcus aureus

<400> 87
atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt 180

agcgttaatg ctgcacctaa aacagacaac acaaacgtga gtgatactaa aacaacgtca 240

aacactaata atggcgaaac gagtgtggcg caatatctag cacaacagga aacgacacaa 300

tcagtatcaa caaatgcaac tacggaagaa acaccggtaa ctggtgaagc tactacggca 360

acgaatcaag ctaatacacc ggcaacaact caatcaagca atacaaatgc ggaggaatta 420

gtgaatcaaa caagtaatga aacgacttct aatgatacta atacagtatc atctgtaaat 480

tcacctcaaa attctacaaa tgcggaaaat gtttcaacaa cgcaagatac ttcaactgaa 540

gcaacacctt caaacaatga atcagctcca cagagtacag atgcaagtaa taaagatgta 600

gttaatcaag cggttaatac aagtgcgcct agaatgagag catttagttt agcggctgta 660

gctgcagatg caccggcagc tggcacagat attacgaatc agttgacgaa tgtgacagtt 720

ggtattgact ctggtacgac tgtgtatccg caccaagcag gttatgtcaa actgaattat 780

ggtttttcag tgcctaattc tgctgttaaa ggtgacacat tcaaaataac tgtacctaaa 840

gaattaaact taaatggtgt aacttcaact gctaaagtgc ctccaattat ggctggagat 900

caagtattgg caaatggtgt aatcgataat gatggtaatg ttatttatac atttacagac 960

tatgtaaata ctaaagatga tgttaaagca actttgacta tgcccgctta tattgaccct 1020

gaaaatgtta caaagacagg taatgtgaca ttggctactg gcataggtag tacaacagca 1080

aacaaaacag tattagtaga ttatgaaaaa tatggtaagt tttataactt atctattaaa 1140

ggtacaattg accaaatcga taaaacaaat aatacgtatc gtcagacaat ttatgtcaat 1200

ccaagtggag ataacgttat tgcgccggtt ttaacaggta atttaaaacc aaatacggat 1260

agtaatgcat taatagatca gcaaaataca agtattaaag tatataaagt agataatgca 1320

gctgatttat ctgaaagtta ctttgtgaat ccagaaaact ttgaggatgt cactaatagt 1380

gtgaatatta cattcccaaa tccaaatcaa tataaagtag agtttccaac agacgatgat 1440

caaattacaa caccgtatat tgtagttgtt aatggtcata ttgatccgaa tagcaaaggt 1500

gatttagctt tacgttcaac tttatatggg tataactcga atataatttg gcgctctatg 1560

tcatgggaca acgaagtagc atttaataac ggatcaggtt ctggtgacgg tatcgataaa 1620

cctgttgttc ctgaacaacc tgatgagcct ggtgaaattg aaccaattcc agag 1674

<210> 88
<211> 558
<212> PRT
<213> Staphylococcus aureus

<400> 88

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Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1               5                   10                  15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
            20                  25                  30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
        35                  40                  45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Asn Ala
    50                  55                  60

Ala Pro Lys Thr Asp Asn Thr Asn Val Ser Asp Thr Lys Thr Thr Ser
65                  70                  75                  80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Tyr Leu Ala Gln Gln
                85                  90                  95

Glu Thr Thr Gln Ser Val Ser Thr Asn Ala Thr Thr Glu Glu Thr Pro
            100                 105                 110
```

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Val Thr Gly Glu Ala Thr Thr Ala Thr Asn Gln Ala Asn Thr Pro Ala
        115                 120                 125

Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln Thr
    130                 135                 140

Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val Asn
145                 150                 155                 160

Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln Asp
                165                 170                 175

Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln Ser
            180                 185                 190

Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr Ser
        195                 200                 205

Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp Ala
    210                 215                 220

Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asn Val Thr Val
225                 230                 235                 240

Gly Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr Val
                245                 250                 255

Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly Asp
            260                 265                 270

Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val Thr
        275                 280                 285

Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu Ala
    290                 295                 300

Asn Gly Val Ile Asp Asn Asp Gly Asn Val Ile Tyr Thr Phe Thr Asp
305                 310                 315                 320

Tyr Val Asn Thr Lys Asp Asp Val Lys Ala Thr Leu Thr Met Pro Ala
                325                 330                 335

Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu Ala
            340                 345                 350

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

Glu Lys Tyr Gly Lys Phe Tyr Asn Leu Ser Ile Lys Gly Thr Ile Asp
    370                 375                 380
```

Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val Asn
385 390 395 400

Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu Thr Gly Asn Leu Lys
405 410 415

Pro Asn Thr Asp Ser Asn Ala Leu Ile Asp Gln Gln Asn Thr Ser Ile
420 425 430

Lys Val Tyr Lys Val Asp Asn Ala Ala Asp Leu Ser Glu Ser Tyr Phe
435 440 445

Val Asn Pro Glu Asn Phe Glu Asp Val Thr Asn Ser Val Asn Ile Thr
450 455 460

Phe Pro Asn Pro Asn Gln Tyr Lys Val Glu Phe Pro Thr Asp Asp Asp
465 470 475 480

Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp Pro
485 490 495

Asn Ser Lys Gly Asp Leu Ala Leu Arg Ser Thr Leu Tyr Gly Tyr Asn
500 505 510

Ser Asn Ile Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala Phe
515 520 525

Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val Pro
530 535 540

Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 89
<211> 1674
<212> DNA
<213> Staphylococcus aureus

<400> 89
atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt 180

agcgttagtg ctgcacctaa aacagacgac acaaacgtga gtgatactaa aacatcgtca 240

aacactaata atggcgaaac gagtgtggcg caaaatccag cacaacagga aacgacacaa 300

tcagcattaa caaatgcaac tacggaagaa actccggtaa ctggtgaagc tactacggca 360

acgaatcaag ctaatacacc ggcaacaact caatcaagca atacaaatgc ggaggaatta 420

gtgaatcaaa caagtaatga aacgacttct aatgatacta atacagtatc atctgtaaat 480

tcacctcaaa attctacaaa tgcggaaaat gtttcaacaa cgcaagatac ttcaactgaa 540

gcaacacctt caaacaatga atcagctcca cagaatacag atgcaagtaa taaagatgta 600

gttaatcaag cggttaatac aagtgcgcct agaaagagag catttagttt agcggctgta 660

gctgcagatg caccggcagc tggcacagat attacgaatc agttgacaga tgtgaaagtt 720

actattgact ctggtacgac tgtgtatccg caccaagcag gttatgtcaa actgaattat 780

ggtttttcag tgcctaattc tgctgttaaa ggtgacacat tcaaaataac tgtacctaaa 840

gaattaaact taaatggtgt aacttcaact gctaaagtgc caccaattat ggctggagat 900

caagtattgg caaatggtgt aatcgatagt gatggtaatg ttatttatac atttacagac 960

tatgttgata ataaagaaaa tgtaacagct aatattacta tgccagctta tattgaccct 1020

gaaaatgtta caaagacagg taatgtgaca ttgacaactg gcataggaac caatactgct 1080

agtaagacag tattaatcga ctatgagaaa tatggacaat tccataattt atcaattaaa 1140

ggtacgattg atcaaatcga taaaacaaat aatacgtatc gccaaacaat ttatgtcaat 1200

ccaagcggag ataacgttgt gttacctgcc ttaacaggta atttaattcc taatacaaag 1260

agtaatgcgt taatagatgc aaaaaacact gatattaaag tttatagagt cgataatgct 1320

aatgatttat ctgaaagtta ttatgtgaat cctagcgatt ttgaagatgt aactaatcaa 1380

gttagaattt catttccaaa tgctaatcaa tacaaagtag aatttcctac ggacgatgac 1440

caaattacaa caccgtatat tgtagttgtt aatggccata ttgatcctgc tagtacaggt 1500

gatttagcac tacgttcgac attttatggt tatgattcta attttatatg gagatctatg 1560

tcatgggaca acgaagtagc atttaataac ggatcaggtt ctggtgacgg tatcgataaa 1620

ccagttgttc ctgaacaacc tgatgagcct ggtgaaattg aaccaattcc agag 1674

<210> 90
<211> 558
<212> PRT
<213> Staphylococcus aureus

<400> 90

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Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1               5                  10                  15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
            20                  25                  30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
        35                  40                  45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Ser Ala
    50                  55                  60

Ala Pro Lys Thr Asp Asp Thr Asn Val Ser Asp Thr Lys Thr Ser Ser
65                  70                  75                  80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
                85                  90                  95
```

```
Glu Thr Thr Gln Ser Ala Leu Thr Asn Ala Thr Thr Glu Glu Thr Pro
            100                 105                 110

Val Thr Gly Glu Ala Thr Thr Ala Thr Asn Gln Ala Asn Thr Pro Ala
        115                 120                 125

Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln Thr
    130                 135                 140

Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val Asn
145                 150                 155                 160

Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln Asp
                165                 170                 175

Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln Asn
            180                 185                 190

Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr Ser
        195                 200                 205

Ala Pro Arg Lys Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp Ala
    210                 215                 220

Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asp Val Lys Val
225                 230                 235                 240

Thr Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr Val
                245                 250                 255

Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly Asp
            260                 265                 270

Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val Thr
        275                 280                 285

Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu Ala
    290                 295                 300

Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr Asp
305                 310                 315                 320

Tyr Val Asp Asn Lys Glu Asn Val Thr Ala Asn Ile Thr Met Pro Ala
                325                 330                 335

Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu Thr
            340                 345                 350

Thr Gly Ile Gly Thr Asn Thr Ala Ser Lys Thr Val Leu Ile Asp Tyr
        355                 360                 365
```

```
Glu Lys Tyr Gly Gln Phe His Asn Leu Ser Ile Lys Gly Thr Ile Asp
    370                 375                 380

Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val Asn
385                 390                 395                 400

Pro Ser Gly Asp Asn Val Val Leu Pro Ala Leu Thr Gly Asn Leu Ile
                405                 410                 415

Pro Asn Thr Lys Ser Asn Ala Leu Ile Asp Ala Lys Asn Thr Asp Ile
            420                 425                 430

Lys Val Tyr Arg Val Asp Asn Ala Asn Asp Leu Ser Glu Ser Tyr Tyr
        435                 440                 445

Val Asn Pro Ser Asp Phe Glu Asp Val Thr Asn Gln Val Arg Ile Ser
    450                 455                 460

Phe Pro Asn Ala Asn Gln Tyr Lys Val Glu Phe Pro Thr Asp Asp Asp
465                 470                 475                 480

Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp Pro
                485                 490                 495

Ala Ser Thr Gly Asp Leu Ala Leu Arg Ser Thr Phe Tyr Gly Tyr Asp
            500                 505                 510

Ser Asn Phe Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala Phe
        515                 520                 525

Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val Pro
    530                 535                 540

Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545                 550                 555
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<210> 91
<211> 1674
<212> DNA
<213> Staphylococcus aureus

<400> 91

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atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca     60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt    120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt    180

agcgttagtg ctgcacctaa aacagacgac acaaacgtga gtgatactaa aacatcgtca    240

aacactaata atggcgaaac gagtgtggcg caaaatccag cacaacagga aacgacacaa    300

tcatcattaa caaatgcaac tacggaagaa actccggtaa ctggtgaagc tactacggca    360

acgaatcaag ctaatacacc ggcaacaact caatcaagca atacaaatgc ggaggaatta    420
```

gtgaatcaaa caagtaatga aacgacttct aatgatacta atacagtatc atctgtaaat 480

tcacctcaaa attctacaaa tgcggaaaat gtttcaacaa cgcaagatac ttcaactgaa 540

gcaacacctt caaacaatga atcagctcca cagagtacag atgcaagtaa taaagattta 600

gttaatcaag cggttaatac aagtgcgcct agaatgagag catttagttt agcggcagta 660

gctgcagatg cacctgcagc tggcacagat attacgaatc agttgacaga tgttaaagtt 720

actattgact ctggtacgac tgtgtatccg caccaagcag gttatgtcaa actgaattat 780

ggtttttcag tgcctaattc tgctgttaaa ggtgacacat tcaaaataac tgtacctaaa 840

gaattaaact taaatggtgt aacttcaact gctaaagtgc caccaattat ggctggagat 900

caagtattgg caaatggtgt aatcgatagt gatggtaatg ttatttatac atttacagac 960

tatgttgata ataaaaacga tgttaaagca actttgacca tgcccgctta tattgatcca 1020

gaaaatgtaa cgaaaacagg taatgtaaca ttgacaactg gcataggtag tacaacagca 1080

aacaaaacag tattagtaga ttatgaaaaa tatggtaagt tttataactt atctattaaa 1140

ggtacaattg accaaatcga taaaacaaat aatacgtatc gtcagacaat ttatgtcaat 1200

ccaagtggag ataacgttat tgcgccggtt ttaacaggta atttaaaacc aaatacggat 1260

agtaatgcat taatagatca gcaaaataca agtattaaag tatataaagt agataatgca 1320

gctgatttat ctgaaagtta ctttgtaaat ccagaaaact ttgaggatgt cactaatagt 1380

gtgaatatta cattcccaaa tccaaatcaa tataaagtag agtttaatac gcctgatgat 1440

caaattacaa caccgtatat tgtagttgtt aatggtcata ttgatccgaa tagcaaaggt 1500

gatttagctt tacgttcaac tttatatggg tataactcga atataatttg gcgctctatg 1560

tcatgggaca acgaagtagc atttaataac ggatcaggtt ctggtgacgg tatcgataaa 1620

cctgttgtcc ctgaacaacc tgatgagcct ggtgaaattg aaccaattcc agag 1674

<210> 92
<211> 558
<212> PRT
<213> Staphylococcus aureus

<400> 92

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Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1               5                  10                  15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
            20                  25                  30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
        35                  40                  45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Ser Ala
    50                  55                  60

Ala Pro Lys Thr Asp Asp Thr Asn Val Ser Asp Thr Lys Thr Ser Ser
65                  70                  75                  80
```

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Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
                85                  90                  95

Glu Thr Thr Gln Ser Ser Leu Thr Asn Ala Thr Thr Glu Glu Thr Pro
            100                 105                 110

Val Thr Gly Glu Ala Thr Thr Ala Thr Asn Gln Ala Asn Thr Pro Ala
        115                 120                 125

Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln Thr
    130                 135                 140

Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val Asn
145                 150                 155                 160

Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln Asp
                165                 170                 175

Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln Ser
            180                 185                 190

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

Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp Ala
    210                 215                 220

Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asp Val Lys Val
225                 230                 235                 240

Thr Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr Val
                245                 250                 255

Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly Asp
            260                 265                 270

Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val Thr
        275                 280                 285

Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu Ala
    290                 295                 300

Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr Asp
305                 310                 315                 320

Tyr Val Asp Asn Lys Asn Asp Val Lys Ala Thr Leu Thr Met Pro Ala
                325                 330                 335

Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu Thr
            340                 345                 350
```

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

Glu Lys Tyr Gly Lys Phe Tyr Asn Leu Ser Ile Lys Gly Thr Ile Asp
370 375 380

Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val Asn
385 390 395 400

Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu Thr Gly Asn Leu Lys
405 410 415

Pro Asn Thr Asp Ser Asn Ala Leu Ile Asp Gln Gln Asn Thr Ser Ile
420 425 430

Lys Val Tyr Lys Val Asp Asn Ala Ala Asp Leu Ser Glu Ser Tyr Phe
435 440 445

Val Asn Pro Glu Asn Phe Glu Asp Val Thr Asn Ser Val Asn Ile Thr
450 455 460

Phe Pro Asn Pro Asn Gln Tyr Lys Val Glu Phe Asn Thr Pro Asp Asp
465 470 475 480

Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp Pro
485 490 495

Asn Ser Lys Gly Asp Leu Ala Leu Arg Ser Thr Leu Tyr Gly Tyr Asn
500 505 510

Ser Asn Ile Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala Phe
515 520 525

Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val Pro
530 535 540

Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 93
<211> 1674
<212> DNA
<213> Staphylococcus aureus

<400> 93
atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgatccaagt 180

agcgttaatg ctgcacctaa aacagacaac acaaacgtga gtgatactaa aacatcgtca 240

aacactaata atggcgaaac gagtgtggcg caaaatccag cacaacagga aacgacacaa 300

tcatcattaa caaatgcaac tacggaagaa actccggtaa ctggtgaagc tactacggca 360

acgaatcaag ctaatacacc ggcaacaact caatcaagca atacaaatgc ggaggaatta 420

gtgaatcaaa caagtaatga aacgacttct aatgatacta atacagtatc atctgtaaat 480

tcacctcaaa attctacaaa tgcggaaaat gtttcaacaa cgcaagatac ttcaactgaa 540

gcaacacctt caaacaatga atcagctcca cagagtacag atgcaagtaa taaagattta 600

gttaatcaag cggttaatac aagtgcgcct agaatgagag catttagttt agcggcagta 660

gctgcagatg cacctgcagc tggcacagat attacgaatc agttgacaga tgttaaagtt 720

actattgact ctggtacgac tgtgtatccg caccaagcag gttatgtcaa actgaattat 780

ggtttttcag tgcctaattc tgctgttaaa ggtgacacat tcaaaataac tgtacctaaa 840

gaattaaact taaatggtgt aacttcaact gctaaagtgc ctccaattat ggccggagat 900

caagtattgg caaatggtgt aatcgatagt gatggtaatg ttatttatac atttacagac 960

tatgttgata ctaaagaaaa tgtaacagct aatattacta tgccagctta tattgaccct 1020

gaaaatgtta caaagacagg taatgtaaca ttgacaactg gcataggtag tacaacagca 1080

aacaaaacag tattagtaga ttatgaaaaa tatggtaagt tttataactt atctattaaa 1140

ggtacaattg accaaatcga taaaacaaat aatacgtatc gtcagacaat ttatgtcaat 1200

ccaagtggag ataacgttat tgcgccggtt ttaacaggta atttaaaacc caatacggat 1260

agtaatgcat taatagatca gcaaaataca agtattaaag tatataaagt agataatgca 1320

gctgatttat ctgaaagtta ctttgtaaat ccagaaaact ttgaggatgt cactaatagt 1380

gtgaatatta cattcccaaa tccaaatcaa tataaagtag agtttaatac gcctgatgat 1440

caaattacaa caccgtatat tgtagttgtt aatggtcata ttgatccgaa tagcaaaggt 1500

gatttagctt tacgttcaac tttatatggg tataactcga atataatttg gcgctctatg 1560

tcatgggaca acgaagtagc atttaataac ggatcaggtt ctggtgacgg tatcgataaa 1620

cctgttgtcc ctgaacaacc tgatgagcct ggtgaaattg aaccaattcc agag 1674

<210> 94
<211> 558
<212> PRT
<213> Staphylococcus aureus

<400> 94

Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1 5 10 15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
20 25 30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
35 40 45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Pro Ser Ser Val Asn Ala

```
    50                  55                  60

Ala Pro Lys Thr Asp Asn Thr Asn Val Ser Asp Thr Lys Thr Ser Ser
65                  70                  75                  80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
                85                  90                  95

Glu Thr Thr Gln Ser Ser Leu Thr Asn Ala Thr Thr Glu Glu Thr Pro
            100                 105                 110

Val Thr Gly Glu Ala Thr Thr Ala Thr Asn Gln Ala Asn Thr Pro Ala
        115                 120                 125

Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln Thr
    130                 135                 140

Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val Asn
145                 150                 155                 160

Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln Asp
                165                 170                 175

Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln Ser
            180                 185                 190

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

Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp Ala
    210                 215                 220

Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asp Val Lys Val
225                 230                 235                 240

Thr Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr Val
                245                 250                 255

Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly Asp
            260                 265                 270

Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val Thr
        275                 280                 285

Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu Ala
    290                 295                 300

Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr Asp
305                 310                 315                 320

Tyr Val Asp Thr Lys Glu Asn Val Thr Ala Asn Ile Thr Met Pro Ala
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325 330 335

Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu Thr
340 345 350

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

Glu Lys Tyr Gly Lys Phe Tyr Asn Leu Ser Ile Lys Gly Thr Ile Asp
370 375 380

Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val Asn
385 390 395 400

Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu Thr Gly Asn Leu Lys
405 410 415

Pro Asn Thr Asp Ser Asn Ala Leu Ile Asp Gln Gln Asn Thr Ser Ile
420 425 430

Lys Val Tyr Lys Val Asp Asn Ala Ala Asp Leu Ser Glu Ser Tyr Phe
435 440 445

Val Asn Pro Glu Asn Phe Glu Asp Val Thr Asn Ser Val Asn Ile Thr
450 455 460

Phe Pro Asn Pro Asn Gln Tyr Lys Val Glu Phe Asn Thr Pro Asp Asp
465 470 475 480

Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp Pro
485 490 495

Asn Ser Lys Gly Asp Leu Ala Leu Arg Ser Thr Leu Tyr Gly Tyr Asn
500 505 510

Ser Asn Ile Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala Phe
515 520 525

Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val Pro
530 535 540

Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 95
<211> 1677
<212> DNA
<213> Staphylococcus aureus

<400> 95
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gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt 180
agcgttagtg ctgcacctaa aacagacgac acaaacgtga gtgatactaa aacatcgtca 240
aacactaata atggcgaaac gagtgtggcg caaaatctag cacaacagga aacgacacaa 300
tcatcatcaa caaatgcaac tacggaagaa acgccggtaa ctggtgaagc tactactacg 360
acaacgaatc aagctaatac accggcaaca actcaatcaa gcaatacaaa tgcggaggaa 420
ttagtgaatc aaacaagtaa tgaaacgact tctaatgata ctaatacagt atcatctgta 480
aattcacctc aaaattctac aaatgcggaa aatgtttcaa caacgcaaga tacttcaact 540
gaagcaacac cttcaaacaa tgaatcagct ccacagagta cagatgcaag taataaagat 600
gtagttaatc aagcggttaa tacaagtgcg cctagaatga gagcatttag tttagcggca 660
gtagctgcag atgcaccggc agctggcaca gatattacga atcagttgac gaatgtgaca 720
gttggtattg actctggtac gactgtgtat ccgcaccaag caggttatgt caaactgaat 780
tatggttttt cagtgcctaa ttctgctgtt aaaggtgaca cattcaaaat aactgtacct 840
aaagaattaa acttaaatgg tgtaacttca actgctaaag tgccaccaat tatggctgga 900
gatcaagtat tggcaaatgg tgtaatcgat agtgatggta atgttattta tacatttaca 960
gactatgtaa atactaaaga tgatgttaaa gcaactttga ccatgcccgc ttatattgac 1020
cctgaaaatg ttacaaagac aggtaatgtg acattggcta ctggcatagg aaatacaaca 1080
gcaaacaaaa cagtattagt agattatgaa aaatatggta agttttataa cttatctatt 1140
aaaggtacaa ttgaccaaat cgataaaaca aataatacgt atcgtcagac aatttatgtc 1200
aatccaagtg gagataacgt tattgcgccg gttttaacag gtaatttaaa accaaatacg 1260
gatagtaatg cattaataga tcagcaaaat acaagtatta aagtatataa agtagataat 1320
gcagctgatt tatctgaaag ttactttgtg aatccagaaa actttgagga tgtcactaat 1380
agtgtgaata ttacattccc aaatccaaat caatataaag tagagtttaa tacgcctgat 1440
gatcaaatta caacaccgta tatagtagtt gttaatggtc atattgatcc gaatagcaaa 1500
ggtgatttag ctttacgttc aactttatat gggtataact cgaatataat ttggcgctct 1560
atgtcatggg acaacgaagt agcatttaat aacggatcag gttctggtga cggtatcgat 1620
aaacctgttg ttcctgaaca acctgatgag cctggtgaaa ttgaaccaat tccagag 1677

<210> 96
<211> 559
<212> PRT
<213> Staphylococcus aureus

<400> 96
Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1 5 10 15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
20 25 30

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

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Ser Ala
    50                  55                  60

Ala Pro Lys Thr Asp Asp Thr Asn Val Ser Asp Thr Lys Thr Ser Ser
65                  70                  75                  80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Leu Ala Gln Gln
                85                  90                  95

Glu Thr Thr Gln Ser Ser Ser Thr Asn Ala Thr Thr Glu Glu Thr Pro
            100                 105                 110

Val Thr Gly Glu Ala Thr Thr Thr Thr Thr Asn Gln Ala Asn Thr Pro
        115                 120                 125

Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln
    130                 135                 140

Thr Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val
145                 150                 155                 160

Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln
                165                 170                 175

Asp Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln
            180                 185                 190

Ser Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr
        195                 200                 205

Ser Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
    210                 215                 220

Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asn Val Thr
225                 230                 235                 240

Val Gly Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr
                245                 250                 255

Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly
            260                 265                 270

Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
        275                 280                 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
    290                 295                 300
```

```
Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305                 310                 315                 320

Asp Tyr Val Asn Thr Lys Asp Asp Val Lys Ala Thr Leu Thr Met Pro
                325                 330                 335

Ala Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu
            340                 345                 350

Ala Thr Gly Ile Gly Asn Thr Thr Ala Asn Lys Thr Val Leu Val Asp
        355                 360                 365

Tyr Glu Lys Tyr Gly Lys Phe Tyr Asn Leu Ser Ile Lys Gly Thr Ile
    370                 375                 380

Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385                 390                 395                 400

Asn Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu Thr Gly Asn Leu
                405                 410                 415

Lys Pro Asn Thr Asp Ser Asn Ala Leu Ile Asp Gln Gln Asn Thr Ser
            420                 425                 430

Ile Lys Val Tyr Lys Val Asp Asn Ala Ala Asp Leu Ser Glu Ser Tyr
        435                 440                 445

Phe Val Asn Pro Glu Asn Phe Glu Asp Val Thr Asn Ser Val Asn Ile
    450                 455                 460

Thr Phe Pro Asn Pro Asn Gln Tyr Lys Val Glu Phe Asn Thr Pro Asp
465                 470                 475                 480

Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp
                485                 490                 495

Pro Asn Ser Lys Gly Asp Leu Ala Leu Arg Ser Thr Leu Tyr Gly Tyr
            500                 505                 510

Asn Ser Asn Ile Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala
        515                 520                 525

Phe Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val
    530                 535                 540

Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545                 550                 555

<210> 97
<211> 1674
<212> DNA
<213> Staphylococcus aureus
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<400> 97
atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt 180

agcgttagtg ctgcacctaa aacagacgac acaaacgtga gtgatactaa aacatcgtca 240

aacactaata atggcgaaac gagtgtggcg caaaatccag cacaacagga aacgacacaa 300

tcagcattaa caaatgcaac tacggaagaa actccgttaa ctggtgaagc tactacggca 360

acgaatcaag ctaatacacc ggcaacaact caatcaagca atacaaatgc ggaggaatta 420

gtgaatcaaa caagtaatga aacgacttct aatgatacta atacagtatc atctgtaaat 480

tcacctcaaa attctacaaa tgcggaaaat gtttcaacaa cgcaagatac ttcaactgaa 540

gcaacacctt caaacaatga atcagctcca cagagtacag atgcaagtaa taaagatgta 600

gttaatcaag cggttaatac aagtgcgcct agaatgagag catttagttt agcggcagta 660

gctgcagatg caccggcagc tggcacagat attacgaatc agttgacaga tgtgaaagtt 720

actattgact ctggtacgac tgtgtatccg caccaagcag gttatgtcaa actgaattat 780

ggtttttcag tgcctaattc tgctgttaaa ggtgacacat tcaaaataac tgtacctaaa 840

gaattaaact taaatggtgt aacttcaact gctaaagtgc ctccaattat ggccggagat 900

caagtattgg caaatggtgt aatcgatagt gatggtaatg ttatttatac atttacagac 960

tatgttgata ataaaaacga tgttaaagca acactaactg ttcctgcata cattgatcca 1020

gaaaatgtaa cgaaaacagg taatgtaaca ttgacaactg gcataggaac caatactgct 1080

agtaagacag ttttaatcga ctatgagaaa tatggacaat tccataattt atcaattaaa 1140

ggtacaattg atcaaatcga caaaacaaac aatacgtatc gtcaaacgat ttatgtcaat 1200

ccaagtggag acaatgttgt attaccagtg ttaactggta atctaattcc taagagtaat 1260

agtaatgctt taatagatgc caacaatact aatattaaag tttataaagt ggataatgct 1320

aatgatttat ctgaaagtta ttatgtgaat cctagcgatt ttgaagatgt aactaatcaa 1380

gttagaattt catttccaaa tgctaatcaa tacaaagtag aatttcctac ggacgatgac 1440

caaattacaa caccgtatat tgtagttgtt aatggccata ttgatcctgc tagtacaggt 1500

gatttagcac tacgttcgac attttatggt tatgattcta attttatatg gagatctatg 1560

tcatgggaca acgaagtagc atttaataac ggatcaggtt ctggtgacgg tatcgataaa 1620

ccagttgttc ctgaacaacc tgatgagcct ggtgaaattg aaccaattcc agag 1674

<210> 98
<211> 558
<212> PRT
<213> Staphylococcus aureus

<400> 98
Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1 5 10 15

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Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
            20                  25                  30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
        35                  40                  45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Ser Ala
    50                  55                  60

Ala Pro Lys Thr Asp Asp Thr Asn Val Ser Asp Thr Lys Thr Ser Ser
65                  70                  75                  80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
                85                  90                  95

Glu Thr Thr Gln Ser Ala Leu Thr Asn Ala Thr Thr Glu Glu Thr Pro
            100                 105                 110

Leu Thr Gly Glu Ala Thr Thr Ala Thr Asn Gln Ala Asn Thr Pro Ala
        115                 120                 125

Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln Thr
    130                 135                 140

Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val Asn
145                 150                 155                 160

Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln Asp
                165                 170                 175

Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln Ser
            180                 185                 190

Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr Ser
        195                 200                 205

Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp Ala
    210                 215                 220

Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asp Val Lys Val
225                 230                 235                 240

Thr Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr Val
                245                 250                 255

Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly Asp
            260                 265                 270

Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val Thr
        275                 280                 285
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Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu Ala
    290                 295                 300

Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr Asp
305                 310                 315                 320

Tyr Val Asp Asn Lys Asn Asp Val Lys Ala Thr Leu Thr Val Pro Ala
                325                 330                 335

Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu Thr
            340                 345                 350

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

Glu Lys Tyr Gly Gln Phe His Asn Leu Ser Ile Lys Gly Thr Ile Asp
    370                 375                 380

Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val Asn
385                 390                 395                 400

Pro Ser Gly Asp Asn Val Val Leu Pro Val Leu Thr Gly Asn Leu Ile
                405                 410                 415

Pro Lys Ser Asn Ser Asn Ala Leu Ile Asp Ala Asn Asn Thr Asn Ile
            420                 425                 430

Lys Val Tyr Lys Val Asp Asn Ala Asn Asp Leu Ser Glu Ser Tyr Tyr
        435                 440                 445

Val Asn Pro Ser Asp Phe Glu Asp Val Thr Asn Gln Val Arg Ile Ser
    450                 455                 460

Phe Pro Asn Ala Asn Gln Tyr Lys Val Glu Phe Pro Thr Asp Asp Asp
465                 470                 475                 480

Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp Pro
                485                 490                 495

Ala Ser Thr Gly Asp Leu Ala Leu Arg Ser Thr Phe Tyr Gly Tyr Asp
            500                 505                 510

Ser Asn Phe Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala Phe
        515                 520                 525

Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val Pro
    530                 535                 540

Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545                 550                 555
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<210> 99
<211> 1674
<212> DNA
<213> Staphylococcus aureus

<400> 99
atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt 180

agcgttagtg ctgcacctaa aacagacgac acaaacgtga gtgatactaa aacatcgtca 240

aacactaata atggcgaaac gagtgtggcg caaaatccag cacaacaaga aacgacacaa 300

tcagcattaa caaatgcaac tacggaagaa actccggtaa ctggtgaagc tactacggca 360

acgaatcaag ctaatacacc ggcaacaact caatcaagca atacaaatgc ggaggaatta 420

gtgaatcaaa caagtaatga aacgacttct aatgatacta atacagtatc atctgtaaat 480

tcacctcaaa attctacaaa tgcggaaaat gtttcaacaa cgcaagatac ttcaactgaa 540

gcaacacctt caaacaatga atcagctcca cagaatacag atgcaagtaa taaagatgta 600

gttaatcaag cggttaatac aagtgcgcct agaaagagag catttagttt agcggctgta 660

gctgcagatg caccggcagc tggcacagat attacgaatc agttgacaga tgtgaaagtt 720

actattgact ctggtacgac tgtgtatccg caccaagcag gttatgtcaa actgaattat 780

ggtttttcag tgcctaattc tgctgttaaa ggtgacacat tcaaaataac tgtacctaaa 840

gaattaaact taaatggtgt aacttcaact gctaaagcgc caccaattat ggctggagat 900

caagtattgg caaatggtgt aatcgatagt gatggtaatg ttatttatac atttacagac 960

tatgttgata ataaagaaaa tgtaacagct aatattacta tgccagctta tattgaccct 1020

gaaaatgtta caaagacagg taatgtgaca ttgacaactg gcataggaac caatactgct 1080

agtaagacag tattaatcga ctatgagaaa tatggacaat tccataattt atcaattaaa 1140

ggtacgattg atcaaatcga taaaacaaat aatacgtatc gccaaacaat ttatgtcaat 1200

ccaagcggag ataacgttgt gttacctgcc ttaacaggta atttaattcc taatacaaag 1260

agtaatgcgt taatagatgc aaaaaacact gatattaaag tttatagagt cgataatgct 1320

aatgatttat ctgaaagtta ttatgtgaat cctagcgatt ttgaagatgt aactaatcaa 1380

gttagaattt catttccaaa tgctaatcaa tacaaagtag aatttcctac ggacgatgac 1440

caaattacaa caccgtatat tgtagttgtt aatggccata ttgatcctgc tagtacaggt 1500

gatttagcac tacgttcgac attttatggt tatgattcta attttatatg gagatctatg 1560

tcatgggaca acgaagtagc atttaataac ggatcaggtt ctggtgacgg tatcgataaa 1620

ccagttgttc ctgaacaacc tgatgagcct ggtgaaattg aaccaattcc agag 1674

<210> 100
<211> 558
<212> PRT
<213> Staphylococcus aureus

<400> 100

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Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1               5                  10                  15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
            20                  25                  30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
        35                  40                  45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Ser Ala
    50                  55                  60

Ala Pro Lys Thr Asp Asp Thr Asn Val Ser Asp Thr Lys Thr Ser Ser
65                  70                  75                  80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
                85                  90                  95

Glu Thr Thr Gln Ser Ala Leu Thr Asn Ala Thr Thr Glu Glu Thr Pro
            100                 105                 110

Val Thr Gly Glu Ala Thr Thr Ala Thr Asn Gln Ala Asn Thr Pro Ala
        115                 120                 125

Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln Thr
    130                 135                 140

Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val Asn
145                 150                 155                 160

Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln Asp
                165                 170                 175

Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln Asn
            180                 185                 190

Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr Ser
        195                 200                 205

Ala Pro Arg Lys Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp Ala
    210                 215                 220

Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asp Val Lys Val
225                 230                 235                 240

Thr Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr Val
                245                 250                 255

Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly Asp
            260                 265                 270
```

```
Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val Thr
        275                 280                 285

Ser Thr Ala Lys Ala Pro Pro Ile Met Ala Gly Asp Gln Val Leu Ala
    290                 295                 300

Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr Asp
305                 310                 315                 320

Tyr Val Asp Asn Lys Glu Asn Val Thr Ala Asn Ile Thr Met Pro Ala
                325                 330                 335

Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu Thr
            340                 345                 350

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

Glu Lys Tyr Gly Gln Phe His Asn Leu Ser Ile Lys Gly Thr Ile Asp
    370                 375                 380

Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val Asn
385                 390                 395                 400

Pro Ser Gly Asp Asn Val Val Leu Pro Ala Leu Thr Gly Asn Leu Ile
                405                 410                 415

Pro Asn Thr Lys Ser Asn Ala Leu Ile Asp Ala Lys Asn Thr Asp Ile
            420                 425                 430

Lys Val Tyr Arg Val Asp Asn Ala Asn Asp Leu Ser Glu Ser Tyr Tyr
        435                 440                 445

Val Asn Pro Ser Asp Phe Glu Asp Val Thr Asn Gln Val Arg Ile Ser
    450                 455                 460

Phe Pro Asn Ala Asn Gln Tyr Lys Val Glu Phe Pro Thr Asp Asp Asp
465                 470                 475                 480

Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp Pro
                485                 490                 495

Ala Ser Thr Gly Asp Leu Ala Leu Arg Ser Thr Phe Tyr Gly Tyr Asp
            500                 505                 510

Ser Asn Phe Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala Phe
        515                 520                 525

Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val Pro
    530                 535                 540
```

Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 101
<211> 1677
<212> DNA
<213> Staphylococcus aureus

<400> 101
atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt 180

agcgttagtg ctgcacctaa aacagacgac acaaacgtga gtgatactaa aacatcgtca 240

aacactaata atggcgaaac gagtgtggcg caaaatccag cacaacagga aacgacacaa 300

tcatcatcaa caaatgcaac tacggaagaa acgccggtaa ctggtgaagc tactactacg 360

acaacgaatc aagctaatac accggcaaca actcaatcaa gcaatacaaa tgcggaggaa 420

ttagtgaatc aaacaagtaa tgaaacgact tctaatgata ctaatacagt atcatctgta 480

aattcacctc aaaattctac aaatgcggaa aatgtttcaa caacgcaaga tacttcaact 540

gaagcaacac cttcaaacaa tgaatcagct ccacagagta cagatgcaag taataaagat 600

gtagttaatc aagcggttaa tacaagtgcg cctagaatga gagcatttag tttagcggca 660

gtagctgcag atgcaccggc agctggcaca gatattacga atcagttgac gaatgtgaca 720

gttggtattg actctggaga tacagtttat ccgcaccaag caggctatgt caaactgaat 780

tatggttttt cagtgcctaa ttctgctgtt aaaggtgaca cattcaaaat aactgtacct 840

aaagaattaa acttaaatgg tgtaacttca actgctaaag tgccaccaat tatggctgga 900

gatcaagtat tggcaaatgg tgtaatcgat agtgatggta atgttattta tacatttaca 960

gactatgtaa atactaaaga tgatgttaaa gcaactttga ccatgcccgc ttatattgac 1020

cctgaaaatg ttacaaagac aggtaatgtg acattggcta ctggcatagg aaatacaaca 1080

gcaaacaaaa cagtattagt agattatgaa aaatatggta agttttataa cttatctatt 1140

aaaggtacaa ttgaccaaat cgataaaaca aataatacgt atcgtcagac aatttatgtc 1200

aatccaagtg gagataacgt tattgcgccg gttttaacag gtaatttaaa accaaatacg 1260

gatagtaatg cattaataga tcagcaaaat acaagtatta aagtatataa agtagataat 1320

gcagctgatt tatctgaaag ttactttgtg aatccagaaa actttgagga tgtcactaat 1380

agtgtgaata ttacattccc aaatccaaat caatataaag tagagtttaa tacgcctgat 1440

gatcaaatta caacaccgta tatagtagtt gttaatggtc atattgatcc gaatagcaaa 1500

ggtgatttag ctttacgttc aactttatat gggtatgact caaggtttgt atggagatct 1560

atgtcatggg acaacgaagt agcatttaat aacggatcag gttctggtga cggtatcgat 1620

aaaccagttg ttcctgaaca acctgatgag cctggtgaaa ttgaaccaat tccagag 1677

<210> 102
<211> 559
<212> PRT
<213> Staphylococcus aureus

<400> 102
Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1 5 10 15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
20 25 30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
35 40 45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Ser Ala
50 55 60

Ala Pro Lys Thr Asp Asp Thr Asn Val Ser Asp Thr Lys Thr Ser Ser
65 70 75 80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
85 90 95

Glu Thr Thr Gln Ser Ser Ser Thr Asn Ala Thr Thr Glu Glu Thr Pro
100 105 110

Val Thr Gly Glu Ala Thr Thr Thr Thr Thr Asn Gln Ala Asn Thr Pro
115 120 125

Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln
130 135 140

Thr Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val
145 150 155 160

Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln
165 170 175

Asp Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln
180 185 190

Ser Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr
195 200 205

Ser Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
210 215 220

Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asn Val Thr
225 230 235 240

Val Gly Ile Asp Ser Gly Asp Thr Val Tyr Pro His Gln Ala Gly Tyr

245 250 255

Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly
260 265 270

Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
275 280 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
290 295 300

Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305 310 315 320

Asp Tyr Val Asn Thr Lys Asp Asp Val Lys Ala Thr Leu Thr Met Pro
325 330 335

Ala Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu
340 345 350

Ala Thr Gly Ile Gly Asn Thr Thr Ala Asn Lys Thr Val Leu Val Asp
355 360 365

Tyr Glu Lys Tyr Gly Lys Phe Tyr Asn Leu Ser Ile Lys Gly Thr Ile
370 375 380

Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385 390 395 400

Asn Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu Thr Gly Asn Leu
405 410 415

Lys Pro Asn Thr Asp Ser Asn Ala Leu Ile Asp Gln Gln Asn Thr Ser
420 425 430

Ile Lys Val Tyr Lys Val Asp Asn Ala Ala Asp Leu Ser Glu Ser Tyr
435 440 445

Phe Val Asn Pro Glu Asn Phe Glu Asp Val Thr Asn Ser Val Asn Ile
450 455 460

Thr Phe Pro Asn Pro Asn Gln Tyr Lys Val Glu Phe Asn Thr Pro Asp
465 470 475 480

Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp
485 490 495

Pro Asn Ser Lys Gly Asp Leu Ala Leu Arg Ser Thr Leu Tyr Gly Tyr
500 505 510

Asp Ser Arg Phe Val Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala

515 520 525

Phe Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val
530 535 540

Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 103
<211> 1677
<212> DNA
<213> Staphylococcus aureus

<400> 103
atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc cgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt 180

agcgttagtg ctgcacctaa aacagtcgac acaaacgtga gtgatactaa aacaacgtca 240

aacactaata gtggcgaaac aagtgtggcg caaaatccgg cacaacagga aacgacacaa 300

tcagcatcaa caaatgcaac tacggaagaa actccggcaa ctggtgaagc tactactacg 360

gcaacgaatc aagctaatac accggcaaca actcaatcaa gcaatacaaa tgcggaggaa 420

ttagtgaatc aaacaaataa tgaaacgact tctaatgata ctaatacagt atcatctgta 480

aattcacctc aaaattctac aaatgcggaa aatgtttcaa caacgcaaga tacttcaact 540

gaagcaacac cttcaaacaa tgaatcagct ccacagagta cagatgcaag taataaagat 600

gtagttaatc aagcggttaa tacaagtgcg cctagaatga gagcatttag tttagcggca 660

gtagctgcag atgcaccggc tgctggcaca gatattacga atcagttgac agatgtgaaa 720

gttactattg actctggtac gactgtgtat ccgcaccaag caggttatgt caaactgaat 780

tatggttttt cagtccctaa ttctgctgtt aaaggtgaca cattcaaaat aactgtacct 840

aaagaattaa acttaaatgg tgtaacttca actgctaagg tgccaccaat tatggccgga 900

gatcaagtat tggcaaatgg tgtaatcgat agtgatggta atgttattta tacatttaca 960

gactatgttg ataataaaga aaatgtaaca gctaatatta ctatgccagc ttatattgac 1020

cctgaaaatg ttacaaagac aggtaatgtg acattgacaa ctggcatagg aaccaatact 1080

gctagtaaga cagtattaat cgactatgag aaatatggac aattccataa tttatcaatt 1140

aaaggtacga ttgatcaaat cgataaaaca aataatacgt atcgccaaac aatttatgtc 1200

aatccaagcg gagataacgt tgtgttacct gccttaacag gtaatttaat tcctaataca 1260

aagagtaatg cgttaataga tgcaaaaaac actgatatta aagtttatag agtcgataat 1320

gctaatgatt tatctgaaag ttattatgtg aatcctagcg attttgaaga tgtaactaat 1380

caagttagaa tttcatttcc aaatgctaat caatacaaag tagaatttcc tacggacgat 1440

gaccaaatta caacaccgta tattgtagtt gttaatggcc atattgatcc tgctagtaca 1500

ggtgatttag cactacgttc gacattttat ggttatgatt ctaattttat atggagatct 1560

atgtcatggg acaacgaagt agcatttaat aacggatcag gctctggtga cggtatcgat 1620

aaaccagttg ttcctgaaca acctgatgag cctggtgaaa ttgaaccaat tccagag 1677

<210> 104
<211> 559
<212> PRT
<213> Staphylococcus aureus

<400> 104

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Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1               5                  10                  15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
            20                  25                  30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
        35                  40                  45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Ser Ala
    50                  55                  60

Ala Pro Lys Thr Val Asp Thr Asn Val Ser Asp Thr Lys Thr Thr Ser
65                  70                  75                  80

Asn Thr Asn Ser Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
                85                  90                  95

Glu Thr Thr Gln Ser Ala Ser Thr Asn Ala Thr Thr Glu Glu Thr Pro
            100                 105                 110

Ala Thr Gly Glu Ala Thr Thr Thr Ala Thr Asn Gln Ala Asn Thr Pro
        115                 120                 125

Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln
    130                 135                 140

Thr Asn Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val
145                 150                 155                 160

Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln
                165                 170                 175

Asp Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln
            180                 185                 190

Ser Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr
        195                 200                 205

Ser Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
    210                 215                 220
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Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asp Val Lys
225                 230                 235                 240

Val Thr Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr
                245                 250                 255

Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly
            260                 265                 270

Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
        275                 280                 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
    290                 295                 300

Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305                 310                 315                 320

Asp Tyr Val Asp Asn Lys Glu Asn Val Thr Ala Asn Ile Thr Met Pro
                325                 330                 335

Ala Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu
            340                 345                 350

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

Tyr Glu Lys Tyr Gly Gln Phe His Asn Leu Ser Ile Lys Gly Thr Ile
    370                 375                 380

Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385                 390                 395                 400

Asn Pro Ser Gly Asp Asn Val Val Leu Pro Ala Leu Thr Gly Asn Leu
                405                 410                 415

Ile Pro Asn Thr Lys Ser Asn Ala Leu Ile Asp Ala Lys Asn Thr Asp
            420                 425                 430

Ile Lys Val Tyr Arg Val Asp Asn Ala Asn Asp Leu Ser Glu Ser Tyr
        435                 440                 445

Tyr Val Asn Pro Ser Asp Phe Glu Asp Val Thr Asn Gln Val Arg Ile
    450                 455                 460

Ser Phe Pro Asn Ala Asn Gln Tyr Lys Val Glu Phe Pro Thr Asp Asp
465                 470                 475                 480

Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp
                485                 490                 495
```

Pro Ala Ser Thr Gly Asp Leu Ala Leu Arg Ser Thr Phe Tyr Gly Tyr
500 505 510

Asp Ser Asn Phe Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala
515 520 525

Phe Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val
530 535 540

Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 105
<211> 1677
<212> DNA
<213> Staphylococcus aureus

<400> 105
atgaatatga agaaaaaaga aaaacacgca attcggaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc cgatagcgca agtaacgaaa gcaaaagtaa taatccaagt 180

agcgttaacg ctgcacctaa aacagacaac acaaacgtga gtgatactaa aacaacgtca 240

aacactaata atagcgaaac gagtgtggca caaaatccag cacaacagga aacgacacaa 300

tcagcatcaa caaatgcaac tacggaagaa acaccggtaa ctggtgaagg tactactacg 360

gcaacgaatc aagctaatac accggcagca actcaatcaa acaatacaaa tgcggaggaa 420

ttagtgaatc aaacaagtaa tgaaacgact tctaatgata ctaatacagt atcatctgta 480

aattcacctc aaaattctac aaatgcggaa aatgtttcaa caacgcaaga cacttcaact 540

gaagcaacac cttcaaacaa tgaatcagct ccacagagta cagatgcaag taataaagat 600

gtagttagtc aagccgttaa tccaagtgcg cctagaatga gagcatttag tttagcggct 660

gtagctgcag atgcaccggc tgctggcaca gatattacga atcagttgac agatgttact 720

gttggtattg aatctggaga tacagtttat ccgcaccaag caggttatgt caaactgaat 780

tatggttttt ccgtgcctaa ttctgctgtt aaaggtgaca cattcaaaat aactgtacct 840

aaagaattaa acttaaatgg tgtaacttca actgctaaag ttcctccaat tatggctgga 900

gatcaagtat tagctaatgg tgtaatcgat agtgatggta atgttattta tacatttaca 960

gactatgtaa atactaaaga tgatgttaaa gcaacactaa ctgtgcctgc atacattgac 1020

cctgaatatg ttacacatac tggtaatgtg acattggcta ctggcatagg aaatacaaca 1080

gcaaacaaaa cagtattagt agattatgaa aaatatggta agttttataa cttatctatt 1140

aaaggtacaa ttgaccaagt cgataaaaca aataatacgt atcgtcagac aatttatgtc 1200

aatccaagtg gagataacgt tattgcaccg gttttaacag gtaatttaaa accaaatacg 1260

gatagtaatg cattaataga tcagcaaaat acaagtatta aagtatataa agtagataat 1320

gcagctgatt tatctgaaag ttactttgtg aatccagaaa actttgagga tgtcactaat 1380

agtgtaaata ttacattccc aaatccaaat caatataaag tagagtttaa tacgcctgat 1440

gatcaaatta caacaccgta tattgtagtt gttaatggtc atattgatcc gaatagcaaa 1500

ggtgatttag ctttacgttc aactttatat ggatataact caaatataat ttggcgctct 1560

atgtcatggg acaacgaagt agcatttaat aacggatcag gttctggtga cggtatcgat 1620

aaacctgttg ttcctgaaca acctgatgag ccgggtgaaa ttgaaccaat tccagag 1677

<210> 106
<211> 559
<212> PRT
<213> Staphylococcus aureus

<400> 106

Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1 5 10 15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
20 25 30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
35 40 45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asn Pro Ser Ser Val Asn Ala
50 55 60

Ala Pro Lys Thr Asp Asn Thr Asn Val Ser Asp Thr Lys Thr Thr Ser
65 70 75 80

Asn Thr Asn Asn Ser Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
85 90 95

Glu Thr Thr Gln Ser Ala Ser Thr Asn Ala Thr Thr Glu Glu Thr Pro
100 105 110

Val Thr Gly Glu Gly Thr Thr Thr Ala Thr Asn Gln Ala Asn Thr Pro
115 120 125

Ala Ala Thr Gln Ser Asn Asn Thr Asn Ala Glu Glu Leu Val Asn Gln
130 135 140

Thr Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val
145 150 155 160

Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln
165 170 175

Asp Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln
180 185 190

Ser Thr Asp Ala Ser Asn Lys Asp Val Val Ser Gln Ala Val Asn Pro
195 200 205

```
Ser Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
    210                 215                 220

Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asp Val Thr
225                 230                 235                 240

Val Gly Ile Glu Ser Gly Asp Thr Val Tyr Pro His Gln Ala Gly Tyr
                245                 250                 255

Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly
            260                 265                 270

Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
        275                 280                 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
    290                 295                 300

Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305                 310                 315                 320

Asp Tyr Val Asn Thr Lys Asp Asp Val Lys Ala Thr Leu Thr Val Pro
                325                 330                 335

Ala Tyr Ile Asp Pro Glu Tyr Val Thr His Thr Gly Asn Val Thr Leu
            340                 345                 350

Ala Thr Gly Ile Gly Asn Thr Thr Ala Asn Lys Thr Val Leu Val Asp
        355                 360                 365

Tyr Glu Lys Tyr Gly Lys Phe Tyr Asn Leu Ser Ile Lys Gly Thr Ile
    370                 375                 380

Asp Gln Val Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385                 390                 395                 400

Asn Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu Thr Gly Asn Leu
                405                 410                 415

Lys Pro Asn Thr Asp Ser Asn Ala Leu Ile Asp Gln Gln Asn Thr Ser
            420                 425                 430

Ile Lys Val Tyr Lys Val Asp Asn Ala Ala Asp Leu Ser Glu Ser Tyr
        435                 440                 445

Phe Val Asn Pro Glu Asn Phe Glu Asp Val Thr Asn Ser Val Asn Ile
    450                 455                 460

Thr Phe Pro Asn Pro Asn Gln Tyr Lys Val Glu Phe Asn Thr Pro Asp
465                 470                 475                 480
```

Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp
485 490 495

Pro Asn Ser Lys Gly Asp Leu Ala Leu Arg Ser Thr Leu Tyr Gly Tyr
500 505 510

Asn Ser Asn Ile Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala
515 520 525

Phe Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val
530 535 540

Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 107
<211> 1677
<212> DNA
<213> Staphylococcus aureus

<400> 107
atgaatatga agaaacaaga aaaacacgca attcgtaaaa aatcgattgg cgtggcttca 60

gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagta tgacacaaac ggaaaatacg agtaatgaga gcaaaagtaa tgatccaagt 180

agcgttaatg ctgcacctaa aacagacaac acaaacgtga gtgattctaa tacaacgaca 240

aacactaata gtgacgaaac gaatgtagcg caaaatccag cacaacagga aacgacacaa 300

tcagcatcaa caaatgcaac tacagaagaa acaccggtaa ctggtgaagt tactactacg 360

gcaacgaatc aagctaatac accggcaaca actcaatcaa gcaatacaaa tgcggaagaa 420

tcagtgaatc aaacaagtaa tgaaacgact tctaatgata ctaatacagt atcatctgta 480

aattcacctc aaaattctac aaatgcggaa aatgtttcaa caacgcaaga catttcaact 540

gaagcaacac cttcaaacaa tgaatcagct ccacagagta cagatgcaag taataaagat 600

gtagttaatc aagcggttaa tacaagtgcg cctagaatga gagcatttag tttagcggct 660

gtagctgcag atgcaccggc tgctggcaaa gatattacga atcagttgac gaatgtgaca 720

gttggtattg actctggaga tacagtttat ccgcaccaag caggctatgt caaactgaat 780

tatgggttct cagtaccaaa tgaggctgtt caaggtgaca cattcaaaat aactgtgccc 840

aaagaattaa acttaaatgg tgtaacttca actgctaaag tgccaccaat tatggccgga 900

gatcaagtat tggcaaatgg tgtaatcgat agtgatggta atgttattta tacatttaca 960

gactatgtaa atactaaaga tgatgttaaa gcaactttga ccatgcccgc ttatattgac 1020

cctgaaaatg ttacaaagac aggtaatgtg acattggcta ctggcatagg tagtacaaca 1080

gcaaacaaaa cagtattagt agattatgaa aaatatggta agttttataa cttatctatt 1140

aaaggtacaa ttgaccaaat cgataaaaca aataatacgt atcgtcagac aatttatgtc 1200

aatccaagtg gagataacgt tattgcgccg gttttaacag gtaatttaaa accaaatacg 1260

gatagtaatg cattaataga tgcacaaaat actagtatta aagtatataa agttgataat 1320

gcatcagact tgtctgaaag ttattatgtg aatccagata actttgaaga tgtcactgat 1380

agtgtgaata ttacattccc aaatccaaat caatataaag tagagttcaa tacgcctgat 1440

gatcaaataa caacaccata tattgtagtt gttaatgggc atattgatcc taatagtaaa 1500

ggtgatttag ctttacgttc aactttatat ggatataatt cgaatataat ttggcgatca 1560

atgtcatggg ataatgaagt agcatttaat aacggatcag gttttggtga cggtatcgat 1620

aaacctgttg ttcctgaaca acctgatgag ccgggtgaaa ttgaaccaat tccagag 1677

<210> 108
<211> 559
<212> PRT
<213> Staphylococcus aureus

<400> 108

Met Asn Met Lys Lys Gln Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1 5 10 15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
20 25 30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Met Thr Gln Thr Glu
35 40 45

Asn Thr Ser Asn Glu Ser Lys Ser Asn Asp Pro Ser Ser Val Asn Ala
50 55 60

Ala Pro Lys Thr Asp Asn Thr Asn Val Ser Asp Ser Asn Thr Thr Thr
65 70 75 80

Asn Thr Asn Ser Asp Glu Thr Asn Val Ala Gln Asn Pro Ala Gln Gln
85 90 95

Glu Thr Thr Gln Ser Ala Ser Thr Asn Ala Thr Thr Glu Glu Thr Pro
100 105 110

Val Thr Gly Glu Val Thr Thr Thr Ala Thr Asn Gln Ala Asn Thr Pro
115 120 125

Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Ser Val Asn Gln
130 135 140

Thr Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val
145 150 155 160

Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln
165 170 175

Asp Ile Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln
180 185 190

```
Ser Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr
        195                 200                 205

Ser Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
    210                 215                 220

Ala Pro Ala Ala Gly Lys Asp Ile Thr Asn Gln Leu Thr Asn Val Thr
225                 230                 235                 240

Val Gly Ile Asp Ser Gly Asp Thr Val Tyr Pro His Gln Ala Gly Tyr
                245                 250                 255

Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Glu Ala Val Gln Gly
            260                 265                 270

Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
        275                 280                 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
    290                 295                 300

Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305                 310                 315                 320

Asp Tyr Val Asn Thr Lys Asp Asp Val Lys Ala Thr Leu Thr Met Pro
                325                 330                 335

Ala Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu
            340                 345                 350

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

Tyr Glu Lys Tyr Gly Lys Phe Tyr Asn Leu Ser Ile Lys Gly Thr Ile
    370                 375                 380

Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385                 390                 395                 400

Asn Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu Thr Gly Asn Leu
                405                 410                 415

Lys Pro Asn Thr Asp Ser Asn Ala Leu Ile Asp Ala Gln Asn Thr Ser
            420                 425                 430

Ile Lys Val Tyr Lys Val Asp Asn Ala Ser Asp Leu Ser Glu Ser Tyr
        435                 440                 445

Tyr Val Asn Pro Asp Asn Phe Glu Asp Val Thr Asp Ser Val Asn Ile
    450                 455                 460
```

Thr Phe Pro Asn Pro Asn Gln Tyr Lys Val Glu Phe Asn Thr Pro Asp
465 470 475 480

Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Asn Gly His Ile Asp
485 490 495

Pro Asn Ser Lys Gly Asp Leu Ala Leu Arg Ser Thr Leu Tyr Gly Tyr
500 505 510

Asn Ser Asn Ile Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala
515 520 525

Phe Asn Asn Gly Ser Gly Phe Gly Asp Gly Ile Asp Lys Pro Val Val
530 535 540

Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu
545 550 555

<210> 109
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 109
cacaaaattt acgaatagaa agaaacgag 29

<210> 110
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 110
aaaatattgg agataccaat attttaggtt g 31

<210> 111
<211> 37
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 111
tttcttggat ccggtactgg tggtaaacaa agcagtg 37

<210> 112
<211> 39
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic primer

<400> 112
tttcttgcat gcttatttca tgcttccgtg tacagtttc 39

<210> 113
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 113
tttcttccat gggtactggt ggtaaacaaa gcag 34

<210> 114
<211> 37
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 114
tttcttgctc agcattattt catgcttccg tgtacag 37

<210> 115
<211> 309
<212> PRT
<213> Staphylococcus epidermidis

<400> 115

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

Gly Glu Glu Gly Asn Lys Asn Lys Gln Asp Pro His Ala Trp Leu Ser
130 135 140

Leu Glu Asn Gly Ile Lys Tyr Val Lys Thr Ile Gln Lys Ser Leu Glu
145 150 155 160

His His Asp Lys Lys Asp Lys Ser Thr Tyr Glu Lys Gln Gly Asn Ala
165 170 175

Tyr Ile Ser Lys Leu Glu Glu Leu Asn Lys Asp Ser Lys Asn Lys Phe
180 185 190

Asp Asp Ile Pro Lys Asn Gln Arg Ala Met Met Thr Ser Glu Gly Ala
195 200 205

Phe Lys Tyr Phe Ala Gln Gln Phe Asp Val Lys Pro Gly Tyr Ile Trp
210 215 220

Glu Ile Asn Thr Glu Lys Gln Gly Thr Pro Gly Gln Met Lys Gln Ala
225 230 235 240

Ile Lys Phe Val Lys Asp Asn His Leu Lys His Leu Leu Val Glu Thr
245 250 255

Ser Val Asp Lys Lys Ala Met Gln Ser Leu Ser Glu Glu Thr Lys Lys
260 265 270

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

Lys Gly Asp Ser Tyr Tyr Lys Met Met Lys Ser Asn Ile Asp Thr Ile
290 295 300

His Gly Ser Met Lys
305

<210> 116
<211> 930
<212> DNA
<213> Staphylococcus epidermidis

<400> 116
gtgaaaaaaa ttctcgcttt agcaatagca tttttaatta tccttgccgc atgtgggaat 60

cacagtaacc atgaacatca ctcacatgaa ggaaaattaa aagttgtaac tacaaactct 120

attctctatg acatggttaa acgtgtcggt ggaaataagg tcgatgttca tagcatcgtt 180

ccagtaggac aagatccaca tgaatatgag gttaaaccta aagatattaa agcattaaca 240

gatgctgacg ttgtatttta taatggttta aacctagaaa ctggaaatgg ttggtttgaa 300

aaagcacttg accaagcagg aaaatcaaca aaagataaaa atgtgatagc agcatcaaat 360

aatgttaaac caatatactt aaatggtgag gaaggtaaca aaaacaaaca agatccacat 420

gcatggttaa gtttagagaa tggaattaaa tacgtaaaaa caatacaaaa atcactagaa 480

catcatgata aaaaagataa gtctacatat gaaaaacaag ggaatgcata tatatcaaaa 540

ttagaagaac ttaataaaga tagtaaaaat aaatttgatg acatacccaa aaatcaacgt 600

gccatgatga caagtgaagg tgcatttaaa tattttgctc aacaattcga tgttaaacca 660

ggttatattt gggagataaa cacagaaaaa caaggtacac ctggtcaaat gaaacaagcc 720

attaaatttg ttaaagataa tcatttaaaa catttattag tcgaaacaag cgtagataaa 780

aaagctatgc aaagtttatc agaagaaact aagaaagata tttatggtga agtatttacc 840

gactctatag gtaaggcagg tactaaaggt gactcatact ataaaatgat gaaatctaat 900

attgatacaa tacatggtag tatgaaataa 930

<210> 117
<211> 510
<212> PRT
<213> Staphylococcus aureus

<400> 117

Met Ala Ser Met Thr Gly Gly Gln Gln Met Gly Ala Ser Glu Gln Ser
1 5 10 15

Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
20 25 30

Lys Asn Asn Met Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
35 40 45

Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
50 55 60

Thr Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
65 70 75 80

Ala Ser Thr Asn Glu Thr Pro Gln Pro Thr Ala Ile Lys Asn Gln Ala
85 90 95

Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
100 105 110

Gln Val Asp Asn Lys Thr Thr Asn Asp Ala Asn Ser Ile Ala Thr Asn
115 120 125

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

Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
145 150 155 160

Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
165 170 175

Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Ser Asn Phe
180 185 190

Lys Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
195 200 205

Met Ala Ala Asn Phe Thr Val Thr Asp Lys Val Lys Ser Gly Asp Tyr
210 215 220

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

Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
245 250 255

Asn Gly Asp Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
260 265 270

Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asn Lys Glu Asn Ile Asn
275 280 285

Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
290 295 300

Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
305 310 315 320

Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
325 330 335

Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
340 345 350

Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
355 360 365

Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
370 375 380

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
385 390 395 400

Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
405 410 415

Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asp Gln Phe Lys Asn
420 425 430

Arg Ile Tyr Tyr Glu His Pro Asn Val Ala Ser Ile Lys Phe Gly Asp
435 440 445

```
Ile Thr Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
    450                 455                 460

Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Val Asp Pro Val
465                 470                 475                 480

Thr Asn Arg Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
                485                 490                 495

Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn
            500                 505                 510
```

<210> 118
<211> 1533
<212> DNA
<213> Staphylococcus aureus

<400> 118

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atggctagca tgactggtgg acagcaaatg ggtgcttcag aacaatcgaa cgatacaacg     60
caatcttcga aaaataatgc aagtgcagat tccgaaaaaa acaatatgat agaaacacct    120
caattaaata caacggctaa tgatacatct gatattagtg caaacacaaa cagtgcgaat    180
gtagatagca caacaaaacc aatgtctaca caaacgagca ataccactac aacagagcca    240
gcttcaacaa atgaaacacc tcaaccgacg gcaattaaaa atcaagcaac tgctgcaaaa    300
atgcaagatc aaactgttcc tcaagaagca aattctcaag tagataataa aacaacgaat    360
gatgctaata gcatagcaac aaacagtgag cttaaaaatt ctcaaacatt agatttacca    420
caatcatcac cacaaacgat ttccaatgcg caaggaacta gtaaaccaag tgttagaacg    480
agagctgtac gtagtttagc tgttgctgaa ccggtagtaa atgctgctga tgctaaaggt    540
acaaatgtaa atgataaagt tacggcaagt aatttcaagt tagaaaagac tacatttgac    600
cctaatcaaa gtggtaacac atttatggcg gcaaatttta cagtgacaga taaagtgaaa    660
tcaggggatt attttacagc gaagttacca gatagtttaa ctggtaatgg agacgtggat    720
tattctaatt caaataatac gatgccaatt gcagacatta aaagtacgaa tggcgatgtt    780
gtagctaaag caacatatga tatcttgact aagacgtata catttgtctt tacagattat    840
gtaaataata aagaaaatat taacggacaa ttttcattac ctttatttac agaccgagca    900
aaggcaccta aatcaggaac atatgatgcg aatattaata ttgcggatga aatgtttaat    960
aataaaatta cttataacta tagttcgcca attgcaggaa ttgataaacc aaatggcgcg   1020
aacatttctt ctcaaattat tggtgtagat acagcttcag gtcaaaacac atacaagcaa   1080
acagtatttg ttaaccctaa gcaacgagtt ttaggtaata cgtgggtgta tattaaaggc   1140
taccaagata aaatcgaaga aagtagcggt aaagtaagtg ctacagatac aaaactgaga   1200
atttttgaag tgaatgatac atctaaatta tcagatagct actatgcaga tccaaatgac   1260
tctaacctta aagaagtaac agaccaattt aaaaatagaa tctattatga gcatccaaat   1320
gtagctagta ttaaatttgg tgatattact aaaacatatg tagtattagt agaagggcat   1380
```

tacgacaata caggtaagaa cttaaaaact caggttattc aagaaaatgt tgatcctgta 1440

acaaatagag actacagtat tttcggttgg aataatgaga atgttgtacg ttatggtggt 1500

ggaagtgctg atggtgattc agcagtaaat taa 1533

<210> 119
<211> 292
<212> PRT
<213> Staphylococcus aureus

<400> 119

```
Met Gly Thr Gly Gly Lys Gln Ser Ser Asp Lys Ser Asn Gly Lys Leu
1               5                  10                  15

Lys Val Val Thr Thr Asn Ser Ile Leu Tyr Asp Met Ala Lys Asn Val
            20                  25                  30

Gly Gly Asp Asn Val Asp Ile His Ser Ile Val Pro Val Gly Gln Asp
        35                  40                  45

Pro His Glu Tyr Glu Val Lys Pro Lys Asp Ile Lys Lys Leu Thr Asp
    50                  55                  60

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

Trp Phe Glu Lys Ala Leu Glu Gln Ala Gly Lys Ser Leu Lys Asp Lys
                85                  90                  95

Lys Val Ile Ala Val Ser Lys Asp Val Lys Pro Ile Tyr Leu Asn Gly
            100                 105                 110

Glu Glu Gly Asn Lys Asp Lys Gln Asp Pro His Ala Trp Leu Ser Leu
        115                 120                 125

Asp Asn Gly Ile Lys Tyr Val Lys Thr Ile Gln Gln Thr Phe Ile Asp
    130                 135                 140

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

Ile Ala Gln Leu Glu Lys Leu Asn Asn Asp Ser Lys Asp Lys Phe Asn
                165                 170                 175

Asp Ile Pro Lys Glu Gln Arg Ala Met Ile Thr Ser Glu Gly Ala Phe
            180                 185                 190

Lys Tyr Phe Ser Lys Gln Tyr Gly Ile Thr Pro Gly Tyr Ile Trp Glu
        195                 200                 205

Ile Asn Thr Glu Lys Gln Gly Thr Pro Glu Gln Met Arg Gln Ala Ile
    210                 215                 220
```

Glu Phe Val Lys Lys His Lys Leu Lys His Leu Leu Val Glu Thr Ser
225 230 235 240

Val Asp Lys Lys Ala Met Glu Ser Leu Ser Glu Glu Thr Lys Lys Asp
245 250 255

Ile Phe Gly Glu Val Tyr Thr Asp Ser Ile Gly Lys Glu Gly Thr Lys
260 265 270

Gly Asp Ser Tyr Tyr Lys Met Met Lys Ser Asn Ile Glu Thr Val His
275 280 285

Gly Ser Met Lys
290

<210> 120
<211> 879
<212> DNA
<213> Staphylococcus aureus

<400> 120
atgggtactg gtggtaaaca aagcagtgat aagtcaaatg gcaaattaaa agtagtaacg 60

acgaattcaa ttttatatga tatggctaaa aatgttggtg gagacaacgt cgatattcat 120

agtattgtac ctgttggtca agatcctcat gaatatgaag ttaaacctaa agatattaaa 180

aagttaactg acgctgacgt tattttatac aacggattaa atttagagac tggtaacggt 240

tggtttgaaa aagccttaga acaggctggt aaatcattaa aagataaaaa agttatcgca 300

gtatcaaaag atgttaaacc tatctattta aacggtgaag aaggcaacaa agataaacaa 360

gatccacacg catggttaag tttagataat ggtattaaat acgtaaaaac aattcaacaa 420

acatttatcg ataacgacaa aaaacataaa gcagattatg aaaagcaagg taacaaatac 480

attgctcaat tggaaaaatt aaataatgac agtaaagaca aatttaatga cattccaaaa 540

gaacaacgtg ccatgattac aagtgaaggt gccttcaagt acttctcaaa acaatacggt 600

attacaccag gttatatttg ggaaattaac actgaaaaac aaggtacacc tgaacaaatg 660

agacaagcta ttgagtttgt taaaaagcac aaattaaaac acttattagt agaaacaagt 720

gttgataaga aagcaatgga aagtttatct gaagaaacga agaaagatat ctttggtgaa 780

gtgtacacag attcaatcgg taaagaaggc actaaaggtg actcttacta caaaatgatg 840

aaatcaaata ttgaaactgt acacggaagc atgaaataa 879

<210> 121
<211> 292
<212> PRT
<213> Staphylococcus epidermidis

<400> 121
Met Gly Asn His Ser Asn His Glu His His Ser His Glu Gly Lys Leu
1 5 10 15

```
Lys Val Val Thr Thr Asn Ser Ile Leu Tyr Asp Met Val Lys Arg Val
            20                  25                  30

Gly Gly Asn Lys Val Asp Val His Ser Ile Val Pro Val Gly Gln Asp
        35                  40                  45

Pro His Glu Tyr Glu Val Lys Pro Lys Asp Ile Lys Ala Leu Thr Asp
    50                  55                  60

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

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

Asn Val Ile Ala Ala Ser Asn Asn Val Lys Pro Ile Tyr Leu Asn Gly
            100                 105                 110

Glu Glu Gly Asn Lys Asn Lys Gln Asp Pro His Ala Trp Leu Ser Leu
        115                 120                 125

Glu Asn Gly Ile Lys Tyr Val Lys Thr Ile Gln Lys Ser Leu Glu His
    130                 135                 140

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

Ile Ser Lys Leu Glu Glu Leu Asn Lys Asp Ser Lys Asn Lys Phe Asp
                165                 170                 175

Asp Ile Pro Lys Asn Gln Arg Ala Met Met Thr Ser Glu Gly Ala Phe
            180                 185                 190

Lys Tyr Phe Ala Gln Gln Phe Asp Val Lys Pro Gly Tyr Ile Trp Glu
        195                 200                 205

Ile Asn Thr Glu Lys Gln Gly Thr Pro Gly Gln Met Lys Gln Ala Ile
    210                 215                 220

Lys Phe Val Lys Asp Asn His Leu Lys His Leu Leu Val Glu Thr Ser
225                 230                 235                 240

Val Asp Lys Lys Ala Met Gln Ser Leu Ser Glu Glu Thr Lys Lys Asp
                245                 250                 255

Ile Tyr Gly Glu Val Phe Thr Asp Ser Ile Gly Lys Glu Gly Thr Lys
            260                 265                 270

Gly Asp Ser Tyr Tyr Lys Met Met Lys Ser Asn Ile Asp Thr Ile His
        275                 280                 285
```

Gly Ser Met Lys
290

<210> 122
<211> 879
<212> DNA
<213> Staphylococcus epidermidis

<400> 122
atggggaatc acagtaacca tgaacatcac tcacatgaag gaaaattaaa agttgtaact 60

acaaactcta ttctctatga catggttaaa cgtgtcggtg gaaataaggt cgatgttcat 120

agcatcgttc cagtaggaca agatccacat gaatatgagg ttaaacctaa agatattaaa 180

gcattaacag atgctgacgt tgtattttat aatggtttaa acctagaaac tggaaatggt 240

tggtttgaaa aagcacttga ccaagcagga aaatcaacaa aagataaaaa tgtgatagca 300

gcatcaaata atgttaaacc aatatactta aatggtgagg aaggtaacaa aaacaaacaa 360

gatccacatg catggttaag tttagagaat ggaattaaat acgtaaaaac aatacaaaaa 420

tcactagaac atcatgataa aaaagataag tctacatatg aaaaacaagg gaatgcatat 480

atatcaaaat tagaagaact taataaagat agtaaaaata aatttgatga catacccaaa 540

aatcaacgtg ccatgatgac aagtgaaggt gcatttaaat attttgctca acaattcgat 600

gttaaaccag gttatatttg ggagataaac acagaaaaac aaggtacacc tggtcaaatg 660

aaacaagcca ttaaatttgt taaagataat catttaaaac atttattagt cgaaacaagc 720

gtagataaaa aagctatgca aagtttatca gaagaaacta agaaagatat ttatggtgaa 780

gtatttaccg actctatagg taaggaaggt actaaaggtg actcatacta taaaatgatg 840

aaatctaata ttgatacaat acatggtagt atgaaataa 879

<210> 123
<211> 531
<212> PRT
<213> Staphylococcus aureus

<400> 123
Met Ala Ser Met Thr Gly Gly Gln Gln Met Gly Ser Glu Asn Ser Val
1 5 10 15

Thr Gln Ser Asp Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser
20 25 30

Ser Val Ser Ala Ala Pro Lys Thr Asp Asp Thr Asn Val Ser Asp Thr
35 40 45

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

Pro Ala Gln Gln Glu Thr Thr Gln Ser Ser Ser Thr Asn Ala Thr Thr
65 70 75 80

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Glu Glu Thr Pro Val Thr Gly Glu Ala Thr Thr Thr Thr Thr Asn Gln
                85                  90                  95

Ala Asn Thr Pro Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu
            100                 105                 110

Leu Val Asn Gln Thr Ser Asn Glu Thr Thr Phe Asn Asp Thr Asn Thr
        115                 120                 125

Val Ser Ser Val Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val
    130                 135                 140

Ser Thr Thr Gln Asp Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu
145                 150                 155                 160

Ser Ala Pro Gln Ser Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln
                165                 170                 175

Ala Val Asn Thr Ser Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala
            180                 185                 190

Val Ala Ala Asp Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu
        195                 200                 205

Thr Asn Val Thr Val Gly Ile Asp Ser Gly Thr Thr Val Tyr Pro His
    210                 215                 220

Gln Ala Gly Tyr Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser
225                 230                 235                 240

Ala Val Lys Gly Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn
                245                 250                 255

Leu Asn Gly Val Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly
            260                 265                 270

Asp Gln Val Leu Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile
        275                 280                 285

Tyr Thr Phe Thr Asp Tyr Val Asn Thr Lys Asp Asp Val Lys Ala Thr
    290                 295                 300

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

Asn Val Thr Leu Ala Thr Gly Ile Gly Ser Thr Thr Ala Asn Lys Thr
                325                 330                 335

Val Leu Val Asp Tyr Glu Lys Tyr Gly Lys Phe Tyr Asn Leu Ser Ile
            340                 345                 350
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Lys Gly Thr Ile Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln
        355                 360                 365

Thr Ile Tyr Val Asn Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu
    370                 375                 380

Thr Gly Asn Leu Lys Pro Asn Thr Asp Ser Asn Ala Leu Ile Asp Gln
385                 390                 395                 400

Gln Asn Thr Ser Ile Lys Val Tyr Lys Val Asp Asn Ala Ala Asp Leu
                405                 410                 415

Ser Glu Ser Tyr Phe Val Asn Pro Glu Asn Phe Glu Asp Val Thr Asn
            420                 425                 430

Ser Val Asn Ile Thr Phe Pro Asn Pro Asn Gln Tyr Lys Val Glu Phe
        435                 440                 445

Asn Thr Pro Asp Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn
    450                 455                 460

Gly His Ile Asp Pro Asn Ser Lys Gly Asp Leu Ala Leu Arg Ser Thr
465                 470                 475                 480

Leu Tyr Gly Tyr Asn Ser Asn Ile Ile Trp Arg Ser Met Ser Trp Asp
                485                 490                 495

Asn Glu Val Ala Phe Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp
            500                 505                 510

Lys Pro Val Val Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro
        515                 520                 525

Ile Pro Glu
    530
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<210> 124
<211> 1596
<212> DNA
<213> Staphylococcus aureus

<400> 124

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atggctagca tgactggtgg acagcaaatg ggtagtgaaa atagtgttac gcaatctgat     60

agcgcaagta acgaaagcaa aagtaatgat tcaagtagcg ttagtgctgc acctaaaaca    120

gacgacacaa acgtgagtga tactaaaaca tcgtcaaaca ctaataatgg cgaaacgagt    180

gtggcgcaaa atccagcaca acaggaaacg acacaatcat catcaacaaa tgcaactacg    240

gaagaaacgc cggtaactgg tgaagctact actacgacaa cgaatcaagc taatacaccg    300

gcaacaactc aatcaagcaa tacaaatgct gaagaattag tgaatcaaac aagtaatgaa    360

acgactttta atgatactaa tacagtatca tctgtaaatt cacctcaaaa ttctacaaat    420
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gcggaaaatg tttcaacaac gcaagatact tcaactgaag caacaccttc aaacaatgaa 480

tcagctccac agagtacaga tgcaagtaat aaagatgtag ttaatcaagc ggttaataca 540

agtgcgccta gaatgagagc atttagttta gcggcagtag ctgcagatgc accggcagct 600

ggcacagata ttacgaatca gttgacgaat gtgacagttg gtattgactc tggtacgact 660

gtgtatccac accaagcagg ttatgtcaaa ctgaattatg gtttttcagt gcctaattct 720

gctgttaaag gtgacacatt caaaataact gtacctaaag aattaaactt aaatggtgta 780

acttcaactg ctaaagtgcc accaattatg gctggagatc aagtattggc aaatggtgta 840

atcgatagtg atggtaatgt tatttataca tttacagact atgtaaatac taaagatgat 900

gtaaaagcaa ctttgaccat gcccgctgct attgaccctg aaaatgttaa aaagacaggt 960

aatgtgacat tggctactgg cataggtagt acaacagcaa acaaaacagt attagtagat 1020

tatgaaaaat atggtaagtt ttataactta tctattaaag gtacaattga ccaaatcgat 1080

aaaacaaata atacgtatcg tcagacaatt tatgtcaatc caagtggaga taacgttatt 1140

gcgccggttt taacaggtaa tttaaaacca aatacggata gtaatgcatt aatagatcag 1200

caaaatacaa gtattaaagt atataaagta gataatgcag ctgatttatc tgaaagttac 1260

tttgtgaatc cagaaaactt tgaggatgtc actaatagtg tgaatattac attcccaaat 1320

ccaaatcaat ataaagtaga gtttaatacg cctgatgatc aaattacaac accgtatata 1380

gtagttgtta atggtcatat tgatccgaat agcaaaggtg atttagcttt acgttcaact 1440

ttatatgggt ataactcgaa tataatttgg cgctctatgt catgggacaa cgaagtagca 1500

tttaataacg gatcaggttc tggtgacggt atcgataaac cagttgttcc tgaacaacct 1560

gatgagcctg gtgaaattga accaattcca gagtag 1596

<210> 125
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<221> MOD_RES
<222> (3)..(3)
<223> Any amino acid

<400> 125
Leu Pro Xaa Thr Gly
1 5

<210> 126
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 126
Thr Tyr Thr Phe Thr Asp Tyr Val Asp
1 5

<210> 127
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 127
Met Arg Gly Ser His His His His His His Gly Ser
1 5 10

<210> 128
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 128
Met Ala Ser Met Thr Gly Gly Gln Gln Met Gly Arg Gly Ser
1 5 10

<210> 129
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 129
Met Ala Ser Met Thr Gly Gly Gln Gln Met Gly
1 5 10

<210> 130
<211> 933
<212> PRT
<213> Staphylococcus aureus

<400> 130
Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1 5 10 15

Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
20 25 30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
35 40 45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Ser Ala
50 55 60

Ala Pro Lys Thr Asp Asp Thr Asn Val Ser Asp Thr Lys Thr Ser Ser
65 70 75 80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
85 90 95

Glu Thr Thr Gln Ser Ser Ser Thr Asn Ala Thr Thr Glu Glu Thr Pro
100 105 110

Val Thr Gly Glu Ala Thr Thr Thr Thr Thr Asn Gln Ala Asn Thr Pro
115 120 125

Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln
130 135 140

Thr Ser Asn Glu Thr Thr Phe Asn Asp Thr Asn Thr Val Ser Ser Val
145 150 155 160

Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln
165 170 175

Asp Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln
180 185 190

Ser Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr
195 200 205

Ser Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
210 215 220

Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asn Val Thr
225 230 235 240

Val Gly Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr
245 250 255

Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly
260 265 270

Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
275 280 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
290 295 300

Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305 310 315 320

Asp Tyr Val Asn Thr Lys Asp Asp Val Lys Ala Thr Leu Thr Met Pro
325 330 335

Ala Tyr Ile Asp Pro Glu Asn Val Lys Lys Thr Gly Asn Val Thr Leu
340 345 350

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

Tyr Glu Lys Tyr Gly Lys Phe Tyr Asn Leu Ser Ile Lys Gly Thr Ile
    370                 375                 380

Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385                 390                 395                 400

Asn Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu Thr Gly Asn Leu
                405                 410                 415

Lys Pro Asn Thr Asp Ser Asn Ala Leu Ile Asp Gln Gln Asn Thr Ser
            420                 425                 430

Ile Lys Val Tyr Lys Val Asp Asn Ala Ala Asp Leu Ser Glu Ser Tyr
        435                 440                 445

Phe Val Asn Pro Glu Asn Phe Glu Asp Val Thr Asn Ser Val Asn Ile
    450                 455                 460

Thr Phe Pro Asn Pro Asn Gln Tyr Lys Val Glu Phe Asn Thr Pro Asp
465                 470                 475                 480

Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp
                485                 490                 495

Pro Asn Ser Lys Gly Asp Leu Ala Leu Arg Ser Thr Leu Tyr Gly Tyr
            500                 505                 510

Asn Ser Asn Ile Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala
        515                 520                 525

Phe Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val
    530                 535                 540

Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu Asp
545                 550                 555                 560

Ser Asp Ser Asp Pro Gly Ser Asp Ser Gly Ser Asp Ser Asn Ser Asp
                565                 570                 575

Ser Gly Ser Asp Ser Gly Ser Asp Ser Thr Ser Asp Ser Gly Ser Asp
            580                 585                 590

Ser Ala Ser Asp Ser Asp Ser Ala Ser Asp Ser Asp Ser Ala Ser Asp
        595                 600                 605

Ser Asp Ser Ala Ser Asp Ser Asp Ser Ala Ser Asp Ser Asp Ser Asp
    610                 615                 620
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Asn Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
625 630 635 640

Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
645 650 655

Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
660 665 670

Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
675 680 685

Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
690 695 700

Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
705 710 715 720

Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
725 730 735

Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
740 745 750

Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Ala
755 760 765

Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
770 775 780

Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
785 790 795 800

Ser Asp Ser Asp Ser Asp Ser Glu Ser Asp Ser Asp Ser Glu Ser Asp
805 810 815

Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
820 825 830

Ser Asp Ser Asp Ser Ala Ser Asp Ser Asp Ser Gly Ser Asp Ser Asp
835 840 845

Ser Ser Ser Asp Ser Asp Ser Glu Ser Asp Ser Asn Ser Asp Ser Glu
850 855 860

Ser Gly Ser Asn Asn Asn Val Val Pro Pro Asn Ser Pro Lys Asn Gly
865 870 875 880

Thr Asn Ala Ser Asn Lys Asn Glu Ala Lys Asp Ser Lys Glu Pro Leu
885 890 895

Pro Asp Thr Gly Ser Glu Asp Glu Ala Asn Thr Ser Leu Ile Trp Gly
900 905 910

Leu Leu Ala Ser Ile Gly Ser Leu Leu Leu Phe Arg Arg Lys Lys Glu
915 920 925

Asn Lys Asp Lys Lys
930

<210> 131
<211> 2802
<212> DNA
<213> Staphylococcus aureus

<400> 131
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gtgcttgtag gtacgttaat cggttttgga ctactcagca gtaaagaagc agatgcaagt 120

gaaaatagtg ttacgcaatc tgatagcgca agtaacgaaa gcaaaagtaa tgattcaagt 180

agcgttagtg ctgcacctaa aacagacgac acaaacgtga gtgatactaa aacatcgtca 240

aacactaata atggcgaaac gagtgtggcg caaaatccag cacaacagga aacgacacaa 300

tcatcatcaa caaatgcaac tacggaagaa acgccggtaa ctggtgaagc tactactacg 360

acaacgaatc aagctaatac accggcaaca actcaatcaa gcaatacaaa tgcggaggaa 420

ttagtgaatc aaacaagtaa tgaaacgact tttaatgata ctaatacagt atcatctgta 480

aattcacctc aaaattctac aaatgcggaa aatgtttcaa caacgcaaga tacttcaact 540

gaagcaacac cttcaaacaa tgaatcagct ccacagagta cagatgcaag taataaagat 600

gtagttaatc aagcggttaa tacaagtgcg cctagaatga gagcatttag tttagcggca 660

gtagctgcag atgcaccggc agctggcaca gatattacga atcagttgac gaatgtgaca 720

gttggtattg actctggtac gactgtgtat ccgcaccaag caggttatgt caaactgaat 780

tatggttttt cagtgcctaa ttctgctgtt aaaggtgaca cattcaaaat aactgtacct 840

aaagaattaa acttaaatgg tgtaacttca actgctaaag tgccaccaat tatggctgga 900

gatcaagtat tggcaaatgg tgtaatcgat agtgatggta atgttattta tacatttaca 960

gactatgtaa atactaaaga tgatgtaaaa gcaactttga ccatgcccgc ttatattgac 1020

cctgaaaatg ttaaaaagac aggtaatgtg acattggcta ctggcatagg tagtacaaca 1080

gcaaacaaaa cagtattagt agattatgaa aaatatggta agttttataa cttatctatt 1140

aaaggtacaa ttgaccaaat cgataaaaca aataatacgt atcgtcagac aatttatgtc 1200

aatccaagtg gagataacgt tattgcgccg gttttaacag gtaatttaaa accaaatacg 1260

gatagtaatg cattaataga tcagcaaaat acaagtatta aagtatataa agtagataat 1320

gcagctgatt tatctgaaag ttactttgtg aatccagaaa actttgagga tgtcactaat 1380

agtgtgaata ttacattccc aaatccaaat caatataaag tagagtttaa tacgcctgat 1440

gatcaaatta caacaccgta tatagtagtt gttaatggtc atattgatcc gaatagcaaa 1500

ggtgatttag ctttacgttc aactttatat gggtataact cgaatataat ttggcgctct 1560

atgtcatggg acaacgaagt agcatttaat aacggatcag gttctggtga cggtatcgat 1620

aaaccagttg ttcctgaaca acctgatgag cctggtgaaa ttgaaccaat tccagaggat 1680

tcagattctg acccaggttc agattctggc agcgattcta attcagatag cggttcagat 1740

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agtgattcag actcagcgag tgattcagat tcagcaagcg attccgactc agcgagcgat 1860

tccgactcag acaatgactc ggattcagat agcgattctg actcagacag tgactcagat 1920

tccgacagtg actcagattc agatagcgat tctgactcag acagtgactc agattcagat 1980

agcgattcag attcagatag cgattcagat tccgacagtg attccgactc agacagcgat 2040

tctgactccg acagtgattc cgactcagac agcgattcag attccgacag tgattccgac 2100

tcagatagcg attccgactc agatagcgac tcagattcag acagcgattc agattcagac 2160

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agtgactcgg attcagatag cgactcagac tcggatagcg actcggattc agatagcgat 2400

tcggactcag atagcgattc agaatcagac agcgattcag aatcagacag cgattcagat 2460

tcagacagcg actcagacag tgactcagat tcagatagtg actcggattc agcgagtgat 2520

tcagactcag gtagtgactc cgattcatca agtgattccg actcagaaag tgattcaaat 2580

agcgattccg agtcaggttc taacaataat gtagttccgc ctaattcacc taaaaatggt 2640

actaatgctt ctaataaaaa tgaggctaaa gatagtaaag aaccattacc agatacaggt 2700

tctgaagatg aagcaaatac gtcactaatt tggggattat tagcatcaat aggttcatta 2760

ctacttttca gaagaaaaaa agaaaataaa gataagaaat aa 2802