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(54) **COMPOSITIONS AND METHODS RELATED TO *STAPHYLOCOCCAL* BACTERIUM PROTEINS**

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None
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(57) **ABSTRACT**

The present invention concerns methods and compositions for treating or preventing a bacterial infection, particularly infection by a *Staphylococcus* bacterium. The invention provides methods and compositions for stimulating an immune response against the bacteria. In certain embodiments, the methods and compositions involve an EsaC polypeptide.

9 Claims, 7 Drawing Sheets

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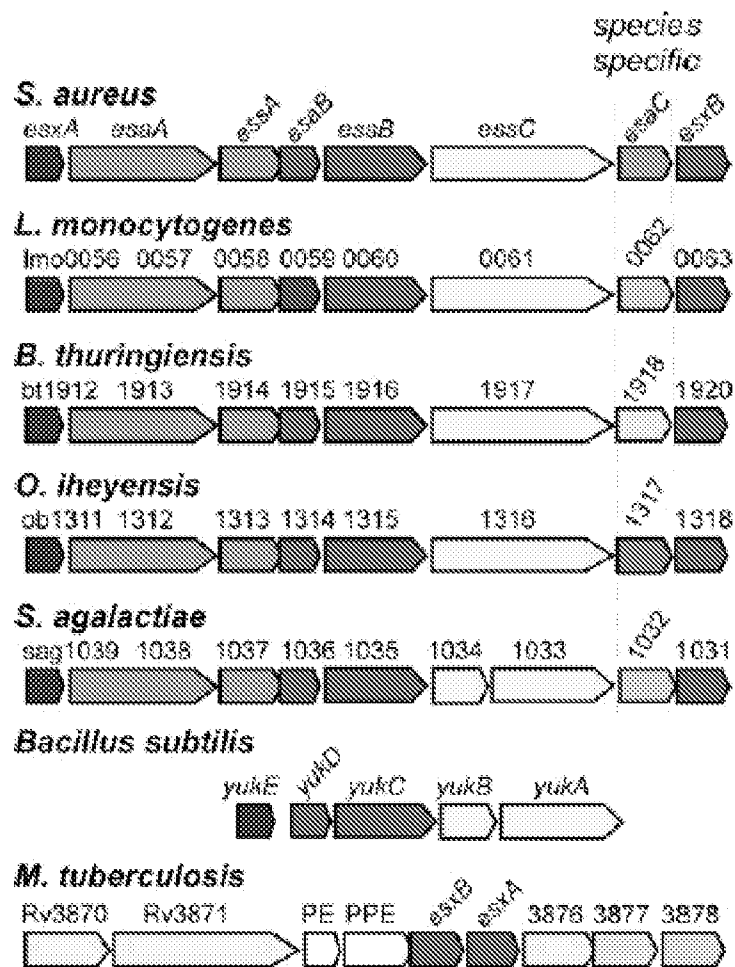


FIG. 1

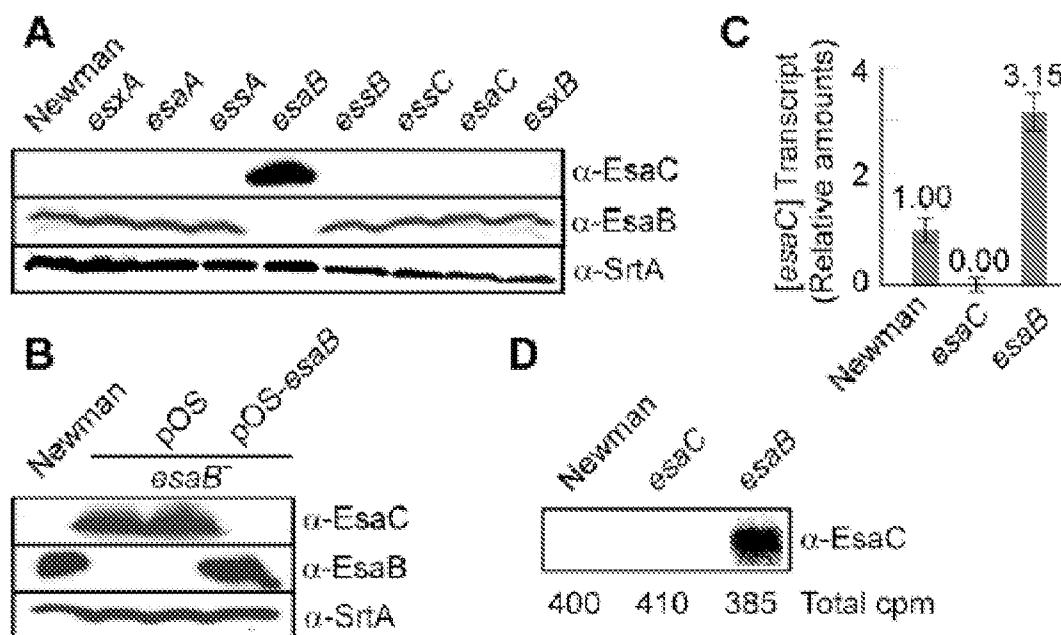


FIG. 2A-D

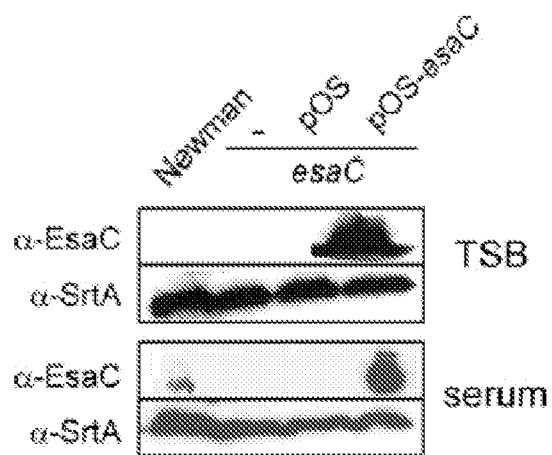


FIG. 3

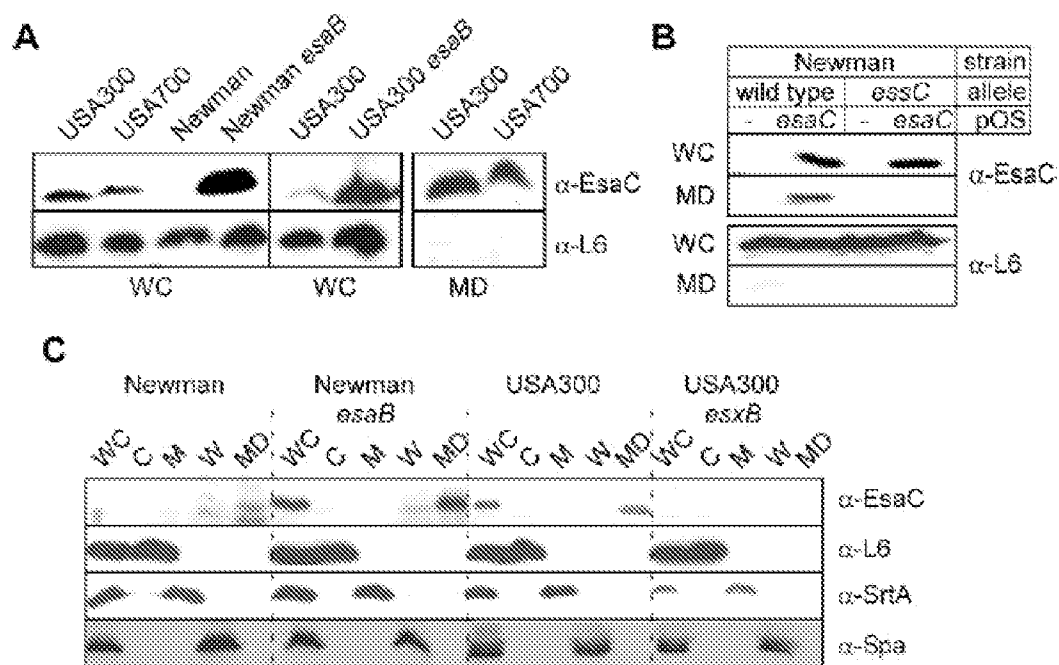


FIG. 4A-C

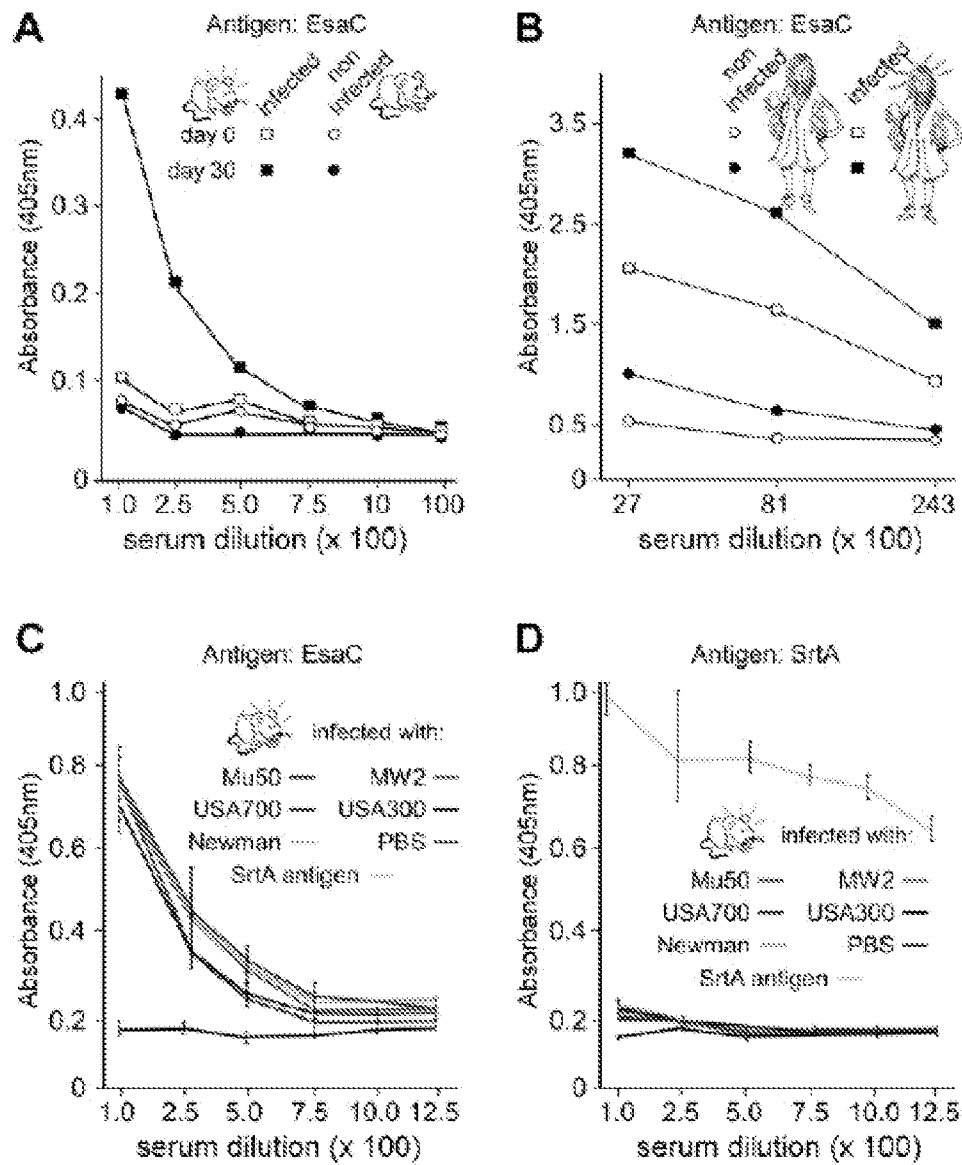
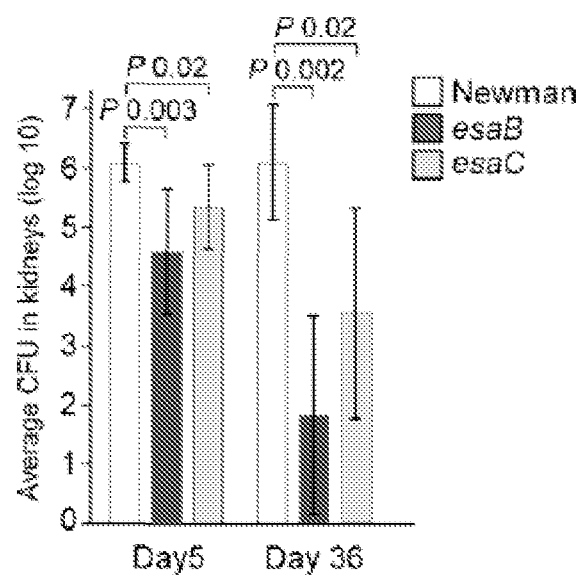


FIG. 5A-D

**FIG. 6**

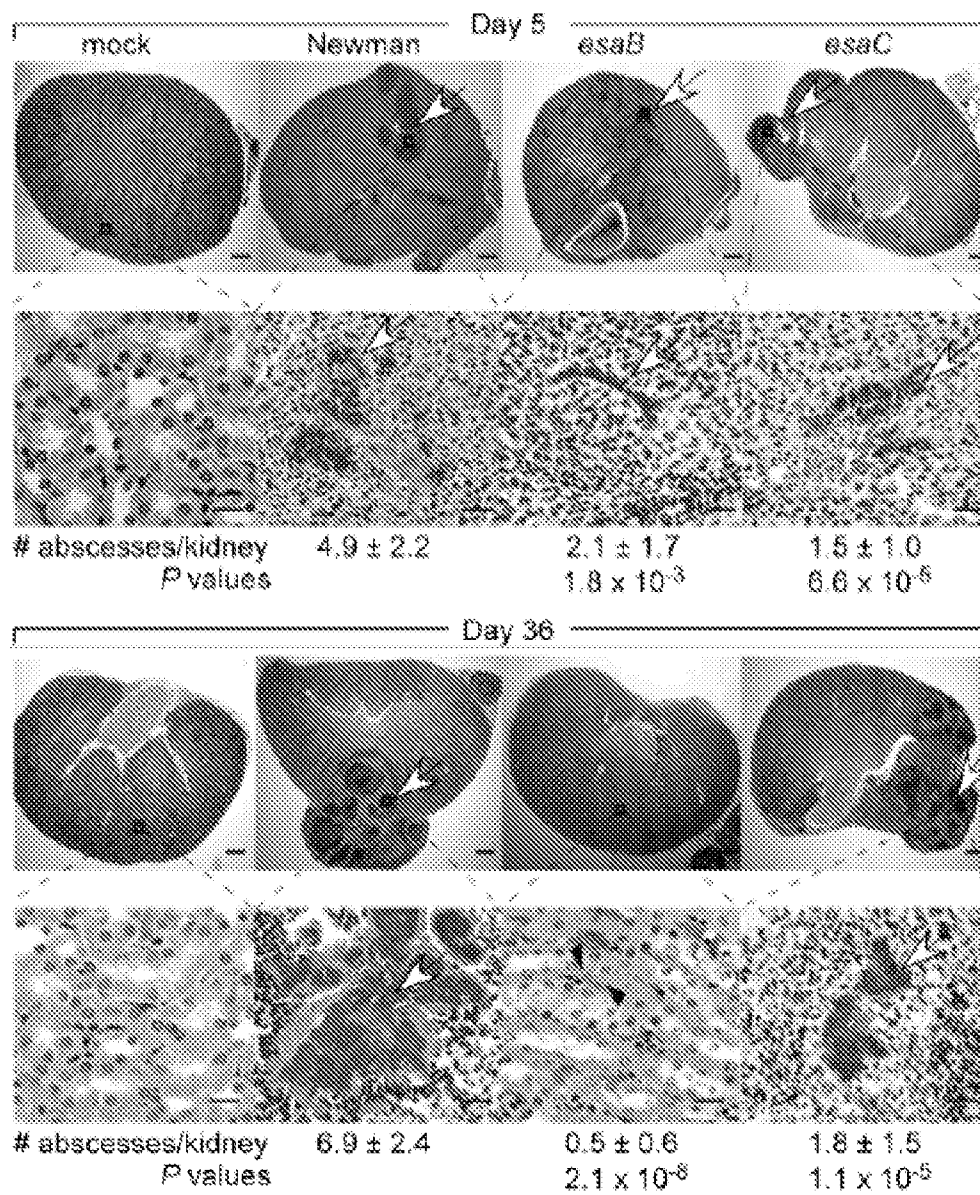


FIG. 7

COMPOSITIONS AND METHODS RELATED TO *STAPHYLOCOCCAL* BACTERIUM PROTEINS

The present application is a national phase application under 35 U.S.C. §371 of International Patent Application PCT Application No. PCT/US2009/047990, filed 19 Jun. 2009, which claims the benefit of U.S. Provisional Application No. 61/084,472, filed 29 Jul. 2008. The entire contents of these applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

I. Field of the Invention

The present invention relates generally to the fields of immunology, microbiology, and pathology. More particularly, it concerns methods and compositions involving bacterial proteins, which can be used to invoke an immune response against the bacteria. The proteins include proteins of the Ess pathway (e.g., EsaC) and/or peptides or proteins processed by the sortase pathway, including proteins or polypeptides of *Staphylococcus* and other gram-positive bacteria.

II. Background

The number of both community acquired and hospital acquired infections have increased over recent years with the increased use of intravascular devices. Hospital acquired (nosocomial) infections are a major cause of morbidity and mortality, more particularly in the United States, where it affects more than 2 million patients annually. The most frequent infections are urinary tract infections (33% of the infections), followed by pneumonia (15.5%), surgical site infections (14.8%) and primary bloodstream infections (13%) (Emorl and Gaynes, 1993).

Staphylococcus aureus, Coagulase-negative *Staphylococcus* (mostly *Staphylococcus epidermidis*), *enterococcus* spp., *Escherichia coli* and *Pseudomonas aeruginosa* are the major nosocomial pathogens. Although these pathogens almost cause the same number of infections, the severity of the disorders they can produce combined with the frequency of antibiotic resistant isolates balance this ranking towards *S. aureus* and *S. epidermidis* as being the most significant nosocomial pathogens.

Staphylococcus can cause a wide variety of diseases in humans and other animals through either toxin production or invasion. *Staphylococcal* toxins are a common cause of food poisoning, as the bacteria can grow in improperly-stored food.

Staphylococcus epidermidis is a normal skin commensal which is also an important opportunistic pathogen responsible for infections of impaired medical devices and infections at sites of surgery. Medical devices infected by *S. epidermidis* include cardiac pacemakers, cerebrospinal fluid shunts, continuous ambulatory peritoneal dialysis catheters, orthopedic devices and prosthetic heart valves.

Staphylococcus aureus is the most common cause of nosocomial infections with a significant morbidity and mortality. It is the cause of some cases of osteomyelitis, endocarditis, septic arthritis, pneumonia, abscesses and toxic shock syndrome.

S. aureus can survive on dry surfaces, increasing the chance of transmission. Any *S. aureus* infection can cause the staphylococcal scalded skin syndrome, a cutaneous reaction to exotoxin absorbed into the bloodstream. It can also cause a type of septicemia called pyaemia. The infection can be life-threatening. Problematically, Methicillin-resistant *Staphylococcus aureus* (MRSA) has become a major cause of hospital-acquired infections.

S. aureus and *S. epidermidis* infections are typically treated with antibiotics, with penicillin being the drug of choice, whereas vancomycin is used for methicillin resistant isolates. The percentage of staphylococcal strains exhibiting wide-spectrum resistance to antibiotics has become increasingly prevalent, posing a threat for effective antimicrobial therapy. In addition, the recent emergence of vancomycin resistant *S. aureus* strain has aroused fear that methicillin resistant *S. aureus* strains for which no effective therapy is available will emerge and spread.

An alternative approach of using antibodies against staphylococcal antigens in passive immunotherapy has been investigated. Therapy involving administration of polyclonal antisera are under development (WO00/15238, WO00/12132) as well as treatment with monoclonal antibody against lipoteichoic acid (WO98/57994).

An alternative approach would be use of active vaccination to generate an immune response against staphylococci. The *S. aureus* genome has been sequenced and many of the coding sequences have been identified (WO02/094868, EP0786519). The same is true for *S. epidermidis* (WO01/34809). As a refinement of this approach, others have identified proteins that are recognized by hyperimmune sera from patients who have suffered staphylococcal infection (WO01/98499, WO02/059148).

S. aureus secretes a plethora of virulence factors into the extracellular milieu (Archer, 1998; Dinges et al., 2000; Foster, 2005; Shaw et al., 2004; Sibbald et al., 2006). Like most secreted proteins, these virulence factors are translocated by the Sec machinery across the plasma membrane. Proteins secreted by the Sec machinery bear an N-terminal leader peptide that is removed by leader peptidase once the pre-protein is engaged in the Sec translocon (Dalbey and Wickner, 1985; van Wely et al., 2001). Recent genome analysis suggests that Actinobacteria and members of the Firmicutes encode an additional secretion system that recognizes a subset of proteins in a Sec-independent manner (Pallen, 2002). ESAT-6 (early secreted antigen target 6 kDa) and CFP-10 (culture filtrate antigen 10 kDa) of *Mycobacterium tuberculosis* represent the first substrates of this novel secretion system termed ESX-1 or 5 nm in *M. tuberculosis* (Andersen et al., 1995; Hsu et al., 2003; Pym et al., 2003; Stanley et al., 2003). In *S. aureus*, two ESAT-6 like factors designated EsxA and EsxB are secreted by the Ess pathway (ESAT-6 secretion system) (Burts et al., 2005).

M. tuberculosis variants lacking ESAT-6 (esxA) or CFP-10 (esxB) display severe defects in the establishment of tuberculosis (Guinn et al., 2004; Hsu et al., 2003; Sorensen et al., 1995; Stanley et al., 2003). In *S. aureus*, failure to produce EsxA and EsxB leads to decreased virulence in a murine abscess model of infection, suggesting that the Ess pathway is involved in the pathogenesis of staphylococcal infections as well (Burts et al., 2005). Thus far, three genes, *essA*, *essB*, and *essC*, appear to be important for production of EsxA and EsxB and possibly secretion across the staphylococcal envelope. The genes are encoded within an eight gene cluster conserved in other Gram positive bacteria (FIG. 1). Of those only *esxA*, *esxB*, and *essC*, share homologues with genes of *M. tuberculosis* (Burts et al., 2005; Pallen, 2002). The remaining genes in the cluster, *esaA*, *esaB*, and *esaC*, are dispensable for secretion of EsxA and EsxB and are referred to as "accessory" factors for lack of attributable function (*esa*, ESAT-6 secretion accessory) (Burts et al., 2005).

The first generation of vaccines targeted against *S. aureus* or against the exoproteins it produces have met with limited success (Lee, 1996). There remains a need to develop effective

tive vaccines against *staphylococcus* infections. Additional compositions for treating staphylococcal infections are also needed.

SUMMARY OF THE INVENTION

Staphylococcus aureus encodes the specialized secretion system Ess (ESAT-6 secretion system). The *ess* locus is a cluster of eight genes (*esxA*, *essABC*, *esaABC*) of which *esxA* and *esxB* display homology to secreted ESAT-6 proteins of *Mycobacterium tuberculosis*. *EsxA* and *EsxB* require *EssA*, *EssB* and *EssC* for transport across the staphylococcal envelope. Herein, the role of *EsaB* and *EsaC* are described and it is shown that *EsaB* is a negative regulator of *EsaC*. Further, *EsaC* production is repressed when staphylococci are grown in broth and increased when staphylococci replicate in serum or infected hosts. *EsaB* is constitutively produced and remains in the cytoplasm whereas *EsaC* is secreted. This secretion requires an intact *Ess* pathway. Mutants lacking *esaB* or *esaC* display only a small defect in acute infection, but remarkably are unable to promote persistent abscesses during animal infection. Together, the data indicate that *EsaB* controls the production of effector molecules that are important for host pathogen interaction. One such effector, *EsaC*, is a secretion substrate of the *Ess* pathway that implements its pathogenic function during infection.

The inventors have identified a *S. aureus* *EsaC* polypeptide that is useful for immunization, either alone or in combination. *EsaC* polypeptides may be combined with *S. aureus* saccharides or other *S. aureus* polypeptides. *EsaC* antigens are useful in *S. aureus* vaccines but may also be used as components in vaccines for immunising against multiple pathogens. Thus, in one embodiment the invention provides an immunogenic composition comprising a *EsaC* antigen or immunogenic fragment thereof. In a second embodiment the invention provides an immunogenic composition comprising a combination of antigens, said combination comprising a *EsaC* antigen or immunogenic fragment thereof, and one or more antigens selected from the group consisting of: (1) a *clfA* antigen; (2) a *clfB* antigen; (3) a *sdrE2* antigen; (4) a *sdrC* antigen; (5) a *sasF* antigen; (6) a *emp* antigen; (7) a *sdrD* antigen; (8) a *spa* antigen; (9) a *ebh* antigen; (10) a *esxA* antigen; (11) a *esxB* antigen; (12) a *isdC* antigen; (13) a *hla* antigen; (14) a *isdA* antigen; (15) a *isdB* antigen; (16) an immunogenic fragment of any one of the preceding antigens. In a third embodiment, the invention provides an immunogenic composition comprising a *EsaC* antigen or immunogenic fragment thereof and a staphylococcal saccharide. For example, an immunogenic composition of the invention can usefully include one or more *S. aureus* capsular saccharide conjugate(s) e.g. against a serotype 5 and/or a serotype 8 strain.

Advantageous combinations of the invention are those in which two or more antigens act synergistically. Thus the protection against *S. aureus* disease achieved by their combined administration exceeds that expected by mere addition of their individual protective efficacy.

The present invention also provides for the use of *EsaC* in methods and compositions for the treatment of bacterial and/or staphylococcal infection. This application also provides an immunogenic composition comprising an *EsaC* antigen or immunogenic fragment thereof. In certain embodiments, the compositions of the invention are used in the manufacture of medicaments for the therapeutic and/or prophylactic treatment of bacterial infections, particularly *staphylococcus* infections. Furthermore, the present invention provides methods and compositions that can be used to treat (e.g., limiting

staphylococcal abscess formation and/or persistence in a subject) or prevent bacterial infection. In some cases, methods for stimulating an immune response involve administering to the subject an effective amount of a composition including or encoding all or part of the *EsaC* polypeptide or antigen, and in certain aspects other bacterial proteins. Other bacterial proteins include, but are not limited to (i) a secreted virulence factor, and/or a cell surface protein or peptide, or (ii) a recombinant nucleic acid molecule encoding a secreted virulence factor, and/or a cell surface protein or peptide.

The term “providing” is used according to its ordinary meaning to indicate “to supply or furnish for use.” In some embodiments, the protein is provided directly by administering the protein, while in other embodiments, the protein is effectively provided by administering a nucleic acid that encodes the protein. In certain aspects the invention contemplates compositions comprising various combinations of nucleic acid, antigens, peptides, and/or epitopes.

The subject typically will have (e.g., diagnosed with a persistent staphylococcal infection), will be suspected of having, or will be at risk of developing a staphylococcal infection. Compositions of the present invention include immunogenic compositions wherein the antigen(s) or epitope(s) are contained in an amount effective to achieve the intended purpose. More specifically, an effective amount means an amount of active ingredients necessary to stimulate or elicit an immune response, or provide resistance to, amelioration of, or mitigation of infection. In more specific aspects, an effective amount prevents, alleviates or ameliorates symptoms of disease or infection, or prolongs the survival of the subject being treated. Determination of the effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. For any preparation used in the methods of the invention, an effective amount or dose can be estimated initially from in vitro, cell culture, and/or animal model assays. For example, a dose can be formulated in animal models to achieve a desired immune response or circulating antibody concentration or titer. Such information can be used to more accurately determine useful doses in humans.

In other aspects the subject can be administered an *EsaC* modulator, such as an antibody that binds *EsaC*. An *EsaC* modulator may bind *EsaC* directly. The *EsaC* modulator can be an antibody or cell that binds *EsaC*. An antibody can be an antibody fragment, a humanized antibody, a monoclonal antibody or the like. In certain aspects, the *EsaC* modulator is elicited by providing an *EsaC* peptide that results in the production of an antibody that binds *EsaC* in the subject. The *EsaC* modulator is typically formulated in a pharmaceutically acceptable composition. The *EsaC* modulator composition can further comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 for more staphylococcal antigens or immunogenic fragments thereof. Staphylococcal antigens include, but are not limited to all or a segment of *Eap*, *Ebh*, *Emp*, *EsaB*, *EsxA*, *EsxB*, *SdrC*, *SdrD*, *SdrE*, *IsdA*, *IsdB*, *ClfA*, *ClfB*, *Coa*, *Hla* (e.g., H35 mutants), *IsdC*, *SasF*, *vWa*, *SpA* and variants thereof (See U.S. Provisional Application Ser. Nos. 61/166,432, filed Apr. 3, 2009; 61/170,779, filed Apr. 20, 2009; and 61/103,196, filed Oct. 6, 2009; each of which is incorporated herein by reference in their entirety), *vWh*, 52 kDa vitronectin binding protein (WO 01/60852), *Aaa* (GenBank CAC80837), *Aap* (GenBank accession AJ249487), *Ant* (GenBank accession NP_372518), autolysin glucosaminidase, autolysin amidase, *Cna*, collagen binding protein (U.S. Pat. No. 6,288,214), *EFB* (FIB), *Elastin* binding protein (*EbpS*), *EPB*, *FbpA*, *fibrinogen* binding protein (U.S. Pat. No. 6,008,341), *Fibronectin* binding protein

(U.S. Pat. No. 5,840,846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/P isA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (U.S. Pat. No. 5,648,240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK, SBI, SdrF (WO 00/12689), SdrG/Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (U.S. Pat. No. 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein (see PCT publications WO2007/113222, WO2007/113223, WO2006/032472, WO2006/032475, WO2006/032500, each of which is incorporated herein by reference in their entirety). The staphylococcal antigen, or immunogenic fragment or segment can be administered concurrently with the EsaC modulator. The staphylococcal antigen or immunogenic fragment and the EsaC modulator can be administered in the same composition. The EsaC modulator can also be a recombinant nucleic acid molecule encoding an EsaC peptide. A recombinant nucleic acid molecule can encode the EsaC peptide and at least one staphylococcal antigen or immunogenic fragment. As used herein, the term “modulate” or “modulation” encompasses the meanings of the words “enhance,” or “inhibit.” “Modulation” of activity may be either an increase or a decrease in activity. As used herein, the term “modulator” refers to compounds that effect the function of a moiety, including up-regulation, induction, stimulation, potentiation, inhibition, down-regulation, or suppression of a protein, nucleic acid, gene, organism or the like.

In certain embodiments the methods and compositions use or include or encode all or part of the EsaC polypeptide, peptide, or antigen. In other aspects EsaC may be used in combination with other secreted factors such as an Esx protein, for instance, all or part of an EsxA or EsxB protein. In certain aspects, other staphylococcal antigens that can be included in the compositions and methods include, but are not limited to all or a segment of an isolated Eap, Ebh, Emp, EsaB, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla, IsdC, SasF, SpA, vWa, vWh, 52 kDa vitronectin binding protein (WO 01/60852), Aaa, Aap, Ant, autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (U.S. Pat. No. 6,288,214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (U.S. Pat. No. 6,008,341), Fibronectin binding protein (U.S. Pat. No. 5,840,846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/P isA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (U.S. Pat. No. 5,648,240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK, SBI, SdrF (WO 00/12689), SdrG/Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (U.S. Pat. No. 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein. In certain embodiments, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of Eap, Ebh, Emp, EsaB, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla, IsdC, SasF, SpA, vWa, vWh, 52 kDa vitronectin binding protein (WO 01/60852), Aaa, Aap, Ant, autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (U.S. Pat. No. 6,288,214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (U.S. Pat. No. 6,008,341), Fibronectin binding protein (U.S. Pat. No. 5,840,846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/P isA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue

(U.S. Pat. No. 5,648,240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK, SBI, SdrF (WO 00/12689), SdrG/Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (U.S. Pat. No. 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein can be specifically excluded from a formulation, composition, or method of the invention.

Embodiments of the invention include compositions that contain or do not contain a bacterium. A composition may or may not include an attenuated or viable or intact staphylococcal bacterium. In certain aspects, the composition comprises a bacterium that is not a Staphylococci bacterium or does not contain Staphylococci bacteria. In certain embodiments a bacterial composition comprises an isolated or recombinantly expressed EsaC polypeptide or a nucleotide encoding the same. In still further aspects, the isolated EsaC polypeptide is multimerized, e.g., a dimer, a trimer, a tetramer, etc. In certain aspects of the invention, a composition comprises multimers of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more isolated cell surface proteins or segments thereof. In a further aspect the other polypeptides or peptides can be expressed or included in a bacterial composition including, but not limited to Eap, Ebh, Emp, EsaB, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla, IsdC, SasF, SpA, vWa, vWh, 52 kDa vitronectin binding protein (WO 01/60852), Aaa, Aap, Ant, autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (U.S. Pat. No. 6,288,214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (U.S. Pat. No. 6,008,341), Fibronectin binding protein (U.S. Pat. No. 5,840,846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/P isA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (U.S. Pat. No. 5,648,240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK, SBI, SdrF (WO 00/12689), SdrG/Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (U.S. Pat. No. 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein, or immunogenic fragments thereof. Alternatively, the composition may be or may include a recombinantly engineered *Staphylococcus* bacterium that has been altered in a way that comprises specifically altering the bacterium with respect to a secreted virulence factor or cell surface protein. For example, the bacteria may be recombinantly modified to express more of the virulence factor or cell surface protein than it would express if unmodified.

The term “isolated” can refer to a nucleic acid or polypeptide that is substantially free of cellular material, bacterial material, viral material, or culture medium (when produced by recombinant DNA techniques) of their source of origin, or chemical precursors or other chemicals (when chemically synthesized). Moreover, an isolated compound refers to one that can be administered to a subject as an isolated compound; in other words, the compound may not simply be considered “isolated” if it is adhered to a column or embedded in an agarose gel. Moreover, an “isolated nucleic acid fragment” or “isolated peptide” is a nucleic acid or protein fragment that is not naturally occurring as a fragment and/or is not typically in the functional state.

Moieties of the invention, such as polypeptides, peptides, antigens or immunogens, may be conjugated or linked covalently or noncovalently to other moieties such as adjuvants, proteins, peptides, supports, fluorescence moieties, or labels. The term “conjugate” or “immunoconjugate” is

broadly used to define the operative association of one moiety with another agent and is not intended to refer solely to any type of operative association, and is particularly not limited to chemical "conjugation." Recombinant fusion proteins are particularly contemplated. Compositions of the invention may further comprise an adjuvant or a pharmaceutically acceptable excipient. An adjuvant may be covalently or non-covalently coupled to a polypeptide or peptide of the invention. In certain aspects, the adjuvant is chemically conjugated to a protein, polypeptide, or peptide.

The term "EsaC polypeptide" refers to polypeptides that include isolated wild-type EsaC proteins from *staphylococcus* bacteria, as well as variants that stimulate an immune response against *staphylococcus* bacteria EsaC proteins. Similarly, the terms Eap, Ebh, Emp, EsaB, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla, IsdC, SasF, SpA, vWa, vWh, 52 kDa vitronectin binding protein (WO 01/60852), Aaa, Aap, Ant, autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (U.S. Pat. No. 6,288,214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (U.S. Pat. No. 6,008,341), Fibronectin binding protein (U.S. Pat. No. 5,840,846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/P isA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (U.S. Pat. No. 5,648,240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK, SBI, SdrF (WO 00/12689), SdrG/Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (U.S. Pat. No. 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein refer to a proteins that include an amino acid sequence that is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% identical to isolated wild-type Eap, Ebh, Emp, EsaB, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla, IsdC, SasF, SpA, vWa, vWh, 52 kDa vitronectin binding protein (WO 01/60852), Aaa, Aap, Ant, autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (U.S. Pat. No. 6,288,214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (U.S. Pat. No. 6,008,341), Fibronectin binding protein (U.S. Pat. No. 5,840,846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/P isA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (U.S. Pat. No. 5,648,240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK, SBI, SdrF (WO 00/12689), SdrG/Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (U.S. Pat. No. 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein polypeptides from *staphylococcus* bacteria, as well as variants that stimulate an immune response against *staphylococcus* bacteria. An immune response refers to a humoral response, a cellular response, or both a humoral and cellular response in an organism. An immune response can be measured by assays that include, but are not limited to, assays measuring the presence or amount of antibodies that specifically recognize a protein or cell surface protein, assays measuring T-cell activation or proliferation, and/or assays that measure modulation in terms of activity or expression of one or more cytokines.

Embodiments of the present invention include methods for eliciting an immune response against a *staphylococcus* bacterium or staphylococci in a subject comprising providing to the subject an effective amount of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more staphylococcal polypeptides or segments/fragments

thereof. A staphylococcal polypeptide includes, but is not limited to an EsaC, EsxA, or EsxB protein and immunogenic fragments thereof. Other staphylococcal polypeptides include, but are not limited to Eap, Ebh, Emp, EsaB, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla, IsdC, SasF, SpA, vWa, vWh, 52 kDa vitronectin binding protein (WO 01/60852), Aaa, Aap, Ant, autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (U.S. Pat. No. 6,288,214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (U.S. Pat. No. 6,008,341), Fibronectin binding protein (U.S. Pat. No. 5,840,846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/P isA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (U.S. Pat. No. 5,648,240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK, SBI, SdrF (WO 00/12689), SdrG/Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (U.S. Pat. No. 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein, and immunogenic fragments thereof.

In certain embodiments EsaC polypeptides or immunogenic fragments thereof can be provided in combination with one or more antigens or immunogenic fragments thereof, including, but not limited to Eap, Ebh, Emp, EsaB, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla, IsdC, SasF, SpA, vWa, vWh, 52 kDa vitronectin binding protein (WO 01/60852), Aaa, Aap, Ant, autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (U.S. Pat. No. 6,288,214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (U.S. Pat. No. 6,008,341), Fibronectin binding protein (U.S. Pat. No. 5,840,846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/P isA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (U.S. Pat. No. 5,648,240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK, SBI, SdrF (WO 00/12689), SdrG/Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (U.S. Pat. No. 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein.

Embodiments of the invention include compositions that may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity or similarity to EsaC, a secreted protein, a surface protein, or other staphylococcal proteins, polypeptides or segments thereof. In a further embodiment of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an EsaC polypeptide (SEQ ID NO:2) or EsaC nucleic acid (SEQ ID NO:1), in certain aspects the EsaC polypeptide will have an amino acid sequence of SEQ ID NO:2. Similarity or identity, with identity being preferred, is known in the art and a number of different programs can be used to identify whether a protein (or nucleic acid) has sequence identity or similarity to a known sequence. Sequence identity and/or similarity is determined using standard techniques known in the art, including, but not limited to, the local sequence identity algorithm of Smith & Waterman (1981), by the sequence identity alignment algorithm of Needleman & Wunsch (1970), by the search for similarity method of Pearson & Lipman (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science

Drive, Madison, Wis.), the Best Fit sequence program described by Devereux et al. (1984), preferably using the default settings, or by inspection. Preferably, percent identity is calculated by using alignment tools known to and readily ascertainable to those of skill in the art. Typically, identity is the number of identical amino acids in the same or similar location divided by the total the number of amino acids in the polypeptide as a whole or in the number of amino acids within a specified segment.

In still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an EsxA protein. In certain aspects the EsxA protein will have the amino acid sequence of SEQ ID NO:4.

In still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an EsxB protein. In certain aspects the EsxB protein will have the amino acid sequence of SEQ ID NO:6.

In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an SdrD protein. In certain aspects the SdrD protein will have the amino acid sequence of SEQ ID NO:8.

In further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an SdrE protein. In certain aspects the SdrE protein will have the amino acid sequence of SEQ ID NO:10.

In still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an IsdA protein. In certain aspects the IsdA protein will have the amino acid sequence of SEQ ID NO:12.

In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an IsdB protein. In certain aspects the IsdB protein will have the amino acid sequence of SEQ ID NO:14.

Embodiments of the invention include compositions that include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to a Spa protein. In certain aspects the Spa protein will have the amino acid sequence of SEQ ID NO:16.

In a further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to a ClfB protein. In certain aspects the ClfB protein will have the amino acid sequence of SEQ ID NO:18.

In still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an IsdC protein. In certain aspects the IsdC protein will have the amino acid sequence of SEQ ID NO:20.

In yet further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or

99% identical or similar to a SasF protein. In certain aspects the SasF protein will have the amino acid sequence of SEQ ID NO:22.

In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an SdrC protein. In certain aspects the SdrC protein will have the amino acid sequence of SEQ ID NO:24.

In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an ClfA protein. In certain aspects the ClfA protein will have the amino acid sequence of SEQ ID NO: 26.

In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an Eap protein. In certain aspects the Eap protein will have all or part of the amino acid sequence of SEQ ID NO:28.

In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an Ebh protein. In certain aspects the Ebh protein will have all or part of the amino acid sequence of SEQ ID NO:29.

In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an Emp protein. In certain aspects the Emp protein will have all or part of the amino acid sequence of SEQ ID NO:30.

In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to a Coa protein. In certain aspects the Coa protein will have all or part of the amino acid sequence of SEQ ID NO:31.

In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to a Hla protein. In certain aspects the Hla protein will have all or part of the amino acid sequence of SEQ ID NO:41. In certain aspects Hla peptide has an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to amino acids 30 to 80 of SEQ ID NO:41.

In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to a EsaB protein. In certain aspects the EsaB protein will have all or part of the amino acid sequence of SEQ ID:42.

In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to a vWa protein. In certain aspects the vWa protein will have all or part of the amino acid sequence of SEQ ID NO:33.

In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to a vWh protein. In certain aspects the vWh protein will have all or part of the amino acid sequence of SEQ ID NO:34.

In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to the all or a segment of the amino acid sequence of 52 kDa vitronectin binding protein (WO 01/60852), Aaa, Aap, Ant, autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (U.S. Pat. No. 6,288,214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (U.S. Pat. No. 6,008,341), Fibronectin binding protein (U.S. Pat. No. 5,840,846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/P isA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (U.S. Pat. No. 5,648,240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK, SBI, SdrF (WO 00/12689), SdrG/Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (U.S. Pat. No. 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein.

In certain aspects, a polypeptide or segment/fragment can have a sequence that is at least 85%, preferably at least 90%, more preferably at least 95%, and most preferably at least 98% or 99% or more identical to the amino acid sequence of the reference polypeptide. The term "similarity" refers to a polypeptide that has a sequence that has a certain percentage of amino acids that are either identical with the reference polypeptide or constitute conservative substitutions with the reference polypeptides.

The polypeptides described herein may include the following, or at least, or at most 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250 contiguous amino acids, or any range derivable therein, of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, and/or SEQ ID NO:34 respectively.

The compositions may be formulated in a pharmaceutically acceptable composition. In certain aspects of the invention the *staphylococcus* bacterium is an *S. aureus* bacterium.

In further aspects of the invention a composition may be administered more than one time to the subject, and may be administered 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 or more times. The administration of the compositions include, but is not limited to oral, parenteral, subcutaneous, intramuscular, intravenous administration, or various combinations thereof, including inhalation or aspiration.

Embodiments of the invention include administering to the subject a composition comprising a non-EsaC Ess protein. The Ess protein may be in the same composition as EsaC polypeptide, but need not be.

In still further embodiments, a composition comprises a recombinant nucleic acid molecule encoding an EsaC polypeptide or segments/fragments thereof. Typically a recombinant nucleic acid molecule encoding an EsaC polypeptide contains a heterologous promoter. In certain aspects, a recombinant nucleic acid molecule of the invention is a vector, in still other aspects the vector is a plasmid. In certain embodiments the vector is a viral vector. Aspects of the invention include compositions that further comprise a nucleic acid encoding an Esx or Ess protein. In certain aspects a composition includes a recombinant, non-staphylococcus bacterium containing or expressing the EsaC polypeptide. In particular aspects the recombinant non-staphylococcus bacteria is *Salmonella* or another gram-positive bacteria. A composition is typically administered to mammals, such as human subjects, but administration to other animals that are capable of eliciting an immune response is contemplated. In further aspects the *staphylococcus* bacterium containing or expressing the EsaC polypeptide is a *Staphylococcus aureus*. In further embodiments the immune response is a protective immune response.

In further embodiments a composition comprises a recombinant nucleic acid molecule encoding a EsaC, Eap, Ebh, Emp, EsaB, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla, IsdC, SasF, SpA, vWa, vWh, 52 kDa vitronectin binding protein (WO 01/60852), Aaa, Aap, Ant, autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (U.S. Pat. No. 6,288,214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (U.S. Pat. No. 6,008,341), Fibronectin binding protein (U.S. Pat. No. 5,840,846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/P isA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (U.S. Pat. No. 5,648,240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK, SBI, SdrF (WO 00/12689), SdrG/ Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (U.S. Pat. No. 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein. In certain aspects a nucleic acid molecule encodes 2, 3, 4, 5, 6, 7, 8, 9, 10, or more of Eap, Ebh, Emp, EsaB, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla, IsdC, SasF, SpA, vWa, vWh, 52 kDa vitronectin binding protein (WO 01/60852), Aaa, Aap, Ant, autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (U.S. Pat. No. 6,288,214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (U.S. Pat. No. 6,008,341), Fibronectin binding protein (U.S. Pat. No. 5,840,846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/P isA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (U.S. Pat. No. 5,648,240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK, SBI, SdrF (WO 00/12689), SdrG/ Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (U.S. Pat. No. 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein. A polypeptide or polynucleotide can comprise 2, 3, 4, 5, 6, 7, 8, 9, 10 more of the same (homologous multimer) or two or more different (heterologous multimer) polypeptides or polypeptide segments.

Typically a recombinant nucleic acid molecule contains a heterologous promoter. In certain aspects, a recombinant nucleic acid molecule of the invention is a vector, in still other aspects the vector is a plasmid. In certain embodiments the vector is a viral vector. Aspects of the invention include compositions that further comprise a nucleic acid encoding another sortase substrate protein or secreted virulence factor. In certain aspects a composition includes a recombinant, non-*staphylococcus* bacterium containing or expressing EsaC, Eap, Ebh, Emp, EsaB, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla, IsdC, SasF, Spa, vWa, vWh, 52 kDa vitronectin binding protein (WO 01/60852), Aaa, Aap, Ant, autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (U.S. Pat. No. 6,288,214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (U.S. Pat. No. 6,008,341), Fibronectin binding protein (U.S. Pat. No. 5,840,846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/P isA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (U.S. Pat. No. 5,648,240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK, SBI, SdrF (WO 00/12689), SdrG/Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (U.S. Pat. No. 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein. In particular aspects the recombinant non-staphylococcus bacteria is *Salmonella* or another gram-positive bacteria.

Compositions of the invention are typically administered to human subjects, but administration to other animals that are capable of eliciting an immune response to a *staphylococcus* bacterium is contemplated, particularly cattle, horses, goats, sheep and other domestic animals, i.e., mammals. In further aspects the *staphylococcus* bacterium is a *Staphylococcus aureus*. In further embodiments the immune response is a protective immune response. In still further aspects, the methods and compositions of the invention can be used to prevent, ameliorate, reduce, or treat infection of tissues or glands, e.g., mammary glands, particularly mastitis and other infections. Other methods include, but are not limited to prophylactically reducing bacterial burden in a subject not exhibiting signs of infection, particularly those subjects suspected of or at risk of being colonized by a target bacteria, e.g., patients that are or will be at risk or susceptible to infection during a hospital stay, treatment, and/or recovery.

Still further embodiments include methods for stimulating in a subject a protective or therapeutic immune response against a *staphylococcus* bacterium comprising administering to the subject an effective amount of a composition including (i) an EsaC polypeptide or peptide thereof; or, (ii) a nucleic acid molecule encoding an EsaC polypeptide or peptide thereof, or (iii) administering an EsaC polypeptide with any combination or permutation of bacterial proteins described herein. In a preferred embodiment the composition is not a *staphylococcus* bacterium. In certain aspects the subject is a human or a cow. In a further aspect the composition is formulated in a pharmaceutically acceptable formulation. The staphylococci may be *Staphylococcus aureus*.

Yet still further embodiments include vaccines comprising a pharmaceutically acceptable composition having an isolated EsaC polypeptide, or any other combination or permutation of protein(s) or peptide(s) described, wherein the composition is capable of stimulating an immune response against a *staphylococcus* bacterium. The vaccine may comprise an isolated EsaC polypeptide, or any other combination or permutation of protein(s) or peptide(s) described. In cer-

tain aspects of the invention the isolated EsaC polypeptide, or any other combination or permutation of protein(s) or peptide(s) described are multimerized, e.g., dimerized, trimerized, tetramerized etc. In a further aspect, the vaccine composition is contaminated by less than about 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0.5, 0.25, 0.05% (or any range derivable therein) of other *Staphylococcal* proteins. A composition may further comprise an isolated non-EsaC polypeptide. Typically the vaccine comprises an adjuvant. In certain aspects a protein or peptide of the invention is linked (covalently or non-covalently coupled) to the adjuvant, preferably the adjuvant is chemically conjugated to the protein.

In still yet further embodiments, a vaccine composition is a pharmaceutically acceptable composition having a recombinant nucleic acid encoding all or part of an EsaC polypeptide, or any other combination or permutation of protein(s) or peptide(s) described, wherein the composition is capable of stimulating an immune response against a *staphylococcus* bacteria. The vaccine composition may comprise a recombinant nucleic acid encoding all or part of an EsaC polypeptide, or any other combination or permutation of protein(s) or peptide(s) described. In certain embodiments the recombinant nucleic acid contains a heterologous promoter. Preferably the recombinant nucleic acid is a vector. More preferably the vector is a plasmid or a viral vector. A vaccine may also comprise a nucleic acid encoding a member of the Esx and/or Ess proteins. In some aspects the vaccine includes a recombinant, non-staphylococcus bacterium containing the nucleic acid. The recombinant non-staphylococci may be *Salmonella* or another gram-positive bacteria. The vaccine may comprise a pharmaceutically acceptable excipient, more preferably an adjuvant.

Still further embodiments include methods for stimulating in a subject a protective or therapeutic immune response against a *staphylococcus* bacterium comprising administering to the subject an effective amount of a composition of an EsaC polypeptide or segment/fragment thereof comprising one or more of (i) a SdrC, SdrD, SdrE, IsdA, IsdB, Spa, ClfA, ClfB, IsdC and/or SasF protein or peptide thereof; or, (ii) a nucleic acid molecule encoding a SdrC, SdrD, SdrE, IsdA, IsdB, Spa, ClfA, ClfB, IsdC and/or SasF protein or peptide thereof. In a preferred embodiment the composition comprises a non-staphylococcus bacterium. In a further aspect the composition is formulated in a pharmaceutically acceptable formulation. The staphylococci for which a subject is being treated may be *Staphylococcus aureus*. Methods of the invention also include EsaC compositions that contain 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more secreted virulence factors and/or cell surface proteins, such as EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, Spa, ClfA, ClfB, IsdC and/or SasF in various combinations. In certain aspects a vaccine formulation includes SdrD, SdrE, IsdA and IsdB; or SdrC, SdrD, SdrE, IsdA, IsdB, Spa, ClfA, ClfB, IsdC, and SasF. A vaccine formulation can also comprise a Eap, Ebh, Emp, EsaB, Coa, Hla, Spa, vWa, vWh, 52 kDa vitronectin binding protein (WO 01/60852), Aaa, Aap, Ant, autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (U.S. Pat. No. 6,288,214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (U.S. Pat. No. 6,008,341), Fibronectin binding protein (U.S. Pat. No. 5,840,846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/P isA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (U.S. Pat. No. 5,648,240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK, SBI, SdrF (WO 00/12689), SdrG/Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins

(WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (U.S. Pat. No. 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein.

In still a further aspect the invention includes a staphylococcal bacterium lacking an EsaC polypeptide and/or EsaB polypeptide. Such a bacterium will be limited or attenuated with respect to prolonged or persistent abscess formation. This characteristic can be used to provide an additional bacterial strain for the production of attenuated bacteria for use in the preparation of vaccines or treatments for staphylococcal infections or related diseases. In yet a further aspect, EsaC can be overexpressed in an attenuated bacterium to further enhance or supplement an immune response or vaccine formulation.

Any embodiment discussed with respect to one aspect of the invention applies to other aspects of the invention as well, e.g. embodiments discussed with respect to compositions apply to methods claims as well. In particular, any embodiment discussed in the context of an EsaC peptide or nucleic acid may be implemented with respect to other secreted virulence factors, and/or cell surface proteins, such as Eap, Ehb, Emp, EsaB, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla, IsdC, SasF, SpA, vWa, vWh, 52 kDa vitronectin binding protein (WO 01/60852), Aaa, Aap, Ant, autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (U.S. Pat. No. 6,288,214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (U.S. Pat. No. 6,008,341), Fibronectin binding protein (U.S. Pat. No. 5,840,846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/P isA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (U.S. Pat. No. 5,648,240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK, SBI, SdrF (WO 00/12689), SdrG/ Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (U.S. Pat. No. 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein (or nucleic acids), and vice versa.

The embodiments in the Example section are understood to be embodiments of the invention that are applicable to all aspects of the invention, including compositions and methods.

The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or." It is also contemplated that anything listed using the term "or" may also be specifically excluded.

Throughout this application, the term "about" is used to indicate that a value includes the standard deviation of error for the device or method being employed to determine the value.

Following long-standing patent law, the words "a" and "an," when used in conjunction with the word "comprising" in the claims or specification, denotes one or more, unless specifically noted.

As used in this specification and claim(s), the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "includes" and "include") or "containing" (and any form of containing, such as "contains" and "contain") are inclusive or open-ended and do not exclude additional, unrecited elements or method steps.

Other objects, features and advantages of the present invention will become apparent from the following detailed

description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DESCRIPTION OF THE DRAWINGS

So that the matter in which the above-recited features, advantages and objects of the invention as well as others which will become clear are attained and can be understood in detail, more particular descriptions and certain embodiments of the invention briefly summarized above are illustrated in the appended drawings. These drawings form a part of the specification. It is to be noted, however, that the appended drawings illustrate certain embodiments of the invention and therefore are not to be considered limiting in their scope.

FIG. 1. Schematic drawing of the ess cluster found in various Gram-positive bacteria as well as *M. tuberculosis*. Genes and proteins indicated: FtsK-SpoIIIE ATPases (FSD factors); ESAT-6 like protein; conserved proteins.

FIGS. 2A-2D. EsaB regulates EsaC production. (FIGS. 2A and 2B) Total cell cultures of strain Newman and variants were examined for production of EsaC. Staphylococci were grown in tryptic soy broth. Proteins in whole culture lysates were precipitated with TCA, separated by SDS-PAGE and detected by immunoblotting with specific antibodies [α -EsaC, α -EsaB and α -SrtA as a loading control]. FIG. 2A shows extracts of wild type Newman and isogenic mutants as indicated. Complementation analysis of esaB mutant is shown in FIG. 2B. Immunoblot analysis of total cell extracts of Newman, esaB⁻ with no vector (-), vector alone (pOS), vector carrying esaB (pOS-esaB). (FIG. 2C) Quantitative RT-PCR analysis of esaC transcripts was performed by isolating RNA from *S. aureus* isogenic strains Newman, esaC, and esaB. Reverse transcriptional polymerase chain reaction (RT-PCR) was carried out using oligos specific for sdrE and esaC transcripts. sdrE transcript levels did not change in all three backgrounds (not shown). The ratio of sdrE/esaC transcripts in Newman was 3/1. (FIG. 2D) Cultures of wild type (Newman) and esaB or esaC mutant cells were radiolabeled with [³⁵S]-methionine for 2 min. Labeling was quenched by addition of trichloroacetic acid, staphylococci were lysed with lysostaphin and extracts solubilized in hot SDS. Total radioactive counts were measured using 5 μ A of each sample in a scintillation counter. Total cell extracts were subjected to immunoprecipitation with anti-EsaC antibodies. Samples were separated on SDS-PAGE and analyzed by autoradiography using a PhosphorImager.

FIG. 3. Staphylococci grown in serum produce EsaC. Staphylococci, Newman, esaC mutant with no vector (-), vector alone (pOS), vector carrying esaC (pOS-esaC), were grown in TSB or serum to the same density, washed and lysed with lysostaphin. Proteins in these extracts were precipitated with TCA, separated by SDS-PAGE and detected by immunoblotting with specific antibodies [α -EsaC, and α -SrtA as a loading control].

FIGS. 4A-4C. EsaC is a ubiquitous secreted antigen of the *S. aureus* Ess pathway. (FIG. 4A) *S. aureus* USA300 and USA700 secrete EsaC into the extracellular medium (MD). As control, regulation of EsaC expression in *S. aureus* Newman as well as USA300 is dependent on esaB as measured in whole culture lysates (WC). Antibodies against ribosomal protein L6 were used as a control for proper fractionation. (FIG. 4B) EssC is required for secretion of EsaC. Immunob-

lot analysis of total cell extracts of Newman or isogenic *essC* mutant, with vector alone (pOS) or vector carrying *esaC* (pOS-*esaC*). Production and secretion of *EsaC* was measured in whole culture lysates (WC) and culture supernatants (MD). Antibodies against ribosomal protein L6 were used as a control for loading and fractionation. (FIG. 4C) Subcellular location of *EsaC*. *S. aureus* cultures of strains Newman, Newman *esaB*, USA300 and USA300 *esxB* were grown to OD_{660nm} 0.8. Equal volumes of cultures were removed for preparation of whole cell lysates (WC) and fractionation of staphylococci into cytoplasm (C), membrane (M), cell wall (W) and medium (MD) fractions. Hence each cellular compartment is kept equimolar to the WC fraction. Proteins were precipitated with TCA, separated on SDS/PAGE, and detected by immunoblotting with specific antibodies [α -*EsaC*, α -ribosomal protein L6, α -SrtA (protein A)].

FIGS. 5A-5D. Mice and humans infected with *S. aureus* generate *EsaC* IgG specific antibodies. (FIG. 5A) Three-week-old BALB/c mice were injected retro-orbitally with $\sim 10^6$ CFU of strain Newman. Sera were collected on day 0 and 30 days post infection and analyzed for the presence of *EsaC* reactive antibodies. (FIG. 5B) Quantification of *EsaC* IgG levels in human sera obtained from patients infected or not with *S. aureus* (two sera each, respectively). (FIGS. 5C and 5D) Three-week-old BALB/c mice were injected as in FIG. 5A with clinical strains as indicated on the figure. Sera were collected 0 and 30 days post infection (the 30-day data set is shown). IgG titers to *EsaC* and Sortase A are shown in FIG. 5C and FIG. 5D, respectively. In FIG. 5D, a rabbit polyclonal antibody raised against recombinant SrtA was used as a control. All IgG titers were determined in triplicate by ELISA and reported as an absorbance at 405 nm.

FIG. 6. Virulence of *S. aureus* *esaB* and *esaC* mutants. BALB/c mice were infected retro-orbitally with $\sim 10^6$ CFU for each strain. Both kidneys were harvested from mock (PBS) infected animals or mice infected with Newman, *esaB* or *esaC* isogenic variants, for 5 and 36 days and the right kidney for each animal was homogenized. Viable bacteria were counted after dilution and colony formation on tryptic soy agar. Statistical significance was examined with Student's t test, and averages and P values are indicated. The limit of detection was determined to be 10 CFU.

FIG. 7. Pathological substrate of infection caused by *S. aureus* wild type and *esaB* or *esaC* mutants. Kidneys of mice infected as described in FIG. 6 were removed 5 and 36 days post infection. The right kidney was used for CFU counts and the left was fixed with formalin. Formalin-fixed tissues were embedded, sectioned, and stained with hematoxylin/eosin. Microscopic images of whole kidneys ($\times 10$, top panels) or organ tissue at higher magnification ($\times 100$, lower panels) revealed fewer and less persistent abscesses in *esaB* or *esaC* infected animals. White arrows point to abscesses with a central concentration of staphylococci and peripheral mononuclear cell (PMN) infiltrate. Numbers under each panel indicate the average number of abscesses per kidney with standard deviation, between 8 and 12 kidneys were examined per group. Statistical significance was examined with the Student t test, and P values were recorded.

DETAILED DESCRIPTION OF THE INVENTION

Research over the past several decades identified *S. aureus* exotoxins, surface proteins and regulatory molecules as important virulence factors (Foster, 2005; Mazmanian et al., 2001; Novick, 2003). Much progress has been achieved regarding the regulation of these genes. For example, staphylococci perform a bacterial census via the secretion of auto-

inducing peptides that bind to a cognate receptor at threshold concentration, thereby activating phospho-relay reactions and transcriptional activation of many of exotoxin genes (Novick, 2003). During infection, this bacterial census termed Agr ensures massive secretion of virulence factors when staphylococcal counts are high, increasing the likelihood of bacterial spread in infected tissues and/or systemic dissemination (Novick, 2003). As described herein, staphylococci produce and secrete *EsaC* under conditions that occur when bacteria enter host tissues. Production of *EsaC* is regulated by *EsaB*, a cytoplasmic conserved protein also encoded within the *Ess* cluster. *EsaB* represses *EsaC* production in a post-transcriptional manner. Bacteria lacking *EsaB* overproduce *EsaC* while wild type bacteria do not, unless they are replicating in host tissues.

EsaC is an unusual factor that is transported by the *Ess* pathway (a type VII secretion system (TVIIS)). The *Ess* pathway is an alternate secretion system reminiscent of alternate secretion systems of Gram-negative pathogens (Pugsley, 1993) that transport polypeptides across the bacterial envelope. Like most alternate secretion system, the *Ess* pathway appears to have limited substrate specificity. In mycobacteria and staphylococci, the *ESX-1* and *Ess* pathways transport proteins that belong to the *WXG100* family such as *ESAT-6*, *CFP-10*, *EsxA* and *EsxB* (Burts et al., 2005; Champion et al., 2006; Stanley et al., 2003). The genetic determinants of the *ESX-1* and *Ess* pathways are clustered in discrete loci, dispensable for laboratory growth and essential for the pathogenesis of infectious diseases (Burts et al., 2005; Hsu et al., 2003; Pym et al., 2002; Stanley et al., 2003).

The pathogenesis of staphylococcal infections relies on a multiple virulence factors such as secreted exotoxins, exopolysaccharides, and surface adhesins. However, deletion of single genes encoding such factors cause either no defect or results in only modest reduction of virulence. Thus, the development of staphylococcal vaccines is hindered by the multifaceted nature of staphylococcal invasion mechanisms. It is well established that live attenuated micro-organisms are highly effective vaccines; immune responses elicited by such vaccines are often of greater magnitude and longer duration than those produced by non-replicating immunogens. One explanation for this may be that live attenuated strains establish limited infections in the host and mimic the early stages of natural infection. Embodiments of the invention are directed to compositions and methods including *EsaC* polypeptides and peptides, and inhibitors thereof, as well as other immunogenic extracellular proteins, polypeptides, and peptides (including both secreted and cell surface proteins or peptides) of gram positive bacteria for use in mitigating or immunizing against infection. In particular embodiments the bacteria is a *staphylococcus* bacteria. Extracellular proteins, polypeptides, or peptides include, but are not limited to secreted and cell surface proteins of the targeted bacteria.

The human pathogen *S. aureus* secretes *EsxA* and *EsxB*, two *ESAT-6* like proteins across the bacterial envelope (Burts et al., 2005, which is incorporated herein by reference). Staphylococcal *esxA* and *esxB* are clustered with six other genes in the order of transcription: *esxA* *esaA* *essA* *esaB* *essB* *essC* *esaC* *esxB*. The acronyms *esa*, *ess*, and *esx* stand for *ESAT-6* secretion accessory, system, and extracellular, respectively, depending whether the encoded proteins play an accessory (*esa*) or direct (*ess*) role for secretion, or are secreted (*esx*) in the extracellular milieu. The entire cluster of eight genes is herein referred to as the *Ess* cluster. *EsxA*, *esxB*, *essA*, *essB*, and *essC* are all required for synthesis or secretion of *EsxA* and *EsxB*. Mutants that fail to produce *EsxA*, *EsxB*, and *EssC* display defects in the pathogenesis of *S. aureus* murine

abscesses, suggesting that this specialized secretion system may be a general strategy of human bacterial pathogenesis.

I. Staphylococcal Antigens

EsaC (SEQ ID NO:1 and SEQ ID NO:2) is regulated and secreted by the Ess pathway; it represents a unique effector of this secretion system that enables staphylococcal persistence in host tissues. Sequences of other EsaC polypeptides can be found in the protein databases and include, but are not limited to accession numbers ZP_02760162 (GI:168727885), NP_645081.1 (GI:21281993), and NP_370813.1 (GI:15923279), each of which is incorporated herein by reference as of the priority date of this application. EsaC is found exclusively in the genome of staphylococci. Other Gram positive bacteria encode a protein with similar predicted mass but unrelated sequence in the same genetic locus. Consistent with this conjecture is the finding that animals and humans can mount a humoral immune response to EsaC during infection. During infection all *S. aureus* strains secrete EsaC, and the more virulent clinical isolates have retained this activity even in vitro. EsaC does not bear any features of the WXG100 family of proteins and it is unclear how it is recognized by the Ess pathway. Secretion of non-WXG100 substrates by the ESX-1 pathway has also been reported for several antigens including EspA, EspB, Rv3483c, and Rv3615c (Fortune et al., 2005; MacGurn et al., 2005; McLaughlin et al., 2007; Xu et al., 2007). The alternate ESX-5 pathway has also been shown to secrete both WXG100 and non-WXG100 proteins in pathogenic mycobacteria (Abdallah et al., 2007; Abdallah et al., 2006).

The *Staphylococcus aureus* Ess pathway can be viewed as a secretion module equipped with specialized transport components (Ess), accessory factors (Esa) and cognate secretion substrates (Esx). EssA, EssB and EssC are required for EsxA and EsxB secretion. Because EssA, EssB and EssC are predicted to be transmembrane proteins, it is contemplated that these proteins form a secretion apparatus. Some of the proteins in the ess gene cluster may actively transport secreted substrates (acting as motor) while others may regulate transport (regulator). Regulation may be achieved, but need not be limited to, transcriptional or post-translational mechanisms for secreted polypeptides, sorting of specific substrates to defined locations (e.g., extracellular medium or host cells), or timing of secretion events during infection. At this point, it is unclear whether all secreted Esx proteins function as toxins or contribute indirectly to pathogenesis.

Staphylococci rely on surface protein mediated-adhesion to host cells or invasion of tissues as a strategy for escape from immune defenses. Furthermore, *S. aureus* utilize surface proteins to sequester iron from the host during infection. The majority of surface proteins involved in staphylococcal pathogenesis carry C-terminal sorting signals, i.e., they are covalently linked to the cell wall envelope by sortase. Further, staphylococcal strains lacking the genes required for surface protein anchoring, i.e., sortase A and B, display a dramatic defect in the virulence in several different mouse models of disease. Thus, surface protein antigens represent a validated vaccine target as the corresponding genes are essential for the development of staphylococcal disease and can be exploited in various embodiments of the invention. The sortase enzyme superfamily are Gram-positive transpeptidases responsible for anchoring surface protein virulence factors to the peptidoglycan cell wall layer. Two sortase isoforms have been identified in *Staphylococcus aureus*, SrtA and SrtB. These enzymes have been shown to recognize a LPXTG motif in substrate proteins. The SrtB isoform appears to be important

in heme iron acquisition and iron homeostasis, whereas the SrtA isoform plays a critical role in the pathogenesis of Gram-positive bacteria by modulating the ability of the bacterium to adhere to host tissue via the covalent anchoring of adhesions and other proteins to the cell wall peptidoglycan. Embodiments of the invention include, but are not limited to compositions and methods related to EsaC. In certain embodiments EsaC can be used in combination with other staphylococcal proteins such as EsxA, EsxB, Emp, SdrC, SdrD, SdrE, IsdA, IsdB, SpA, ClfA, ClfB, IsdC, Ehb, Hla, and/or SasF proteins.

Certain aspects of the invention include methods and compositions concerning proteinaceous compositions including polypeptides, peptides, or nucleic acids encoding EsaC and other staphylococcal antigens such as other proteins transported by the Ess pathway, or sortase substrates including, but not limited to EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, SpA, ClfA, ClfB, IsdC, SasF or combinations thereof. In certain aspects the methods and compositions include Eap, Ehb, Emp, EsaB, Coa, Hla, vWa, vWh, 52 kDa vitronectin binding protein (WO 01/60852), Aaa, Aap, Ant, autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (U.S. Pat. No. 6,288,214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (U.S. Pat. No. 6,008,341), Fibronectin binding protein (U.S. Pat. No. 5,840,846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/P isA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (U.S. Pat. No. 5,648,240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK, SBI, SdrF (WO 00/12689), SdrG/Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (U.S. Pat. No. 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein. These proteins may be modified by deletion, insertion, and/or substitution.

The Esx polypeptides include the amino acid sequences of Esx proteins from bacteria in the *Staphylococcus* genus. The Esx sequence may be from a particular *staphylococcus* species, such as *Staphylococcus aureus*, and may be from a particular strain, such as Newman. In certain embodiments, the EsxA sequence is SAV0282 from strain Mu50 (which is the same amino acid sequence for Newman) and can be accessed using Genbank Accession Number Q99WU4 (gil68565539), which is hereby incorporated by reference. In other embodiments, the EsxB sequence is SAV0290 from strain Mu50 (which is the same amino acid sequence for Newman) and can be accessed using Genbank Accession Number Q99WT7 (gil68565532), which is hereby incorporated by reference. In further embodiments, other polypeptides transported by the Ess pathway may be used, the sequences of which may be identified by one of skill in the art using databases and internet accessible resources.

The sortase substrate polypeptides include, but are not limited to the amino acid sequence of SdrC, SdrD, SdrE, IsdA, IsdB, Spa, ClfA, ClfB, IsdC or SasF proteins from bacteria in the *Staphylococcus* genus. The sortase substrate polypeptide sequence may be from a particular *staphylococcus* species, such as *Staphylococcus aureus*, and may be from a particular strain, such as Newman. In certain embodiments, the SdrD sequence is from strain N315 and can be accessed using Genbank Accession Number NP_373773.1 (gil15926240), which is incorporated by reference. In other embodiments, the SdrE sequence is from strain N315 and can be accessed using Genbank Accession Number NP_373774.1 (gil15926241), which is incorporated by reference. In other embodiments, the IsdA sequence is SAV1130

from strain Mu50 (which is the same amino acid sequence for Newman) and can be accessed using Genbank Accession Number NP_371654.1 (gil15924120), which is incorporated by reference. In other embodiments, the IsdB sequence is SAV 1129 from strain Mu50 (which is the same amino acid sequence for Newman) and can be accessed using Genbank Accession Number NP_371653.1 (gil15924119), which is incorporated by reference. In further embodiments, other polypeptides transported by the Ess pathway or processed by sortase may be used, the sequences of which may be identified by one of skill in the art using databases and internet accessible resources.

Examples of various proteins that can be used in the context of the present invention can be identified by analysis of database submissions of bacterial genomes, including but not limited to accession numbers NC_002951 (GI:57650036 and GenBank CP000046), NC_002758 (GI:57634611 and GenBank BA000017), NC_002745 (GI:29165615 and GenBank BA000018), NC_003923 (GI:21281729 and GenBank BA000033), NC_002952 (GI:49482253 and GenBank BX571856), NC_002953 (GI:49484912 and GenBank BX571857), NC_007793 (GI:87125858 and GenBank CP000255), NC_007795 (GI:87201381 and GenBank CP000253) each of which are incorporated by reference.

The 'clfA' antigen is annotated as 'clumping factor A'. In the NCTC 8325 strain clfA is SAOUHSC_00812 (GI:88194572). In the Newman strain it is nwmn_0756 (GI:151220968). Useful clfA antigens can elicit an antibody response (e.g. when administered to a human), and include variants and fragments.

The 'clfB' antigen is annotated as 'clumping factor B'. In the NCTC 8325 strain clfB is SAOUHSC_02963 (GI:88196585). In the Newman strain it is nwmn_2529 (GI:151222741). Useful clfB antigens can elicit an antibody response (e.g. when administered to a human), and include variants and fragments.

The 'eap' antigen is annotated as 'MHC class II analog protein'. In the NCTC 8325 strain eap is SAOUHSC_02161 (GI:88195840). In the Newman strain it is nwmn_1872 (GI:151222084). Useful eap antigens can elicit an antibody response (e.g. when administered to a human), and include variants and fragments.

The 'ebhA' antigen is annotated as 'EbhA'. In the NCTC 8325 strain ebhA is SAOUHSC_01447 and has amino acid sequence (GI:88195168). Useful ebhA antigens can elicit an antibody response (e.g. when administered to a human), and include variants and fragment.

The 'emp' antigen is annotated as 'extracellular matrix and plasma binding protein'. In the NCTC 8325 strain emp is SAOUHSC_00816 (GI:88194575). In the Newman strain it is nwmn_0758 (GI:151220970). Useful emp antigens can elicit an antibody response (e.g. when administered to a human), and include variants and fragments.

The 'esxA' antigen is annotated as 'protein'. In the NCTC 8325 strain esxA is SAOUHSC_00257 (GI:88194063). Useful esxA antigens can elicit an antibody response (e.g. when administered to a human), and include variants and fragments.

The 'esxB' antigen is annotated as 'esxB'. In the NCTC 8325 strain esxB is SAOUHSC_00265 (GI:88194070). Useful esxB antigens can elicit an antibody response (e.g. when administered to a human), and include variants and fragments.

The 'Hla' antigen is the 'alpha-hemolysin precursor' also known as 'alpha toxin' or simply 'hemolysin'. In the Newman strain it is nwmn_1073 (GI:151221285). Hla is an important virulence determinant produced by most strains of *S. aureus*,

having pore-forming and haemolytic activity. Anti-Hla antibodies can neutralise the detrimental effects of the toxin in animal models. Useful Hla antigens can elicit an antibody response (e.g. when administered to a human), and include variants and fragments.

Hla's toxicity can be avoided in compositions of the invention by chemical inactivation (e.g. using formaldehyde, glutaraldehyde or other cross-linking reagents). Instead, however, it is preferred to use mutant forms of Hla which remove its toxic activity while retaining its immunogenicity. Such detoxified mutants are already known in the art, including Hla-H35L.

The 'isdA' antigen is annotated as 'IsdA protein'. In the NCTC 8325 strain isdA is SAOUHSC_01081 (GI:88194829). In the Newman strain it is nwmn_1041 (GI:151221253). Useful isdA antigens can elicit an antibody response (e.g. when administered to a human), and includes variants and fragments.

The 'isdB' antigen is annotated as 'neurofilament protein isdB'. In the NCTC 8325 strain isdB is SAOUHSC_01079 (GI:88194828). Useful isdB antigens can elicit an antibody response (e.g. when administered to a human), and includes fragments and variants.

The 'isdC' antigen is annotated as 'protein'. In the NCTC 8325 strain isdC is SAOUHSC_01082 (GI:88194830). Useful isdC antigens can elicit an antibody response (e.g. when administered to a human), and fragments and variants.

The 'sasF' antigen is annotated as 'sasF protein'. In the NCTC 8325 strain sasF is SAOUHSC_02982 (GI:88196601). Useful sasF antigens can elicit an antibody response (e.g. when administered to a human), and fragments and variants.

The 'sdrC' antigen is annotated as 'sdrC protein'. In the NCTC 8325 strain sdrC is SAOUHSC_00544 and has amino acid sequence (GI:88194324). Useful sdrC antigens can elicit an antibody response (e.g. when administered to a human), and fragments and variants.

The 'sdrD' antigen is annotated as 'sdrD protein'. In the NCTC 8325 strain sdrD is SAOUHSC_00545 (GI:88194325). Useful sdrD antigens can elicit an antibody response (e.g. when administered to a human), and fragments and variants.

The 'sdrE2' antigen is annotated as 'Ser-Asp rich fibrinogen/bone sialoprotein-binding protein SdrE'. In the Newman strain sdrE2 is NWMN 0525 (GI:151220737). Useful sdrE2 antigens can elicit an antibody response (e.g. when administered to a human), and includes fragments and variants.

The 'spa' antigen is annotated as 'protein A' or 'SpA'. All *Staphylococcus aureus* strains express the structural gene for spa, a well characterized virulence factor whose cell wall anchored surface protein product (SpA) encompasses five highly homologous immunoglobulin binding domains designated E, D, A, B, and C (Sjodahl, 1977). These domains display ~80% identity at the amino acid level, are 56 to 61 residues in length, and are organized as tandem repeats (Uhlen et al., 1984). SpA is synthesized as a precursor protein with an N-terminal YSIRK/GS signal peptide and a C-terminal LPXTG motif sorting signal (DeDent et al., 2008; Schneewind et al., 1992). Cell wall anchored Protein A is displayed in great abundance on the staphylococcal surface (DeDent et al., 2007; Sjoquist et al., 1972). Each of its immunoglobulin binding domains is composed of anti-parallel α -helices that assemble into a three helix bundle and bind the Fc domain of immunoglobulin G (IgG) (Deisenhofer, 1981; Deisenhofer et al., 1978), the VH3 heavy chain (Fab) of IgM (i.e., the B cell receptor) (Graille et al., 2000), the von Willebrand factor at its A1 domain [vWF A1 is a ligand for plate-

lets] (O'Seaghdha et al., 2006) and the tumor necrosis factor α (TNF- α) receptor I (TNFRI) (Gomez et al., 2006), which is displayed on surfaces of airway epithelia (Gomez et al., 2004; Gomez et al., 2007).

In the NCTC 8325 strain spa is SAOUHSC_00069 (GI: 88193885). In the Newman strain it is nwmn_0055 (GI: 151220267). Useful spa antigens can elicit an antibody response (e.g. when administered to a human), and includes variants and fragments. Useful spa antigens include SpA variants comprising a variant A, B, C, D and E domain. Useful spa antigens also include SpA segments and SpA variants comprising a segment of SpA. The SpA segment can comprise at least or at most 1, 2, 3, 4, 5 or more IgG binding domains. The IgG domains can be at least or at most 1, 2, 3, 4, 5 or more variant A, B, C, D or E domains. Useful spa antigens also include SpA variants comprising a variant A domain, a variant B domain, a variant C domain, a variant D domain or a variant E domain.

In certain aspects an SpA variant includes a substitution of (a) one or more amino acid substitution in an IgG Fc binding sub-domain of SpA domain A, B, C, D and/or E that disrupts or decreases binding to IgG Fc, and (b) one or more amino acid substitution in a V_H3 binding sub-domain of SpA domain A, B, C, D, and/or E that disrupts or decreases binding to V_H3 . In certain embodiments, a variant SpA comprises at least or at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more variant SpA domain D peptides.

As used herein, a "protein" or "polypeptide" refers to a molecule comprising at least ten amino acid residues. In some embodiments, a wild-type version of a protein or polypeptide are employed, however, in many embodiments of the invention, a modified protein or polypeptide is employed to generate an immune response. The terms described above may be used interchangeably. A "modified protein" or "modified polypeptide" refers to a protein or polypeptide whose chemical structure, particularly its amino acid sequence, is altered with respect to the wild-type protein or polypeptide. In some embodiments, a modified protein or polypeptide has at least one modified activity or function (recognizing that proteins or polypeptides may have multiple activities or functions). It is specifically contemplated that a modified protein or polypeptide may be altered with respect to one activity or function yet retain a wild-type activity or function in other respects, such as immunogenicity.

In certain embodiments the size of a protein or polypeptide (wild-type or modified) may comprise, but is not limited to, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675, 700, 725, 750, 775, 800, 825, 850, 875, 900, 925, 950, 975, 1000, 1100, 1200, 1300, 1400, 1500, 1750, 2000, 2250, 2500 amino molecules or greater, and any range derivable therein, or derivative of a corresponding amino sequence described or referenced herein. It is contemplated that polypeptides may be mutated by truncation, rendering them shorter than their corresponding wild-type form, but also they might be altered by fusing or conjugating a heterologous protein sequence with a particular function (e.g., for targeting or localization, for enhanced immunogenicity, for purification purposes, etc.).

As used herein, an "amino molecule" refers to any amino acid, amino acid derivative, or amino acid mimic known in the

art. In certain embodiments, the residues of the proteinaceous molecule are sequential, without any non-amino molecule interrupting the sequence of amino molecule residues. In other embodiments, the sequence may comprise one or more non-amino molecule moieties. In particular embodiments, the sequence of residues of the proteinaceous molecule may be interrupted by one or more non-amino molecule moieties.

Accordingly, the term "proteinaceous composition" encompasses amino molecule sequences comprising at least one of the 20 common amino acids in naturally synthesized proteins, or at least one modified or unusual amino acid.

Proteinaceous compositions may be made by any technique known to those of skill in the art, including (i) the expression of proteins, polypeptides, or peptides through standard molecular biological techniques, (ii) the isolation of proteinaceous compounds from natural sources, or (iii) the chemical synthesis of proteinaceous materials. The nucleotide as well as the protein, polypeptide, and peptide sequences for various genes have been previously disclosed, and may be found in the recognized computerized databases. One such database is the National Center for Biotechnology Information's Genbank and GenPept databases (on the World Wide Web at ncbi.nlm.nih.gov/). The coding regions for these genes may be amplified and/or expressed using the techniques disclosed herein or as would be known to those of ordinary skill in the art.

Amino acid sequence variants of EsaC and other polypeptides of the invention ("other Ess pathway polypeptides"), and/or SdrC, SdrD, SdrE, IsdA, IsdB, Spa, ClfA, ClfB, IsdC, SasF or other sortase substrates can be substitutional, insertional, or deletion variants. A modification in a polypeptide of the invention may affect 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449,

450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473,

dissimilar, such as a polar or charged amino acid for a non-polar or uncharged amino acid, and vice versa.

TABLE 1

Exemplary surface proteins of <i>S. aureus</i> strains.								
SAV #	SA#	Surface	MW2	Mu50	N315	Newman	MRSA252*	MSSA476*
SAV0111	SA0107	Spa	492	450	450	520	516	492
SAV2503	SA2291	FnBPA	1015	1038	1038	741	—	1015
SAV2502	SA2290	FnBPB	943	961	961	677	965	957
SAV0811	SA0742	ClfA	946	935	989	933	1029	928
SAV2630	SA2423	ClfB	907	877	877	913	873	905
Np	np	Cna	1183	—	—	—	1183	1183
SAV0561	SA0519	SdrC	955	953	953	947	906	957
SAV0562	SA0520	SdrD	1347	1385	1385	1315	—	1365
SAV0563	SA0521	SdrE	1141	1141	1141	1166	1137	1141
Np	np	Pls	—	—	—	—	—	—
SAV2654	SA2447	SasA	2275	2271	2271	2271	1351	2275
SAV2160	SA1964	SasB	686	2481	2481	2481	2222	685
	SA1577	SasC	2186	213	2186	2186	2189	2186
SAV0134	SA0129	SasD	241	241	241	241	221	241
SAV1130	SA0977	SasE/IsdA	350	350	350	350	354	350
SAV2646	SA2439	SasF	635	635	635	635	627	635
SAV2496		SasG	1371	525	927	—	—	1371
SAV0023	SA0022	SasH	772	—	772	772	786	786
SAV1731	SA1552	SasI	895	891	891	891	534	895
SAV1129	SA0976	SasJ/IsdB	645	645	645	645	652	645
	SA2381	SasK	198	211	211	—	—	197
	np	SasL	—	232	—	—	—	—
SAV1131	SA0978	IsdC	227	227	227	227	227	227

474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500 or more non-contiguous or contiguous amino acids of the polypeptide, as compared to wild-type. A polypeptide processed or secreted by the Ess pathway, and/or SdrC, SdrD, SdrE, IsdA, IsdB, Spa, ClfA, ClfB, IsdC, SasF or other surface proteins (see Table 1) or sortase substrates from any *staphylococcus* species and strain are contemplated for use in methods of the invention.

Deletion variants typically lack one or more residues of the native or wild-type protein. Individual residues can be deleted or a number of contiguous amino acids can be deleted. A stop codon may be introduced (by substitution or insertion) into an encoding nucleic acid sequence to generate a truncated protein. Insertional mutants typically involve the addition of material at a non-terminal point in the polypeptide. This may include the insertion of one or more residues. Terminal additions, called fusion proteins, may also be generated.

Substitutional variants typically contain the exchange of one amino acid for another at one or more sites within the protein, and may be designed to modulate one or more properties of the polypeptide, with or without the loss of other functions or properties. Substitutions may be conservative, that is, one amino acid is replaced with one of similar shape and charge. Conservative substitutions are well known in the art and include, for example, the changes of: alanine to serine; arginine to lysine; asparagine to glutamine or histidine; aspartate to glutamate; cysteine to serine; glutamine to asparagine; glutamate to aspartate; glycine to proline; histidine to asparagine or glutamine; isoleucine to leucine or valine; leucine to valine or isoleucine; lysine to arginine; methionine to leucine or isoleucine; phenylalanine to tyrosine, leucine or methionine; serine to threonine; threonine to serine; tryptophan to tyrosine; tyrosine to tryptophan or phenylalanine; and valine to isoleucine or leucine. Alternatively, substitutions may be non-conservative such that a function or activity of the polypeptide is affected. Non-conservative changes typically involve substituting a residue with one that is chemically

Proteins of the invention may be recombinant, or synthesized in vitro. Alternatively, a non-recombinant or recombinant protein may be isolated from bacteria. It is also contemplated that a bacteria containing such a variant may be implemented in compositions and methods of the invention. Consequently, a protein need not be isolated.

The term “functionally equivalent codon” is used herein to refer to codons that encode the same amino acid, such as the six codons for arginine or serine, and also refers to codons that encode biologically equivalent amino acids (see Table 2, below).

TABLE 2

Amino Acids	Codon Table					
	Codons					
Alanine	Ala	A	GCA	GCC	GCG	GCU
Cysteine	Cys	C	UGC	UGU		
Aspartic acid	Asp	D	GAC	GAU		
Glutamic acid	Glu	E	GAA	GAG		
Phenylalanine	Phe	F	UUC	UUU		
Glycine	Gly	G	GGA	GGC	GGG	GGU
Histidine	His	H	CAC	CAU		
Isoleucine	Ile	I	AUA	AUC	AUU	
Lysine	Lys	K	AAA	AAG		
Leucine	Leu	L	UUA	UUG	CUA	CUC
Methionine	Met	M	AUG			
Asparagine	Asn	N	AAC	AAU		
Proline	Pro	P	CCA	CCC	CCG	CCU

TABLE 2-continued

Amino Acids	Codon Table		Codons					
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

It also will be understood that amino acid and nucleic acid sequences may include additional residues, such as additional N- or C-terminal amino acids, or 5' or 3' sequences, respectively, and yet still be essentially as set forth in one of the sequences disclosed herein, so long as the sequence meets the criteria set forth above, including the maintenance of biological protein activity where protein expression is concerned. The addition of terminal sequences particularly applies to nucleic acid sequences that may, for example, include various non-coding sequences flanking either of the 5' or 3' portions of the coding region.

The following is a discussion based upon changing of the amino acids of a protein to create an equivalent, or even an improved, second-generation molecule. For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid substitutions can be made in a protein sequence, and in its underlying DNA coding sequence, and nevertheless produce a protein with like properties. It is thus contemplated by the inventors that various changes may be made in the DNA sequences of genes without appreciable loss of their biological utility or activity.

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like.

It also is understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U.S. Pat. No. 4,554,101, incorporated herein by reference, states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein. It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still produce a biologically equivalent and immunologically equivalent protein.

As outlined above, amino acid substitutions generally are based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that

take into consideration the various foregoing characteristics are well known and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

It is contemplated that in compositions of the invention, there is between about 0.001 mg and about 10 mg of total polypeptide, peptide, and/or protein per ml. Thus, the concentration of protein in a composition can be about, at least about or at most about 0.001, 0.010, 0.050, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0 mg/ml or more (or any range derivable therein). Of this, about, at least about, or at most about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100% may be EsaC, and may be used in combination with EsxA protein, EsxB protein, or another protein transported by the Ess pathway, and/or SdrD, SdrE, IsdA, IsdB, or other sortase substrates.

The present invention contemplates the administration of EsaC polypeptides or peptides, as well as EsxA, EsxB, and any other protein transported by the Ess pathway, and/or SdrD, SdrE, IsdA, IsdB, or other sortase substrates, to effect a preventative therapy against the development of a disease or condition associated with infection by a *staphylococcus* pathogen.

The present invention also discloses combinations of staphylococcal antigens which when combined, lead to the production of an immunogenic composition that is effective at treating or preventing staphylococcal infection. Staphylococcal infections progress through several different stages. For example, the staphylococcal life cycle involves commensal colonization, initiation of infection by accessing adjoining tissues or the bloodstream, anaerobic multiplication in the blood, interplay between *S. aureus* virulence determinants and the host defense mechanisms and induction of complications including endocarditis, metastatic abscess formation and sepsis syndrome. Different molecules on the surface of the bacterium will be involved in different steps of the infection cycle. Combinations of certain antigens can elicit an immune response which protects against multiple stages of staphylococcal infection. The effectiveness of the immune response can be measured either in animal model assays and/or using an opsonophagocytic assay.

In addition, U.S. Pat. No. 4,554,101 (Hopp), which is incorporated herein by reference, teaches the identification and preparation of epitopes from primary amino acid sequences on the basis of hydrophilicity.

A. Polypeptides and Polypeptide Production

The present invention describes polypeptides, peptides, and proteins and immunogenic fragments thereof for use in various embodiments of the present invention. For example, specific polypeptides are assayed for or used to elicit an immune response. In specific embodiments, all or part of the proteins of the invention can also be synthesized in solution or on a solid support in accordance with conventional techniques. Various automatic synthesizers are commercially available and can be used in accordance with known protocols. See, for example, Stewart and Young, (1984); Tam et al., (1983); Merrifield, (1986); and Barany and Merrifield (1979), each incorporated herein by reference. Alternatively, recombinant DNA technology may be employed wherein a nucleotide sequence which encodes a peptide of the invention is

inserted into an expression vector, transformed or transfected into an appropriate host cell and cultivated under conditions suitable for expression.

One embodiment of the invention includes the use of gene transfer to cells, including microorganisms, for the production and/or presentation of proteins. The gene for the protein of interest may be transferred into appropriate host cells followed by culture of cells under the appropriate conditions. A nucleic acid encoding virtually any polypeptide may be employed. The generation of recombinant expression vectors, and the elements included therein, are discussed herein. Alternatively, the protein to be produced may be an endogenous protein normally synthesized by the cell used for protein production.

Another embodiment of the present invention uses autologous B lymphocyte cell lines, which are transfected with a viral vector that expresses an immunogen product, and more specifically, a protein having immunogenic activity. Other examples of mammalian host cell lines include, but are not limited to Vero and HeLa cells, other B- and T-cell lines, such as CEM, 721.221, H9, Jurkat, Raji, as well as cell lines of Chinese hamster ovary, W138, BHK, COS-7, 293, HepG2, 3T3, RIN and MDCK cells. In addition, a host cell strain may be chosen that modulates the expression of the inserted sequences, or that modifies and processes the gene product in the manner desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed.

A number of selection systems may be used including, but not limited to HSV thymidine kinase, hypoxanthine-guanine phosphoribosyltransferase, and adenine phosphoribosyltransferase genes, in tk-, hgp^rt- or ap^rt- cells, respectively. Also, anti-metabolite resistance can be used as the basis of selection: for dhfr, which confers resistance to trimethoprim and methotrexate; gpt, which confers resistance to mycophenolic acid; neo, which confers resistance to the aminoglycoside G418; and hyg^r, which confers resistance to hygromycin.

Animal cells can be propagated in vitro in two modes: as non-anchorage-dependent cells growing in suspension throughout the bulk of the culture or as anchorage-dependent cells requiring attachment to a solid substrate for their propagation (i.e., a monolayer type of cell growth).

Non-anchorage dependent or suspension cultures from continuous established cell lines are the most widely used means of large scale production of cells and cell products. However, suspension cultured cells have limitations, such as tumorigenic potential and lower protein production than adherent cells.

Where a protein is specifically mentioned herein, it is preferably a reference to a native or recombinant protein or optionally a protein in which any signal sequence has been removed. The protein may be isolated directly from the staphylococcal strain or produced by recombinant DNA techniques. Immunogenic fragments of the protein may be incorporated into the immunogenic composition of the invention. These are fragments comprising at least 10 amino acids, 20 amino acids, 30 amino acids, 40 amino acids, 50 amino acids, or 100 amino acids, including all values and ranges there between, taken contiguously from the amino acid sequence of the protein. In addition, such immunogenic fragments are immunologically reactive with antibodies generated against

the Staphylococcal proteins or with antibodies generated by infection of a mammalian host with Staphylococci. Immunogenic fragments also includes fragments that when administered at an effective dose, (either alone or as a hapten bound to a carrier), elicit a protective immune response against Staphylococcal infection; in certain aspects it is protective against *S. aureus* and/or *S. epidermidis* infection. Such an immunogenic fragment may include, for example, the protein lacking an N-terminal leader sequence, and/or a transmembrane domain and/or a C-terminal anchor domain. In a preferred aspect the immunogenic fragment according to the invention comprises substantially all of the extracellular domain of a protein which has at least 85% identity, at least 90% identity, at least 95% identity, or at least 97-99% identity, including all values and ranges there between, to that a sequence selected over the length of the fragment sequence.

Also included in immunogenic compositions of the invention are fusion proteins composed of Staphylococcal proteins, or immunogenic fragments of staphylococcal proteins. Such fusion proteins may be made recombinantly and may comprise one portion of at least 2, 3, 4, 5 or 6 staphylococcal proteins. Alternatively, a fusion protein may comprise multiple portions of at least 1, 2, 3, 4 or 5 staphylococcal proteins. These may combine different Staphylococcal proteins and/or multiples of the same protein or protein fragment, or immunogenic fragments thereof in the same protein. Alternatively, the invention also includes individual fusion proteins of Staphylococcal proteins or immunogenic fragments thereof, as a fusion protein with heterologous sequences such as a provider of T-cell epitopes or purification tags, for example: [beta]-galactosidase, glutathione-S-transferase, green fluorescent proteins (GFP), epitope tags such as FLAG, myc tag, poly histidine, or viral surface proteins such as influenza virus haemagglutinin, or bacterial proteins such as tetanus toxoid, diphtheria toxoid, CRM 197.

II. Nucleic Acids

In certain embodiments, the present invention concerns recombinant polynucleotides encoding the proteins, polypeptides, or peptides of the invention. The nucleic acid sequences for EsaC and other bacterial proteins including, but not limited to EsxA, EsxB, or any other polypeptide transported by the Ess pathway, and/or SdrD, SdrE, IsdA, IsdB, or other surface proteins or sortase substrates, are included, all of which are incorporated by reference, and can be used to prepare an EsaC, EsxA, EsxB, or any other polypeptide transported by the Ess pathway, and/or SdrC, SdrD, SdrE, IsdA, IsdB, Spa, ClfA, ClfB, IsdC, SasF or other sortase substrates.

As used in this application, the term "polynucleotide" refers to a nucleic acid molecule that either is recombinant or has been isolated free of total genomic nucleic acid. Included within the term "polynucleotide" are oligonucleotides (nucleic acids 100 residues or less in length), recombinant vectors, including, for example, plasmids, cosmids, phage, viruses, and the like. Polynucleotides include, in certain aspects, regulatory sequences, isolated substantially away from their naturally occurring genes or protein encoding sequences. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be RNA, DNA (genomic, cDNA or synthetic), analogs thereof, or a combination thereof. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide.

In this respect, the term "gene," "polynucleotide," or "nucleic acid" is used to refer to a nucleic acid that encodes a protein, polypeptide, or peptide (including any sequences required for proper transcription, post-translational modifi-

cation, or localization). As will be understood by those in the art, this term encompasses genomic sequences, expression cassettes, cDNA sequences, and smaller engineered nucleic acid segments that express, or may be adapted to express, proteins, polypeptides, domains, peptides, fusion proteins, and mutants. A nucleic acid encoding all or part of a polypeptide may contain a contiguous nucleic acid sequence encoding all or a portion of such a polypeptide of the following lengths: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 441, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, 1000, 1010, 1020, 1030, 1040, 1050, 1060, 1070, 1080, 1090, 1095, 1100, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 9000, 10000, or more nucleotides, nucleosides, or base pairs of a polypeptide of the invention. It also is contemplated that a particular polypeptide may be encoded by nucleic acids containing variations having slightly different nucleic acid sequences but, nonetheless, encode the same or substantially similar protein (see Table 2 above).

In particular embodiments, the invention concerns isolated nucleic acid segments and recombinant vectors incorporating nucleic acid sequences that encode an EsaC, that may also be in combination with EsxA, EsxB, or any other protein transported by the Ess pathway, and/or SdrD, SdrE, IsdA, IsdB, or other sortase substrates. Thus, an isolated nucleic acid segment or vector containing a nucleic acid segment may encode, for example, an EsaC, EsxA, EsxB, or other Ess pathway protein, and/or SdrD, SdrE, IsdA, IsdB, or other sortase substrates that is immunogenic. The term “recombinant” may be used in conjunction with a polypeptide or the name of a specific polypeptide, and this generally refers to a polypeptide produced from a nucleic acid molecule that has been manipulated in vitro or that is a replication product of such a molecule.

In other embodiments, the invention concerns isolated nucleic acid segments and recombinant vectors incorporating nucleic acid sequences that encode an EsaC polypeptide that can be used in combination with EsxA, EsxB, or another Ess transported polypeptide or peptide, and/or SdrD, SdrE, IsdA, IsdB, or other sortase substrate polypeptides or peptides to generate an immune response in a subject. In various embodiments the nucleic acids of the invention may be used in genetic vaccines.

The nucleic acid segments used in the present invention, regardless of the length of the coding sequence itself, may be combined with other nucleic acid sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant nucleic acid protocol. In some cases, a nucleic acid sequence may encode a polypeptide sequence with additional heterologous coding sequences, for example to allow for purification of the polypeptide, transport, secretion, post-translational modification, or for therapeutic benefits such as targeting or efficacy. As discussed above, a tag or other heterologous polypeptide may be added to the modified

polypeptide-encoding sequence, wherein “heterologous” refers to a polypeptide that is not the same as the modified polypeptide.

The nucleic acid used in the present invention encodes EsaC. In certain aspects EsaC can be used in combination with EsxA, EsxB, or any other peptide or protein from a polypeptide transported by the Ess pathway, and/or SdrD, SdrE, IsdA, IsdB, or any other peptides or protein processed by the sortase mechanism. Such sequences may arise as a consequence of codon redundancy and functional equivalency that are known to occur naturally within nucleic acid sequences and the proteins thus encoded. Alternatively, functionally equivalent proteins or peptides may be created via the application of recombinant DNA technology, in which changes in the protein structure may be engineered, based on considerations of the properties of the amino acids being exchanged. Changes designed by human may be introduced through the application of site-directed mutagenesis techniques, e.g., to introduce improvements to the antigenicity of the protein.

In certain other embodiments, the invention concerns isolated nucleic acid segments and recombinant vectors that include within their sequence a contiguous nucleic acid sequence from SEQ ID NO:1 (EsaC), SEQ ID NO:3 (EsxA), SEQ ID NO:5 (EsxB), SEQ ID NO:7 (SdrD), SEQ ID NO:9 (SdrE), SEQ ID NO:11 (IsdA), SEQ ID NO:13 (IsdB), SEQ ID NO:15 (Spa), SEQ ID NO:17 (ClfB), SEQ ID NO:19 (IsdC), SEQ ID NO:21 (SasF), SEQ ID NO:23 (SdrC), SEQ ID NO:25 (ClfA) or any other nucleic acid sequences encoding secreted virulence factors and/or surface proteins including proteins transported by the Ess pathway, processed by sortase, or proteins incorporated herein by reference.

In certain embodiments, the present invention provides polynucleotide variants having substantial identity to the sequences disclosed herein; those comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher sequence identity, including all values and ranges there between, compared to a polynucleotide sequence of this invention using the methods described herein (e.g., BLAST analysis using standard parameters). In certain aspects, the isolated polynucleotide of the invention will comprise a nucleotide sequence encoding a polypeptide that has at least 90%, preferably 95% and above, identity to an amino acid sequence of the invention, over the entire length of the sequence; or a nucleotide sequence complementary to said isolated polynucleotide.

The invention also contemplates the use of polynucleotides which are complementary to all the above described polynucleotides.

The invention also provides for the use of a fragment of a polynucleotide of the invention which when administered to a subject has the same immunogenic properties as a polynucleotide.

The invention also provides for the use of a polynucleotide encoding an immunological fragment of a protein of the invention as hereinbefore defined.

A. Vectors

Polypeptides of the invention may be encoded by a nucleic acid molecule comprised in a vector. The term “vector” is used to refer to a carrier nucleic acid molecule into which a heterologous nucleic acid sequence can be inserted for introduction into a cell where it can be replicated and expressed. A nucleic acid sequence can be “heterologous,” which means that it is in a context foreign to the cell in which the vector is being introduced or to the nucleic acid in which is incorporated, which includes a sequence homologous to a sequence in the cell or nucleic acid but in a position within the host cell

or nucleic acid where it is ordinarily not found. Vectors include DNAs, RNAs, plasmids, cosmids, viruses (bacteriophage, animal viruses, and plant viruses), and artificial chromosomes (e.g., YACs). One of skill in the art would be well equipped to construct a vector through standard recombinant techniques (for example Sambrook et al., 2001; Ausubel et al., 1996, both incorporated herein by reference). In addition to encoding an EsaC polypeptide the vector can encode an EsxA, EsxB, or other Ess transported polypeptide, and/or SdrD, SdrE, IsdA, IsdB, or any other peptides or protein processed by sortase, a vector may encode polypeptide sequences such as a tag or immunogenicity enhancing peptide. Useful vectors encoding such fusion proteins include pIN vectors (Inouye et al., 1985), vectors encoding a stretch of histidines, and pGEX vectors, for use in generating glutathione S-transferase (GST) soluble fusion proteins for later purification and separation or cleavage.

Vectors of the invention may be used in a host cell to produce an EsaC polypeptide. In certain aspects the vectors may also produce EsxA, EsxB, or other Ess transported polypeptide, and/or a SdrD, SdrE, IsdA, IsdB, or any other peptides or protein processed by the sortase mechanism that may subsequently be purified for administration to a subject or the vector may be purified for direct administration to a subject for expression of the protein in the subject.

The term "expression vector" refers to a vector containing a nucleic acid sequence coding for at least part of a gene product capable of being transcribed. In some cases, RNA molecules are then translated into a protein, polypeptide, or peptide. Expression vectors can contain a variety of "control sequences," which refer to nucleic acid sequences necessary for the transcription and possibly translation of an operably linked coding sequence in a particular host organism. In addition to control sequences that govern transcription and translation, vectors and expression vectors may contain nucleic acid sequences that serve other functions as well and are described herein.

1. Promoters and Enhancers

A "promoter" is a control sequence. The promoter is typically a region of a nucleic acid sequence at which initiation and rate of transcription are controlled. It may contain genetic elements at which regulatory proteins and molecules may bind such as RNA polymerase and other transcription factors. The phrases "operatively positioned," "operatively linked," "under control," and "under transcriptional control" mean that a promoter is in a correct functional location and/or orientation in relation to a nucleic acid sequence to control transcriptional initiation and expression of that sequence. A promoter may or may not be used in conjunction with an "enhancer," which refers to a cis-acting regulatory sequence involved in the transcriptional activation of a nucleic acid sequence.

A promoter may be one naturally associated with a gene or sequence, as may be obtained by isolating the 5' non-coding sequences located upstream of the coding segment or exon. Such a promoter can be referred to as "endogenous." Similarly, an enhancer may be one naturally associated with a nucleic acid sequence, located either downstream or upstream of that sequence. Alternatively, certain advantages will be gained by positioning the coding nucleic acid segment under the control of a recombinant or heterologous promoter, which refers to a promoter that is not normally associated with a nucleic acid sequence in its natural environment. A recombinant or heterologous enhancer refers also to an enhancer not normally associated with a nucleic acid sequence in its natural state. Such promoters or enhancers may include promoters or enhancers of other genes, and

promoters or enhancers isolated from any other prokaryotic, viral, or eukaryotic cell, and promoters or enhancers not "naturally occurring," i.e., containing different elements of different transcriptional regulatory regions, and/or mutations that alter expression. In addition to producing nucleic acid sequences of promoters and enhancers synthetically, sequences may be produced using recombinant cloning and/or nucleic acid amplification technology, including PCR™, in connection with the compositions disclosed herein (see U.S. Pat. Nos. 4,683,202, 5,928,906, each incorporated herein by reference).

Naturally, it may be important to employ a promoter and/or enhancer that effectively directs the expression of the DNA segment in the cell type or organism chosen for expression. Those of skill in the art of molecular biology generally know the use of promoters, enhancers, and cell type combinations for protein expression (see Sambrook et al., 2001, incorporated herein by reference). The promoters employed may be constitutive, tissue-specific, or inducible and in certain embodiments may direct high level expression of the introduced DNA segment under specified conditions, such as large-scale production of recombinant proteins or peptides.

Various elements/promoters may be employed in the context of the present invention to regulate the expression of a gene. Examples of such inducible elements, which are regions of a nucleic acid sequence that can be activated in response to a specific stimulus, include but are not limited to Immunoglobulin Heavy Chain (Banerji et al., 1983; Gilles et al., 1983; Grosschedl et al., 1985; Atchinson et al., 1986, 1987; Imler et al., 1987; Weinberger et al., 1984; Kiledjian et al., 1988; Porton et al., 1990), Immunoglobulin Light Chain (Queen et al., 1983; Picard et al., 1984), T Cell Receptor (Luria et al., 1987; Winoto et al., 1989; Redondo et al., 1990), HLA DQ α and/or DQ β (Sullivan et al., 1987), β Interferon (Goodbourn et al., 1986; Fujita et al., 1987; Goodbourn et al., 1988), Interleukin-2 (Greene et al., 1989), Interleukin-2 Receptor (Greene et al., 1989; Lin et al., 1990), MHC Class II 5 (Koch et al., 1989), MHC Class II HLA-DR α (Sherman et al., 1989), β -Actin (Kawamoto et al., 1988; Ng et al., 1989), Muscle Creatine Kinase (MCK) (Jaynes et al., 1988; Horlick et al., 1989; Johnson et al., 1989), Prealbumin (Transthyretin) (Costa et al., 1988), Elastase I (Ornitz et al., 1987), Metallothionein (MTII) (Karin et al., 1987; Culotta et al., 1989), Collagenase (Pinkert et al., 1987; Angel et al., 1987), Albumin (Pinkert et al., 1987; Tronche et al., 1989, 1990), α -Fetoprotein (Godbout et al., 1988; Campere et al., 1989), γ -Globin (Bodine et al., 1987; Perez-Stable et al., 1990), 13-Globin (Trudel et al., 1987), c-fos (Cohen et al., 1987), c-Ha-Ras (Triesman, 1986; Deschamps et al., 1985), Insulin (Edlund et al., 1985), Neural Cell Adhesion Molecule (NCAM) (Hirsh et al., 1990), α 1-Antitrypsin (Latimer et al., 1990), H2B (TH2B) Histone (Hwang et al., 1990), Mouse and/or Type I Collagen (Ripe et al., 1989), Glucose-Regulated Proteins (GRP94 and GRP78) (Chang et al., 1989), Rat Growth Hormone (Larsen et al., 1986), Human Serum Amyloid A (SAA) (Edbrooke et al., 1989), Troponin I (TN I) (Yutzey et al., 1989), Platelet-Derived Growth Factor (PDGF) (Pech et al., 1989), Duchenne Muscular Dystrophy (Klamut et al., 1990), SV40 (Banerji et al., 1981; Moreau et al., 1981; Sleight et al., 1985; Firak et al., 1986; Herr et al., 1986; Imbra et al., 1986; Kadesch et al., 1986; Wang et al., 1986; Ondek et al., 1987; Kuhl et al., 1987; Schaffner et al., 1988), Polyoma (Swartzendruber et al., 1975; Vasseur et al., 1980; Katinka et al., 1980, 1981; Tyndell et al., 1981; Dandolo et al., 1983; de Villiers et al., 1984; Hen et al., 1986; Satake et al., 1988; Campbell et al., 1988), Retroviruses (Kriegler et al., 1982, 1983; Levinson et al., 1982; Kriegler et al., 1983, 1984a, b,

1988; Bosze et al., 1986; Miksicek et al., 1986; Celandier et al., 1987; Thiesen et al., 1988; Celandier et al., 1988; Choi et al., 1988; Reisman et al., 1989), Papilloma Virus (Campo et al., 1983; Lusky et al., 1983; Spandidos and Wilkie, 1983; Spalholz et al., 1985; Lusky et al., 1986; Cripe et al., 1987; Gloss et al., 1987; Hirochika et al., 1987; Stephens et al., 1987), Hepatitis B Virus (Bulla et al., 1986; Jameel et al., 1986; Shaul et al., 1987; Spandau et al., 1988; Vannice et al., 1988), Human Immunodeficiency Virus (Muesing et al., 1987; Hauber et al., 1988; Jakobovits et al., 1988; Feng et al., 1988; Takebe et al., 1988; Rosen et al., 1988; Berkhout et al., 1989; Laspia et al., 1989; Sharp et al., 1989; Braddock et al., 1989), Cytomegalovirus (CMV) IE (Weber et al., 1984; Boshart et al., 1985; Foecking et al., 1986), Gibbon Ape Leukemia Virus (Holbrook et al., 1987; Quinn et al., 1989).

Inducible elements include, but are not limited to MT II—Phorbol Ester (TFA)/Heavy metals (Palmiter et al., 1982; Haslinger et al., 1985; Searle et al., 1985; Stuart et al., 1985; Imagawa et al., 1987; Karin et al., 1987; Angel et al., 1987b; McNeall et al., 1989); MMTV (mouse mammary tumor virus)—Glucocorticoids (Huang et al., 1981; Lee et al., 1981; Majors et al., 1983; Chandler et al., 1983; Lee et al., 1984; Ponta et al., 1985; Sakai et al., 1988); β -Interferon—poly(rI) x/poly(rc) (Tavernier et al., 1983); Adenovirus 5 E2-E1A (Imperiale et al., 1984); Collagenase—Phorbol Ester (TPA) (Angel et al., 1987a); Stromelysin—Phorbol Ester (TPA) (Angel et al., 1987b); SV40—Phorbol Ester (TPA) (Angel et al., 1987b); Murine MX Gene—Interferon, Newcastle Disease Virus (Hug et al., 1988); GRP78 Gene—A23187 (Resendez et al., 1988); α -2-Macroglobulin—IL-6 (Kunz et al., 1989); Vimentin—Serum (Rittling et al., 1989); MHC Class I Gene H-2 Kb—Interferon (Blonar et al., 1989); HSP70—E1A/SV40 Large T Antigen (Taylor et al., 1989, 1990a, 1990b); Proliferin—Phorbol Ester/TPA (Mordacq et al., 1989); Tumor Necrosis Factor—PMA (Hensel et al., 1989); and Thyroid Stimulating Hormone a Gene—Thyroid Hormone (Chatterjee et al., 1989).

Also contemplated as useful in the present invention are the dectin-1 and dectin-2 promoters. Additionally any promoter/enhancer combination (as per the Eukaryotic Promoter Data Base EPDB) could also be used to drive expression of structural genes encoding oligosaccharide processing enzymes, protein folding accessory proteins, selectable marker proteins or a heterologous protein of interest.

The particular promoter that is employed to control the expression of peptide or protein encoding polynucleotide of the invention is not believed to be critical, so long as it is capable of expressing the polynucleotide in a targeted cell, preferably a bacterial cell. Where a human cell is targeted, it is preferable to position the polynucleotide coding region adjacent to and under the control of a promoter that is capable of being expressed in a human cell. Generally speaking, such a promoter might include either a bacterial, human or viral promoter.

In various embodiments, the human cytomegalovirus (CMV) immediate early gene promoter, the SV40 early promoter, and the Rous sarcoma virus long terminal repeat can be used to obtain high level expression of an EsaC polynucleotide. In other embodiments EsaC can be used in combination with EsxA-, EsxB-, or other Ess-related polynucleotide, and/or SdrD, SdrE, IsdA, IsdB, or any other sortase substrate related polynucleotide. The use of other viral or mammalian cellular or bacterial phage promoters, which are well known in the art, to achieve expression of polynucleotides is contemplated as well.

In embodiments in which a vector is administered to a subject for expression of the protein, it is contemplated that a

desirable promoter for use with the vector is one that is not down-regulated by cytokines or one that is strong enough that even if down-regulated, it produces an effective amount of an EsaC polypeptide for eliciting an immune response to limit abscess persistence. In other embodiments EsaC can be used in combination with EsxA, EsxB, or other Ess transported protein, and/or SdrD, SdrE, IsdA, IsdB, or any other peptides or protein processed by sortase in a subject to elicit an immune response. Non-limiting examples of these are CMV IE and RSV LTR. In other embodiments, a promoter that is up-regulated in the presence of cytokines is employed. The MHC I promoter increases expression in the presence of IFN- γ .

Tissue specific promoters can be used, particularly if expression is in cells in which expression of an antigen is desirable, such as dendritic cells or macrophages. The mammalian MHC I and MHC II promoters are examples of such tissue-specific promoters.

2. Initiation Signals and Internal Ribosome Binding Sites (IRES)

A specific initiation signal also may be required for efficient translation of coding sequences. These signals include the ATG initiation codon or adjacent sequences. Exogenous translational control signals, including the ATG initiation codon, may need to be provided. One of ordinary skill in the art would readily be capable of determining this and providing the necessary signals. It is well known that the initiation codon must be "in-frame" with the reading frame of the desired coding sequence to ensure translation of the entire insert. The exogenous translational control signals and initiation codons can be either natural or synthetic and may be operable in bacteria or mammalian cells. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements.

In certain embodiments of the invention, the use of internal ribosome entry sites (IRES) elements are used to create multigene, or polycistronic, messages. IRES elements are able to bypass the ribosome scanning model of 5' methylated Cap dependent translation and begin translation at internal sites (Pelletier and Sonenberg, 1988). IRES elements from two members of the picornavirus family (polio and encephalomyocarditis) have been described (Pelletier and Sonenberg, 1988), as well as an IRES from a mammalian message (Macejak and Sarnow, 1991). IRES elements can be linked to heterologous open reading frames. Multiple open reading frames can be transcribed together, each separated by an IRES, creating polycistronic messages. By virtue of the IRES element, each open reading frame is accessible to ribosomes for efficient translation. Multiple genes can be efficiently expressed using a single promoter/enhancer to transcribe a single message (see U.S. Pat. Nos. 5,925,565 and 5,935,819, herein incorporated by reference).

3. Multiple Cloning Sites

Vectors can include a multiple cloning site (MCS), which is a nucleic acid region that contains multiple restriction enzyme sites, any of which can be used in conjunction with standard recombinant technology to digest the vector. (See Carbonelli et al., 1999; Levenson et al., 1998, and Cocea, 1997, incorporated herein by reference.) Frequently, a vector is linearized or fragmented using a restriction enzyme that cuts within the MCS to enable exogenous sequences to be ligated to the vector. Techniques involving restriction enzymes and ligation reactions are well known to those of skill in the art of recombinant technology.

4. Splicing Sites

Most transcribed eukaryotic RNA molecules will undergo RNA splicing to remove introns from the primary transcripts.

Vectors containing genomic eukaryotic sequences may require donor and/or acceptor splicing sites to ensure proper processing of the transcript for protein expression. (See Chandler et al., 1997, incorporated herein by reference.)

5. Termination Signals

The vectors or constructs of the present invention will generally comprise at least one termination signal. A "termination signal" or "terminator" is comprised of the DNA sequences involved in specific termination of an RNA transcript by an RNA polymerase. Thus, in certain embodiments a termination signal that ends the production of an RNA transcript is contemplated. A terminator may be necessary in vivo to achieve desirable message levels.

In eukaryotic systems, the terminator region may also comprise specific DNA sequences that permit site-specific cleavage of the new transcript so as to expose a polyadenylation site. This signals a specialized endogenous polymerase to add a stretch of about 200 A residues (polyA) to the 3' end of the transcript. RNA molecules modified with this polyA tail appear to more stable and are translated more efficiently. Thus, in other embodiments involving eukaryotes, it is preferred that that terminator comprises a signal for the cleavage of the RNA, and it is more preferred that the terminator signal promotes polyadenylation of the message.

Terminators contemplated for use in the invention include any known terminator of transcription described herein or known to one of ordinary skill in the art, including but not limited to, for example, the bovine growth hormone terminator or viral termination sequences, such as the SV40 terminator. In certain embodiments, the termination signal may be a lack of transcribable or translatable sequence, such as due to a sequence truncation.

6. Polyadenylation Signals

In expression, particularly eukaryotic expression, one will typically include a polyadenylation signal to effect proper polyadenylation of the transcript. The nature of the polyadenylation signal is not believed to be crucial to the successful practice of the invention, and/or any such sequence may be employed. Preferred embodiments include the SV40 polyadenylation signal and/or the bovine growth hormone polyadenylation signal, convenient and/or known to function well in various target cells. Polyadenylation may increase the stability of the transcript or may facilitate cytoplasmic transport.

7. Origins of Replication

In order to propagate a vector in a host cell, it may contain one or more origins of replication sites (often termed "ori"), which is a specific nucleic acid sequence at which replication is initiated. Alternatively an autonomously replicating sequence (ARS) can be employed if the host cell is yeast.

8. Selectable and Screenable Markers

In certain embodiments of the invention, cells containing a nucleic acid construct of the present invention may be identified in vitro or in vivo by encoding a screenable or selectable marker in the expression vector. When transcribed and translated, a marker confers an identifiable change to the cell permitting easy identification of cells containing the expression vector. Generally, a selectable marker is one that confers a property that allows for selection. A positive selectable marker is one in which the presence of the marker allows for its selection, while a negative selectable marker is one in which its presence prevents its selection. An example of a positive selectable marker is a drug resistance marker.

Usually the inclusion of a drug selection marker aids in the cloning and identification of transformants, for example, markers that confer resistance to neomycin, puromycin, hygromycin, DHFR, GPT, zeocin or histidinol are useful selectable markers. In addition to markers conferring a phe-

notype that allows for the discrimination of transformants based on the implementation of conditions, other types of markers including screenable markers such as GFP for colorimetric analysis. Alternatively, screenable enzymes such as herpes simplex virus thymidine kinase (tk) or chloramphenicol acetyltransferase (CAT) may be utilized. One of skill in the art would also know how to employ immunologic markers that can be used in conjunction with FACS analysis. The marker used is not believed to be important, so long as it is capable of being expressed simultaneously with the nucleic acid encoding a protein of the invention. Further examples of selectable and screenable markers are well known to one of skill in the art.

B. Host Cells

As used herein, the terms "cell," "cell line," and "cell culture" may be used interchangeably. All of these terms also include their progeny, which is any and all subsequent generations. It is understood that all progeny may not be identical due to deliberate or inadvertent mutations. In the context of expressing a heterologous nucleic acid sequence, "host cell" refers to a prokaryotic or eukaryotic cell, and it includes any transformable organism that is capable of replicating a vector or expressing a heterologous gene encoded by a vector. A host cell can, and has been, used as a recipient for vectors or viruses. A host cell may be "transfected" or "transformed," which refers to a process by which exogenous nucleic acid, such as a recombinant protein-encoding sequence, is transferred or introduced into the host cell. A transformed cell includes the primary subject cell and its progeny.

Host cells may be derived from prokaryotes or eukaryotes, including bacteria, yeast cells, insect cells, and mammalian cells for replication of the vector or expression of part or all of the nucleic acid sequence(s). Numerous cell lines and cultures are available for use as a host cell, and they can be obtained through the American Type Culture Collection (ATCC), which is an organization that serves as an archive for living cultures and genetic materials (available on the world wide web at ATCC.org). An appropriate host can be determined by one of skill in the art based on the vector backbone and the desired result. A plasmid or cosmid, for example, can be introduced into a prokaryote host cell for replication of many vectors or expression of encoded proteins. Bacterial cells used as host cells for vector replication and/or expression include *Staphylococcus* strains, DH5 α , JM109, and KC8, as well as a number of commercially available bacterial hosts such as SURE $\text{\textregistered}$ Competent Cells and SOLOPACK TM Gold Cells (STRATAGENE $\text{\textregistered}$, La Jolla, Calif.). Alternatively, bacterial cells such as *E. coli* LE392 could be used as host cells for phage viruses. Appropriate yeast cells include *Saccharomyces cerevisiae*, *Saccharomyces pombe*, and *Pichia pastoris*.

Examples of eukaryotic host cells for replication and/or expression of a vector include HeLa, NIH3T3, Jurkat, 293, Cos, CHO, Saos, and PC12. Many host cells from various cell types and organisms are available and would be known to one of skill in the art. Similarly, a viral vector may be used in conjunction with either a eukaryotic or prokaryotic host cell, particularly one that is permissive for replication or expression of the vector.

Some vectors may employ control sequences that allow it to be replicated and/or expressed in both prokaryotic and eukaryotic cells. One of skill in the art would further understand the conditions under which to incubate all of the above described host cells to maintain them and to permit replication of a vector. Also understood and known are techniques and conditions that would allow large-scale production of

vectors, as well as production of the nucleic acids encoded by vectors and their cognate polypeptides, proteins, or peptides.

C. Expression Systems

Numerous expression systems exist that comprise at least a part or all of the compositions discussed above. Prokaryote- and/or eukaryote-based systems can be employed for use with the present invention to produce nucleic acid sequences, or their cognate polypeptides, proteins and peptides. Many such systems are commercially and widely available.

The insect cell/baculovirus system can produce a high level of protein expression of a heterologous nucleic acid segment, such as described in U.S. Pat. Nos. 5,871,986, 4,879,236, both herein incorporated by reference, and which can be bought, for example, under the name MAXBAC® 2.0 from INVITROGEN® and BACPACK™ BACULOVIRUS EXPRESSION SYSTEM FROM CLONTECH®.

In addition to the disclosed expression systems of the invention, other examples of expression systems include STRATAGENE®'s COMPLETE CONTROL™ Inducible Mammalian Expression System, which involves a synthetic ecdysone-inducible receptor, or its pET Expression System, an *E. coli* expression system. Another example of an inducible expression system is available from INVITROGEN®, which carries the T-REX™ (tetracycline-regulated expression) System, an inducible mammalian expression system that uses the full-length CMV promoter. INVITROGEN® also provides a yeast expression system called the *Pichia methanolica* Expression System, which is designed for high-level production of recombinant proteins in the methylotrophic yeast *Pichia methanolica*. One of skill in the art would know how to express a vector, such as an expression construct, to produce a nucleic acid sequence or its cognate polypeptide, protein, or peptide.

D. Amplification of Nucleic Acids

Nucleic acids used as a template for amplification may be isolated from cells, tissues or other samples according to standard methodologies (Sambrook et al., 2001). In certain embodiments, analysis is performed on whole cell or tissue homogenates or biological fluid samples without substantial purification of the template nucleic acid. The nucleic acid may be genomic DNA or fractionated or whole cell RNA. Where RNA is used, it may be desired to first convert the RNA to a complementary DNA.

The term "primer," as used herein, is meant to encompass any nucleic acid that is capable of priming the synthesis of a nascent nucleic acid in a template-dependent process. Typically, primers are oligonucleotides from ten to twenty and/or thirty base pairs in length, but longer sequences can be employed. Primers may be provided in double-stranded and/or single-stranded form, although the single-stranded form is preferred.

Pairs of primers designed to selectively hybridize to nucleic acids corresponding to sequences of genes identified herein are contacted with the template nucleic acid under conditions that permit selective hybridization. Depending upon the desired application, high stringency hybridization conditions may be selected that will only allow hybridization to sequences that are completely complementary to the primers. In other embodiments, hybridization may occur under reduced stringency to allow for amplification of nucleic acids containing one or more mismatches with the primer sequences. Once hybridized, the template-primer complex is contacted with one or more enzymes that facilitate template-dependent nucleic acid synthesis. Multiple rounds of amplification, also referred to as "cycles," are conducted until a sufficient amount of amplification product is produced.

The amplification product may be detected or quantified. In certain applications, the detection may be performed by visual means. Alternatively, the detection may involve indirect identification of the product via chemiluminescence, radioactive scintigraphy of incorporated radiolabel or fluorescent label or even via a system using electrical and/or thermal impulse signals (Bellus, 1994).

A number of template dependent processes are available to amplify the oligonucleotide sequences present in a given template sample. One of the best known amplification methods is the polymerase chain reaction (referred to as PCR™) which is described in detail in U.S. Pat. Nos. 4,683,195, 4,683,202 and 4,800,159, and in Innis et al., 1988, each of which is incorporated herein by reference in their entirety.

Alternative methods for amplification of target nucleic acid sequences that may be used in the practice of the present invention are disclosed in U.S. Pat. Nos. 5,843,650, 5,846,709, 5,846,783, 5,849,546, 5,849,497, 5,849,547, 5,858,652, 5,866,366, 5,916,776, 5,922,574, 5,928,905, 5,928,906, 5,932,451, 5,935,825, 5,939,291 and 5,942,391, GB Application No. 2 202 328, and in PCT Application No. PCT/US89/01025, each of which is incorporated herein by reference in its entirety.

E. Methods of Gene Transfer

Suitable methods for nucleic acid delivery to effect expression of compositions of the present invention are believed to include virtually any method by which a nucleic acid (e.g., DNA, including viral and nonviral vectors) can be introduced into a cell, a tissue or an organism, as described herein or as would be known to one of ordinary skill in the art. Such methods include, but are not limited to, direct delivery of DNA such as by injection (U.S. Pat. Nos. 5,994,624, 5,981,274, 5,945,100, 5,780,448, 5,736,524, 5,702,932, 5,656,610, 5,589,466 and 5,580,859, each incorporated herein by reference), including microinjection (Harland and Weintraub, 1985; U.S. Pat. No. 5,789,215, incorporated herein by reference); by electroporation (U.S. Pat. No. 5,384,253, incorporated herein by reference); by calcium phosphate precipitation (Graham and Van Der Eb, 1973; Chen and Okayama, 1987; Rippe et al., 1990); by using DEAE dextran followed by polyethylene glycol (Gopal, 1985); by direct sonic loading (Fechheimer et al., 1987); by liposome mediated transfection (Nicolau and Sene, 1982; Fraley et al., 1979; Nicolau et al., 1987; Wong et al., 1980; Kaneda et al., 1989; Kato et al., 1991); by microprojectile bombardment (PCT Application Nos. WO 94/09699 and 95/06128; U.S. Pat. Nos. 5,610,042; 5,322,783, 5,563,055, 5,550,318, 5,538,877 and 5,538,880, and each incorporated herein by reference); by agitation with silicon carbide fibers (Kaeppeler et al., 1990; U.S. Pat. Nos. 5,302,523 and 5,464,765, each incorporated herein by reference); by *Agrobacterium* mediated transformation (U.S. Pat. Nos. 5,591,616 and 5,563,055, each incorporated herein by reference); or by PEG mediated transformation of protoplasts (Omirulh et al., 1993; U.S. Pat. Nos. 4,684,611 and 4,952,500, each incorporated herein by reference); by desiccation/inhibition mediated DNA uptake (Potrykus et al., 1985). Through the application of techniques such as these, organelle(s), cell(s), tissue(s) or organism(s) may be stably or transiently transformed.

III. Polysaccharides

The immunogenic compositions of the invention may further comprise capsular polysaccharides including one or more of PIA (also known as PNAG) and/or *S. aureus* Type V

and/or type VIII capsular polysaccharide and/or *S. epidermidis* Type I, and/or Type II and/or Type III capsular polysaccharide.

A. PIA (PNAG)

It is now clear that the various forms of staphylococcal surface polysaccharides identified as PS/A, PIA and SAA are the same chemical entity—PNAG (Maira-Litran et al., 2004). Therefore the term PIA or PNAG encompasses all these polysaccharides or oligosaccharides derived from them.

PIA is a polysaccharide intercellular adhesin and is composed of a polymer of β -(1 $\rightarrow$ 6)-linked glucosamine substituted with N-acetyl and O-succinyl constituents. This polysaccharide is present in both *S. aureus* and *S. epidermidis* and can be isolated from either source (Joyce et al., 2003; Maira-Litran et al., 2002). For example, PNAG may be isolated from *S. aureus* strain MN8m (WO04/43407). PIA isolated from *S. epidermidis* is an integral constituent of biofilm. It is responsible for mediating cell-cell adhesion and probably also functions to shield the growing colony from the host's immune response. The polysaccharide previously known as poly-N-succinyl- β -(1 $\rightarrow$ 6)-glucosamine (PNSG) was recently shown not to have the expected structure since the identification of N-succinylation was incorrect (Maira-Litran et al., 2002). Therefore the polysaccharide formally known as PNSG and now found to be PNAG is also encompassed by the term PIA.

PIA (or PNAG) may be of different sizes varying from over 400 kDa to between 75 and 400 kDa to between 10 and 75 kDa to oligosaccharides composed of up to 30 repeat units (of β -(1 $\rightarrow$ 6)-linked glucosamine substituted with N-acetyl and O-succinyl constituents). Any size of PIA polysaccharide or oligosaccharide may be used in an immunogenic composition of the invention, in one aspect the polysaccharide is over 40 kDa. Sizing may be achieved by any method known in the art, for instance by microfluidization, ultrasonic irradiation or by chemical cleavage (WO 03/53462, EP497524, EP497525). In certain aspects PIA (PNAG) is at least or at most 40-400 kDa, 40-300 kDa, 50-350 kDa, 60-300 kDa, 50-250 kDa and 60-200 kDa.

PIA (PNAG) can have different degree of acetylation due to substitution on the amino groups by acetate. PIA produced in vitro is almost fully substituted on amino groups (95-100%). Alternatively, a deacetylated PIA (PNAG) can be used having less than 60%, 50%, 40%, 30%, 20%, 10% acetylation. Use of a deacetylated PIA (PNAG) is preferred since non-acetylated epitopes of PNAG are efficient at mediating opsonic killing of Gram positive bacteria, preferably *S. aureus* and/or *S. epidermidis*. In certain aspects, the PIA (PNAG) has a size between 40 kDa and 300 kDa and is deacetylated so that less than 60%, 50%, 40%, 30% or 20% of amino groups are acetylated.

The term deacetylated PNAG (dPNAG) refers to a PNAG polysaccharide or oligosaccharide in which less than 60%, 50%, 40%, 30%, 20% or 10% of the amino groups are acetylated. In certain aspects, PNAG is deacetylated to form dPNAG by chemically treating the native polysaccharide. For example, the native PNAG is treated with a basic solution such that the pH rises to above 10. For instance the PNAG is treated with 0.1-5 M, 0.2-4 M, 0.3-3 M, 0.5-2 M, 0.75-1.5 M or 1 M NaOH, KOH or NH_4OH . Treatment is for at least 10 to 30 minutes, or 1, 2, 3, 4, 5, 10, 15 or 20 hours at a temperature of 20-100, 25-80, 30-60 or 30-50 or 35-45° C. dPNAG may be prepared as described in WO 04/43405.

The polysaccharide(s) can be conjugated or unconjugated to a carrier protein.

B. Type 5 and Type 8 Polysaccharides from *S. aureus*

Most strains of *S. aureus* that cause infection in humans contain either Type 5 or Type 8 polysaccharides. Approximately 60% of human strains are Type 8 and approximately 30% are Type 5. The structures of Type 5 and Type 8 capsular polysaccharide antigens are described in Moreau et al. (1990) and Fournier et al. (1984). Both have FucNAcP in their repeat unit as well as ManNAcA which can be used to introduce a sulfhydryl group. The structures are:

Type 5
 $\rightarrow 4$)- β -D-ManNAcA(3OAc)-(1 $\rightarrow$ 4)- α -L-FucNAc
 (1 $\rightarrow$ 3)- β -D-FucNAc-(1 $\rightarrow$

Type 8
 $\rightarrow 3$)- β -D-ManNAcA(4OAc)-(1 $\rightarrow$ 3)- α -L-FucNAc
 (1 $\rightarrow$ 3)- β -D-FucNAc-(1 $\rightarrow$

Recently (Jones, 2005) NMR spectroscopy revised the structures to:

Type 5
 $\rightarrow 4$)- β -D-ManNAcA-(1 $\rightarrow$ 4)- α -L-FucNAc(3OAc)-
 (1 $\rightarrow$ 3)- β -D-FucNAc-(1 $\rightarrow$

Type 8
 $\rightarrow 3$)- β -D-ManNAcA(4OAc)-(1 $\rightarrow$ 3)- α -L-FucNAc
 (1 $\rightarrow$ 3)- α -D-FucNAc(1 $\rightarrow$

Polysaccharides may be extracted from the appropriate strain of *S. aureus* using methods well known to persons of skill in the art. See U.S. Pat. No. 6,294,177. For example, ATCC 12902 is a Type 5 *S. aureus* strain and ATCC 12605 is a Type 8 *S. aureus* strain.

Polysaccharides are of native size or alternatively may be sized, for instance by microfluidisation, ultrasonic irradiation, or by chemical treatment. The invention also covers oligosaccharides derived from the type 5 and 8 polysaccharides from *S. aureus*. The type 5 and 8 polysaccharides included in the immunogenic composition of the invention are preferably conjugated to a carrier protein as described below or are alternatively unconjugated. The immunogenic compositions of the invention alternatively contain either type 5 or type 8 polysaccharides.

C. *S. aureus* 336 Antigen

In an embodiment, the immunogenic composition of the invention comprises the *S. aureus* 336 antigen described in U.S. Pat. No. 6,294,177. The 336 antigen comprises β -linked hexosamine, contains no O-acetyl groups, and specifically binds to antibodies to *S. aureus* Type 336 deposited under ATCC 55804. In an embodiment, the 336 antigen is a polysaccharide which is of native size or alternatively may be sized, for instance by microfluidisation, ultrasonic irradiation, or by chemical treatment. The invention also covers oligosaccharides derived from the 336 antigen. The 336 antigen can be unconjugated or conjugated to a carrier protein.

D. Type I, II and III Polysaccharides from *S. epidermidis*

Amongst the problems associated with the use of polysaccharides in vaccination, is the fact that polysaccharides per se are poor immunogens. It is preferred that the polysaccharides utilized in the invention are linked to a protein carrier which provide bystander T-cell help to improve immunogenicity. Examples of such carriers which may be conjugated to polysaccharide immunogens include the Diphtheria and Tetanus toxoids (DT, DT CRM197 and TT respectively), Keyhole Limpet Haemocyanin (KLH), and the purified protein derivative of Tuberculin (PPD), *Pseudomonas aeruginosa* exoprotein A (rEPA), protein D from *Haemophilus influenzae*, pneumolysin or fragments of any of the above. Fragments suitable for use include fragments encompassing T-helper epitopes. In particular the protein D fragment from *H. influenzae* will preferably contain the N-terminal 1/3 of the protein. Protein D is an IgD-binding protein from *Haemophilus influenzae* (EP 0 594

610 B1) and is a potential immunogen. In addition, staphylococcal proteins may be used as carrier proteins in the polysaccharide conjugates of the invention.

A carrier protein that would be particularly advantageous to use in the context of a staphylococcal vaccine is staphylococcal alpha toxoid. The native form may be conjugated to a polysaccharide since the process of conjugation reduces toxicity. Preferably genetically detoxified alpha toxins such as the His35Leu or His35Arg variants are used as carriers since residual toxicity is lower. Alternatively the alpha toxin is chemically detoxified by treatment with a cross-linking reagent, formaldehyde or glutaraldehyde. A genetically detoxified alpha toxin is optionally chemically detoxified, preferably by treatment with a cross-linking reagent, formaldehyde or glutaraldehyde to further reduce toxicity.

The polysaccharides may be linked to the carrier protein(s) by any known method (for example those methods described in U.S. Pat. Nos. 4,372,945, 4,474,757, and 4,356,170). Preferably, CDAP conjugation chemistry is carried out (see WO95/08348). In CDAP, the cyanating reagent 1-cyano-dimethylaminopyridinium tetrafluoroborate (CDAP) is preferably used for the synthesis of polysaccharide-protein conjugates. The cyanilation reaction can be performed under relatively mild conditions, which avoids hydrolysis of the alkaline sensitive polysaccharides. This synthesis allows direct coupling to a carrier protein.

Conjugation preferably involves producing a direct linkage between the carrier protein and polysaccharide. Optionally a spacer (such as adipic dihydride (ADH)) may be introduced between the carrier protein and the polysaccharide.

IV. Immune Response and Assays

As discussed above, the invention concerns evoking or inducing an immune response in a subject against an EsaC polypeptide. In other embodiments an immune response to other secreted virulence factors or surface proteins can be evoked or induced, including EsxA, EsxB, or other polypeptides transported by the Ess pathway, and/or SdrC, SdrD, SdrE, IsdA, IsdB, Spa, ClfA, ClfB, SasF, IsdC or any other peptide or protein processed by sortase. In one embodiment, the immune response can protect against or treat a subject (e.g., limiting abscess persistence) having, suspected of having, or at risk of developing an infection or related disease, particularly those related to staphylococci. One use of the immunogenic compositions of the invention is to prevent nosocomial infections by inoculating a subject prior to hospital treatment.

A. Immunoassays

The present invention includes the implementation of serological assays to evaluate whether and to what extent an immune response is induced or evoked by EsaC, EsxA or EsxB, or any other polypeptide transported by the Ess pathway, and/or SdrD, SdrE, IsdA, IsdB, or any other sortase process peptide or protein. There are many types of immunoassays that can be implemented. Immunoassays encompassed by the present invention include, but are not limited to, those described in U.S. Pat. No. 4,367,110 (double monoclonal antibody sandwich assay) and U.S. Pat. No. 4,452,901 (western blot). Other assays include immunoprecipitation of labeled ligands and immunocytochemistry, both in vitro and in vivo.

Immunoassays generally are binding assays. Certain preferred immunoassays are the various types of enzyme linked immunosorbent assays (ELISAs) and radioimmunoassays (RIA) known in the art. Immunohistochemical detection using tissue sections is also particularly useful.

In one exemplary ELISA, the antibodies or antigens are immobilized on a selected surface, such as a well in a polystyrene microtiter plate, dipstick, or column support. Then, a test composition suspected of containing the desired antigen or antibody, such as a clinical sample, is added to the wells. After binding and washing to remove non specifically bound immune complexes, the bound antigen or antibody may be detected. Detection is generally achieved by the addition of another antibody, specific for the desired antigen or antibody, that is linked to a detectable label. This type of ELISA is known as a "sandwich ELISA". Detection also may be achieved by the addition of a second antibody specific for the desired antigen, followed by the addition of a third antibody that has binding affinity for the second antibody, with the third antibody being linked to a detectable label.

Variations on ELISA techniques are known to those of skill in the art. In one such variation, the samples suspected of containing a target antigen or antibody are immobilized onto the well surface and then contacted with the antibodies or antigens of the invention. After binding and appropriate washing, the bound immune complexes are detected. Where the initial antigen specific antibodies are linked to a detectable label, the immune complexes may be detected directly. Again, the immune complexes may be detected using a second antibody that has binding affinity for the first antigen specific antibody, with the second antibody being linked to a detectable label.

Competition ELISAs are also possible implementations in which test samples compete for binding with known amounts of labeled antigens or antibodies. The amount of reactive species in the unknown sample is determined by mixing the sample with the known labeled species before or during incubation with coated wells. The presence of reactive species in the sample acts to reduce the amount of labeled species available for binding to the well and thus reduces the ultimate signal.

Irrespective of the format employed, ELISAs have certain features in common, such as coating, incubating or binding, washing to remove non specifically bound species, and detecting the bound immune complexes.

Antigen or antibodies may also be linked to a solid support, such as in the form of plate, beads, dipstick, membrane, or column matrix, and the sample to be analyzed is applied to the immobilized antigen or antibody. In coating a plate with either antigen or antibody, one will generally incubate the wells of the plate with a solution of the antigen or antibody, either overnight or for a specified period. The wells of the plate will then be washed to remove incompletely-adsorbed material. Any remaining available surfaces of the wells are then "coated" with a nonspecific protein that is antigenically neutral with regard to the test antisera. These include bovine serum albumin (BSA), casein, and solutions of milk powder. The coating allows for blocking of nonspecific adsorption sites on the immobilizing surface and thus reduces the background caused by nonspecific binding of antisera onto the surface.

In ELISAs, it is more customary to use a secondary or tertiary detection means rather than a direct procedure. Thus, after binding of the antigen or antibody to the well, coating with a non reactive material to reduce background, and washing to remove unbound material, the immobilizing surface is contacted with the clinical or biological sample to be tested under conditions effective to allow immune complex (antigen/antibody) formation. Detection of the immune complex then requires a labeled secondary binding ligand or antibody, or a secondary binding ligand or antibody in conjunction with a labeled tertiary antibody or third binding ligand.

"Under conditions effective to allow immune complex (antigen/antibody) formation" means that the conditions preferably include diluting the antigens and antibodies with solutions such as BSA, bovine gamma globulin (BGG) and phosphate buffered saline (PBS)/Tween. These added agents also tend to assist in the reduction of nonspecific background.

The suitable conditions also mean that the incubation is at a temperature and for a period of time sufficient to allow effective binding. Incubation steps are typically from about 1 to 2 to 4 hours, at temperatures preferably on the order of 25° to 27° C., or may be overnight at about 4° C. or so.

After all incubation steps in an ELISA are followed, the contacted surface is washed so as to remove non complexed material. Washing often includes washing with a solution of PBS/Tween, or borate buffer. Following the formation of specific immune complexes between the test sample and the originally bound material, and subsequent washing, the occurrence of even minute amounts of immune complexes may be determined.

To provide a detecting means, the second or third antibody will have an associated label to allow detection. Preferably, this will be an enzyme that will generate color development upon incubating with an appropriate chromogenic substrate. Thus, for example, one will desire to contact and incubate the first or second immune complex with a urease, glucose oxidase, alkaline phosphatase, or hydrogen peroxidase conjugated antibody for a period of time and under conditions that favor the development of further immune complex formation, e.g., incubation for 2 hours at room temperature in a PBS containing solution such as PBS Tween.

After incubation with the labeled antibody, and subsequent to washing to remove unbound material, the amount of label is quantified, e.g., by incubation with a chromogenic substrate such as urea and bromocresol purple or 2,2' azino-di(3-ethyl benzthiazoline-6-sulfonic acid [ABTS] and H₂O₂, in the case of peroxidase as the enzyme label. Quantification is then achieved by measuring the degree of color generation, e.g., using a visible spectra spectrophotometer. Alternatively, the label may be a chemiluminescent label (see, U.S. Pat. Nos. 5,310,687, 5,238,808 and 5,221,605).

B. Diagnosis of Bacterial Infection

In addition to the use of proteins, polypeptides, and/or peptides, as well as antibodies binding these polypeptides, proteins, and/or peptides to treat or prevent infection as described above, the present invention contemplates the use of these polypeptides, proteins, peptides, and/or antibodies in a variety of ways, including the detection of the presence of Staphylococci to diagnose an infection, whether in a patient or on medical equipment which may also become infected. In accordance with the invention, a preferred method of detecting the presence of infections involves the steps of obtaining a sample suspected of being infected by one or more staphylococcal bacteria species or strains, such as a sample taken from an individual, for example, from one's blood, saliva, tissues, bone, muscle, cartilage, or skin. Following isolation of the sample, diagnostic assays utilizing the polypeptides, proteins, peptides, and/or antibodies of the present invention may be carried out to detect the presence of staphylococci, and such assay techniques for determining such presence in a sample are well known to those skilled in the art and include methods such as radioimmunoassay, western blot analysis and ELISA assays. In general, in accordance with the invention, a method of diagnosing an infection is contemplated wherein a sample suspected of being infected with staphylococci has added to it the polypeptide, protein, peptide, antibody, or monoclonal antibody in accordance with the present invention, and staphylococci are indicated by antibody bind-

ing to the polypeptides, proteins, and/or peptides, or polypeptides, proteins, and/or peptides binding to the antibodies in the sample.

Accordingly, antibodies in accordance with the invention may be used for the prevention of infection from staphylococcal bacteria, for the treatment of an ongoing infection, or for use as research tools. The term "antibodies" as used herein includes monoclonal, polyclonal, chimeric, single chain, bispecific, simianized, and humanized or primatized antibodies as well as Fab fragments, such as those fragments which maintain the binding specificity of the antibodies, including the products of an Fab immunoglobulin expression library. Accordingly, the invention contemplates the use of single chains such as the variable heavy and light chains of the antibodies. Generation of any of these types of antibodies or antibody fragments is well known to those skilled in the art. Specific examples of the generation of an antibody to a bacterial protein can be found in U.S. Patent Application Pub. No. 20030153022, which is incorporated herein by reference in its entirety.

Any of the above described polypeptides, proteins, peptides, and/or antibodies may be labeled directly with a detectable label for identification and quantification of staphylococcal bacteria. Labels for use in immunoassays are generally known to those skilled in the art and include enzymes, radioisotopes, and fluorescent, luminescent and chromogenic substances, including colored particles such as colloidal gold or latex beads. Suitable immunoassays include enzyme-linked immunosorbent assays (ELISA).

C. Protective Immunity

In some embodiments of the invention, proteinaceous compositions confer protective immunity on a subject. Protective immunity refers to a body's ability to mount a specific immune response that protects the subject from developing a particular disease or condition that involves the agent against which there is an immune response. An immunogenically effective amount is capable of conferring protective immunity to the subject.

As used herein in the specification and in the claims section that follows, the term polypeptide refers to a stretch of amino acids covalently linked there amongst via peptide bonds. Different polypeptides have different functionalities according to the present invention. While according to one aspect, a polypeptide is derived from an immunogen designed to induce an active immune response in a recipient, according to another aspect of the invention, a polypeptide is derived from an antibody which results following the elicitation of an active immune response, in, for example, an animal, and which can serve to induce a passive immune response in the recipient. In both cases, however, the polypeptide is encoded by a polynucleotide according to any possible codon usage.

As used herein the phrase "immune response" or its equivalent "immunological response" refers to the development of a humoral (antibody mediated), cellular (mediated by antigen-specific T cells or their secretion products) or both humoral and cellular response directed against a protein, peptide, or polypeptide of the invention in a recipient patient. Such a response can be an active response induced by administration of immunogen or a passive response induced by administration of antibody, antibody containing material, or primed T-cells. A cellular immune response is elicited by the presentation of polypeptide epitopes in association with Class I or Class II MHC molecules, to activate antigen-specific CD4 (+) T helper cells and/or CD8 (+) cytotoxic T cells. The response may also involve activation of monocytes, macroph-

ages, NK cells, basophils, dendritic cells, astrocytes, microglia cells, eosinophils or other components of innate immunity.

As used herein "active immunity" refers to any immunity conferred upon a subject by administration of an antigen.

As used herein "passive immunity" refers to any immunity conferred upon a subject without administration of an antigen to the subject. "Passive immunity" therefore includes, but is not limited to, administration of activated immune effectors including cellular mediators or protein mediators (e.g., monoclonal and/or polyclonal antibodies) of an immune response. A monoclonal or polyclonal antibody composition may be used in passive immunization for the prevention or treatment of infection by organisms that carry the antigen recognized by the antibody. An antibody composition may include antibodies that bind to a variety of antigens that may in turn be associated with various organisms. The antibody component can be a polyclonal antiserum. In certain aspects the antibody or antibodies are affinity purified from an animal or second subject that has been challenged with an antigen(s). Alternatively, an antibody mixture may be used, which is a mixture of monoclonal and/or polyclonal antibodies to antigens present in the same, related, or different microbes or organisms, such as gram-positive bacteria, gram-negative bacteria, including but not limited to *staphylococcus* bacteria.

Passive immunity may be imparted to a patient or subject by administering to the patient immunoglobulins (Ig) and/or other immune factors obtained from a donor or other non-patient source having a known immunoreactivity. In other aspects, an antigenic composition of the present invention can be administered to a subject who then acts as a source or donor for globulin, produced in response to challenge from the composition ("hyperimmune globulin"), that contains antibodies directed against *Staphylococcus* or other organism. A subject thus treated would donate plasma from which hyperimmune globulin would then be obtained, via conventional plasma-fractionation methodology, and administered to another subject in order to impart resistance against or to treat *staphylococcus* infection. Hyperimmune globulins according to the invention are particularly useful for immunocompromised individuals, for individuals undergoing invasive procedures or where time does not permit the individual to produce their own antibodies in response to vaccination. See U.S. Pat. Nos. 6,936,258, 6,770,278, 6,756,361, 5,548,066, 5,512,282, 4,338,298, and 4,748,018, each of which is incorporated herein by reference in its entirety, for exemplary methods and compositions related to passive immunity.

For purposes of this specification and the accompanying claims the terms "epitope" and "antigenic determinant" are used interchangeably to refer to a site on an antigen to which B and/or T cells respond or recognize B-cell epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation. Methods of determining spatial conformation of epitopes include, for example, x-ray crystallography and 2-dimensional nuclear magnetic resonance. See, e.g., Epitope Mapping Protocols (1996). Antibodies that recognize the same epitope can be identified in a simple immunoassay showing the ability of one antibody to block the binding of another antibody to a target antigen. T-cells recognize continuous epitopes of about nine amino acids for CD8 cells or about 13-15 amino acids for CD4 cells. T cells that recog-

nize the epitope can be identified by in vitro assays that measure antigen-dependent proliferation, as determined by ³H-thymidine incorporation by primed T cells in response to an epitope (Burke et al., 1994), by antigen-dependent killing (cytotoxic T lymphocyte assay, Tigges et al., 1996) or by cytokine secretion.

The presence of a cell-mediated immunological response can be determined by proliferation assays (CD4 (+) T cells) or CTL (cytotoxic T lymphocyte) assays. The relative contributions of humoral and cellular responses to the protective or therapeutic effect of an immunogen can be distinguished by separately isolating IgG and T-cells from an immunized syngeneic animal and measuring protective or therapeutic effect in a second subject.

As used herein and in the claims, the terms "antibody" or "immunoglobulin" are used interchangeably and refer to any of several classes of structurally related proteins that function as part of the immune response of an animal or recipient, which proteins include IgG, IgD, IgE, IgA, IgM and related proteins.

Under normal physiological conditions antibodies are found in plasma and other body fluids and in the membrane of certain cells and are produced by lymphocytes of the type denoted B cells or their functional equivalent. Antibodies of the IgG class are made up of four polypeptide chains linked together by disulfide bonds. The four chains of intact IgG molecules are two identical heavy chains referred to as H-chains and two identical light chains referred to as L-chains.

In order to produce polyclonal antibodies, a host, such as a rabbit or goat, is immunized with the antigen or antigen fragment, generally with an adjuvant and, if necessary, coupled to a carrier. Antibodies to the antigen are subsequently collected from the sera of the host. The polyclonal antibody can be affinity purified against the antigen rendering it monospecific.

In order to produce monoclonal antibodies, hyperimmunization of an appropriate donor, generally a mouse, with the antigen is undertaken. Isolation of splenic antibody producing cells is then carried out. These cells are fused to a cell characterized by immortality, such as a myeloma cell, to provide a fused cell hybrid (hybridoma) which can be maintained in culture and which secretes the required monoclonal antibody. The cells are then be cultured, in bulk, and the monoclonal antibodies harvested from the culture media for use. By definition, monoclonal antibodies are specific to a single epitope. Monoclonal antibodies often have lower affinity constants than polyclonal antibodies raised against similar antigens for this reason.

Monoclonal antibodies may also be produced ex-vivo by use of primary cultures of splenic cells or cell lines derived from spleen (Anavi, 1998). In order to produce recombinant antibody (see generally Huston et al., 1991; Johnson et al., 1991; Mernaugh et al., 1995), messenger RNAs from antibody producing B-lymphocytes of animals, or hybridoma are reverse-transcribed to obtain complementary DNAs (cDNAs). Antibody cDNA, which can be full length or partial length, is amplified and cloned into a phage or a plasmid. The cDNA can be a partial length of heavy and light chain cDNA, separated or connected by a linker. The antibody, or antibody fragment, is expressed using a suitable expression system to obtain recombinant antibody. Antibody cDNA can also be obtained by screening pertinent expression libraries.

The antibody can be bound to a solid support substrate or conjugated with a detectable moiety or be both bound and conjugated as is well known in the art. For a general discussion of conjugation of fluorescent or enzymatic moieties see

Johnstone et al. (1982). The binding of antibodies to a solid support substrate is also well known in the art (Harlow et al., 1988; Borrebaeck, 1992).

As used herein and in the claims, the phrase "an immunological portion of an antibody" include a Fab fragment of an antibody, a Fv fragment of an antibody, a heavy chain of an antibody, a light chain of an antibody, an unassociated mixture of a heavy chain and a light chain of an antibody, a heterodimer consisting of a heavy chain and a light chain of an antibody, a catalytic domain of a heavy chain of an antibody, a catalytic domain of a light chain of an antibody, a variable fragment of a light chain of an antibody, a variable fragment of a heavy chain of an antibody, and a single chain variant of an antibody, which is also known as scFv. In addition, the term includes chimeric immunoglobulins which are the expression products of fused genes derived from different species, one of the species can be a human, in which case a chimeric immunoglobulin is said to be humanized. Typically, an immunological portion of an antibody competes with the intact antibody from which it was derived for specific binding to an antigen.

Optionally, an antibody or preferably an immunological portion of an antibody, can be chemically conjugated to, or expressed as, a fusion protein with other proteins. For purposes of this specification and the accompanying claims, all such fused proteins are included in the definition of antibodies or an immunological portion of an antibody.

As used herein the terms "immunogenic agent" or "immunogen" or "antigen" are used interchangeably to describe a molecule capable of inducing an immunological response against itself on administration to a recipient, either alone, in conjunction with an adjuvant, or presented on a display vehicle.

D. Treatment Methods

A method of the present invention includes treatment for a disease or condition caused by a *staphylococcus* pathogen. An immunogenic polypeptide of the invention can be given to induce an immune response in a person infected with *staphylococcus* or suspected of having been exposed to *staphylococcus*. Methods may be employed with respect to individuals who have tested positive for exposure to *staphylococcus* or who are deemed to be at risk for infection based on possible exposure.

In particular, the invention encompasses method of treatment of staphylococcal infection, particularly hospital acquired nosocomial infections. The immunogenic compositions and vaccines of the invention are particularly advantageous to use in cases of elective surgery. Such patients will know the date of surgery in advance and could be inoculated in advance. The immunogenic compositions and vaccines of the invention are also advantageous to use to inoculate health care workers.

In some embodiments, the treatment is administered in the presence of adjuvants or carriers or other staphylococcal antigens. Furthermore, in some examples, treatment comprises administration of other agents commonly used against bacterial infection, such as one or more antibiotics.

The use of peptides for vaccination typically requires conjugation of the peptide to an immunogenic carrier protein, such as hepatitis B surface antigen, keyhole limpet hemocyanin, or bovine serum albumin. Methods for performing this conjugation are well known in the art.

V. Vaccine and Other Pharmaceutical Compositions and Administration

A. Vaccines

The present invention includes methods for preventing or ameliorating *staphylococcus* infections, particularly hospital acquired nosocomial infections. As such, the invention contemplates vaccines for use in both active and passive immunization embodiments. Immunogenic compositions, proposed to be suitable for use as a vaccine, may be prepared most readily directly from immunogenic EsaC polypeptide(s), such as the full-length EsaC antigen or immunogenic fragments thereof. In other embodiments EsaC can be used in combination with other secreted virulence proteins, surface proteins or immunogenic fragments thereof, including EsxA, EsxB, or any other polypeptide transported by the Ess pathway, and/or SdrC, SdrD, SdrE, IsdA, IsdB, IsdC, Spa, ClfA, ClfB, SasF or any other sortase processed peptide or protein prepared in a manner disclosed herein. Preferably the antigenic material is extensively dialyzed to remove undesired small molecular weight molecules and/or lyophilized for more ready formulation into a desired vehicle.

Other viable and important options for a protein/peptide-based vaccine involve introducing nucleic acids encoding the antigen(s) as DNA vaccines. In this regard, recent reports described construction of recombinant vaccinia viruses expressing either 10 contiguous minimal CTL epitopes (Thomson, 1996) or a combination of B cell, cytotoxic T-lymphocyte (CTL), and T-helper (Th) epitopes from several microbes (An, 1997), and successful use of such constructs to immunize mice for priming protective immune responses. Thus, there is ample evidence in the literature for successful utilization of peptides, peptide-pulsed antigen presenting cells (APCs), and peptide-encoding constructs for efficient in vivo priming of protective immune responses. The use of nucleic acid sequences as vaccines is exemplified in U.S. Pat. Nos. 5,958,895 and 5,620,896.

The preparation of vaccines that contain polypeptide or peptide sequence(s) as active ingredients is generally well understood in the art, as exemplified by U.S. Pat. Nos. 4,608,251; 4,601,903; 4,599,231; 4,599,230; 4,596,792; and 4,578,770, all of which are incorporated herein by reference. Typically, such vaccines are prepared as injectables either as liquid solutions or suspensions: solid forms suitable for solution in or suspension in liquid prior to injection may also be prepared. The preparation may also be emulsified. The active immunogenic ingredient is often mixed with excipients that are pharmaceutically acceptable and compatible with the active ingredient. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol, or the like and combinations thereof. In addition, if desired, the vaccine may contain amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, or adjuvants that enhance the effectiveness of the vaccines. In specific embodiments, vaccines are formulated with a combination of substances, as described in U.S. Pat. Nos. 6,793,923 and 6,733,754, which are incorporated herein by reference.

Vaccines may be conventionally administered parenterally, by injection, for example, either subcutaneously or intramuscularly. Additional formulations which are suitable for other modes of administration include suppositories and, in some cases, oral formulations. For suppositories, traditional binders and carriers may include, for example, polyalkylene glycols or triglycerides: such suppositories may be formed from mixtures containing the active ingredient in the range of about 0.5% to about 10%, preferably about 1% to about 2%. Oral formulations include such normally employed excipients as,

for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders and contain about 10% to about 95% of active ingredient, preferably about 25% to about 70%.

The polypeptides and polypeptide-encoding DNA constructs may be formulated into a vaccine as neutral or salt forms. Pharmaceutically-acceptable salts include the acid addition salts (formed with the free amino groups of the peptide) and those that are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups may also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

Typically, vaccines are administered in a manner compatible with the dosage formulation, and in such amount as will be therapeutically effective and immunogenic. The quantity to be administered depends on the subject to be treated, including the capacity of the individual's immune system to synthesize antibodies and the degree of protection desired. Precise amounts of active ingredient required to be administered depend on the judgment of the practitioner. However, suitable dosage ranges are of the order of several hundred micrograms active ingredient per vaccination. Suitable regimes for initial administration and booster shots are also variable, but are typified by an initial administration followed by subsequent inoculations or other administrations.

The manner of application may be varied widely. Any of the conventional methods for administration of a vaccine are applicable. These are believed to include oral application on a solid physiologically acceptable base or in a physiologically acceptable dispersion, parenterally, by injection and the like. The dosage of the vaccine will depend on the route of administration and will vary according to the size and health of the subject.

In certain instances, it will be desirable to have multiple administrations of the vaccine, e.g., 2, 3, 4, 5, 6 or more administrations. The vaccinations can be at 1, 2, 3, 4, 5, 6, 7, 8, to 5, 6, 7, 8, 9, 10, 11, 12 twelve week intervals, including all ranges there between. Periodic boosters at intervals of 1-5 years will be desirable to maintain protective levels of the antibodies. The course of the immunization may be followed by assays for antibodies against the antigens, as described in U.S. Pat. Nos. 3,791,932; 4,174,384 and 3,949,064.

1. Carriers

A given composition may vary in its immunogenicity. It is often necessary therefore to boost the host immune system, as may be achieved by coupling a peptide or polypeptide to a carrier. Exemplary and preferred carriers are keyhole limpet hemocyanin (KLH) and bovine serum albumin (BSA). Other albumins such as ovalbumin, mouse serum albumin, or rabbit serum albumin can also be used as carriers. Means for conjugating a polypeptide to a carrier protein are well known in the art and include glutaraldehyde, m-maleimidobencoyl-N-hydroxysuccinimide ester, carbodiimide, and bis-biazotized benzidine.

2. Adjuvants

The immunogenicity of polypeptide or peptide compositions can be enhanced by the use of non-specific stimulators of the immune response, known as adjuvants. Suitable adjuvants include all acceptable immunostimulatory compounds, such as cytokines, toxins, or synthetic compositions.

A number of adjuvants can be used to enhance an antibody response against an EsaC polypeptide. In other embodiments EsaC can be used in combination with EsxA, EsxB, or any other polypeptide transported by the Ess pathway and/or against a SdrD, SdrE, IsdA, IsdB, or any other sortase processed peptide or protein. Adjuvants can (1) trap the antigen in the body to cause a slow release; (2) attract cells involved in the immune response to the site of administration; (3) induce proliferation or activation of immune system cells; or (4) improve the spread of the antigen throughout the subject's body.

Adjuvants include, but are not limited to, oil-in-water emulsions, water-in-oil emulsions, mineral salts, polynucleotides, and natural substances. Specific adjuvants that may be used include IL-1, IL-2, IL-4, IL-7, IL-12, γ -interferon, GMCSF, BCG, aluminum salts, such as aluminum hydroxide or other aluminum compound, MDP compounds, such as thur-MDP and nor-MDP, CGP (MTP-PE), lipid A, and monophosphoryl lipid A (MPL). RIBI, which contains three components extracted from bacteria, MPL, trehalose dimycolate (TDM), and cell wall skeleton (CWS) in a 2% squalene/Tween 80 emulsion. MHC antigens may even be used. Others adjuvants or methods are exemplified in U.S. Pat. Nos. 6,814, 971, 5,084,269, 6,656,462, each of which is incorporated herein by reference).

Various methods of achieving adjuvant affect for the vaccine includes use of agents such as aluminum hydroxide or phosphate (alum), commonly used as about 0.05 to about 0.1% solution in phosphate buffered saline, admixture with synthetic polymers of sugars (Carbopol®) used as an about 0.25% solution, aggregation of the protein in the vaccine by heat treatment with temperatures ranging between about 70° to about 101° C. for a 30-second to 2-minute period, respectively. Aggregation by reactivating with pepsin-treated (Fab) antibodies to albumin; mixture with bacterial cells (e.g., *C. parvum*), endotoxins or lipopolysaccharide components of Gram-negative bacteria; emulsion in physiologically acceptable oil vehicles (e.g., mannide mono-oleate (Aracel A)); or emulsion with a 20% solution of a perfluorocarbon (Fluosol-DA®) used as a block substitute may also be employed to produce an adjuvant effect.

Examples of and often preferred adjuvants include complete Freund's adjuvant (a non-specific stimulator of the immune response containing killed *Mycobacterium tuberculosis*), incomplete Freund's adjuvants, and aluminum hydroxide.

In some aspects, it is preferred that the adjuvant be selected to be a preferential inducer of either a TH1 or a TH2 type of response. High levels of Th1-type cytokines tend to favor the induction of cell mediated immune responses to a given antigen, while high levels of Th2-type cytokines tend to favor the induction of humoral immune responses to the antigen.

It is important to remember that the distinction of Th1 and Th2-type immune response is not absolute. In reality an individual will support an immune response which is described as being predominantly Th1 or predominantly Th2. However, it is often convenient to consider the families of cytokines in terms of that described in murine CD4+ve T cell clones by Mosmann and Coffman (Mosmann and Coffman, 1989). Traditionally, Th1-type responses are associated with the production of the INF- γ and IL-2 cytokines by T-lymphocytes. Other cytokines often directly associated with the induction of Th1-type immune responses are not produced by T-cells, such as IL-12. In contrast, Th2-type responses are associated with the secretion of IL-4, IL-5, IL-6, IL-10.

In addition to adjuvants, it may be desirable to co-administer biologic response modifiers (BRM) to enhance immune

responses. BRMs have been shown to upregulate T cell immunity or downregulate suppressor cell activity. Such BRMs include, but are not limited to, Cimetidine (CIM; 1200 mg/d) (Smith/Kline, Pa.); or low-dose Cyclophosphamide (CYP; 300 mg/m²) (Johnson/Mead, N.J.) and cytokines such as γ -interferon, IL-2, or IL-12 or genes encoding proteins involved in immune helper functions, such as B-7.

B. Lipid Components and Moieties

In certain embodiments, the present invention concerns compositions comprising one or more lipids associated with a nucleic acid or a polypeptide/peptide. A lipid is a substance that is insoluble in water and extractable with an organic solvent. Compounds other than those specifically described herein are understood by one of skill in the art as lipids, and are encompassed by the compositions and methods of the present invention. A lipid component and a non-lipid may be attached to one another, either covalently or non-covalently.

A lipid may be a naturally occurring lipid or a synthetic lipid. However, a lipid is usually a biological substance. Biological lipids are well known in the art, and include for example, neutral fats, phospholipids, phosphoglycerides, steroids, terpenes, lysolipids, glycosphingolipids, glucolipids, sulphatides, lipids with ether and ester-linked fatty acids and polymerizable lipids, and combinations thereof.

A nucleic acid molecule or a polypeptide/peptide, associated with a lipid may be dispersed in a solution containing a lipid, dissolved with a lipid, emulsified with a lipid, mixed with a lipid, combined with a lipid, covalently bonded to a lipid, contained as a suspension in a lipid or otherwise associated with a lipid. A lipid or lipid-poxvirus-associated composition of the present invention is not limited to any particular structure. For example, they may also simply be interspersed in a solution, possibly forming aggregates which are not uniform in either size or shape. In another example, they may be present in a bilayer structure, as micelles, or with a "collapsed" structure. In another non-limiting example, a lipofectamine (Gibco BRL)-poxvirus or Superfect (Qiagen)-poxvirus complex is also contemplated.

In certain embodiments, a composition may comprise about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or any range therebetween, of a particular lipid, lipid type, or non-lipid component such as an adjuvant, antigen, peptide, polypeptide, sugar, nucleic acid or other material disclosed herein or as would be known to one of skill in the art. In a non-limiting example, a composition may comprise about 10% to about 20% neutral lipids, and about 33% to about 34% of a cerebroside, and about 1% cholesterol. In another non-limiting example, a liposome may comprise about 4% to about 12% terpenes,

wherein about 1% of the micelle is specifically lycopene, leaving about 3% to about 11% of the liposome as comprising other terpenes; and about 10% to about 35% phosphatidyl choline, and about 1% of a non-lipid component. Thus, it is contemplated that compositions of the present invention may comprise any of the lipids, lipid types or other components in any combination or percentage range.

C. Combination Therapy

The compositions and related methods of the present invention, particularly administration of a secreted virulence factor or surface protein, including a polypeptide or peptide of a EsxA, EsxB, or other polypeptide transported by the Ess pathway, and/or a polypeptide or peptide of a SdrC, SdrD, SdrE, IsdA, IsdB, IsdC, Spa, ClfA, ClfB, SasF or any other sortase processed peptide or protein to a patient/subject, may also be used in combination with the administration of traditional therapies. These include, but are not limited to, the administration of antibiotics such as streptomycin, ciprofloxacin, doxycycline, gentamycin, chloramphenicol, trimethoprim, sulfamethoxazole, ampicillin, tetracycline or various combinations of antibiotics.

In one aspect, it is contemplated that a polypeptide vaccine and/or therapy is used in conjunction with antibacterial treatment. Alternatively, the therapy may precede or follow the other agent treatment by intervals ranging from minutes to weeks. In embodiments where the other agents and/or a proteins or polynucleotides are administered separately, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the agent and antigenic composition would still be able to exert an advantageously combined effect on the subject. In such instances, it is contemplated that one may administer both modalities within about 12-24 h of each other and, more preferably, within about 6-12 h of each other. In some situations, it may be desirable to extend the time period for administration significantly, however, where several days (2, 3, 4, 5, 6 or 7) to several weeks (1, 2, 3, 4, 5, 6, 7 or 8) lapse between the respective administrations.

Various combinations may be employed, for example antibiotic therapy is "A" and the immunogenic molecule given as part of an immune therapy regime, such as an antigen, is "B":

A/B/A B/A/B B/B/A A/A/B A/B/B B/A/A A/B/B/B
B/A/B/B

B/B/B/A B/B/A/B A/A/B/B A/B/A/B A/B/B/A B/B/A/A

B/A/B/A B/A/A/B A/A/A/B B/A/A/A A/B/A/A A/A/B/A

Administration of the immunogenic compositions of the present invention to a patient/subject will follow general protocols for the administration of such compounds, taking into account the toxicity, if any, of the EsxA composition, EsxB composition, or composition of any other polypeptide transported by the Ess pathway and/or a SdrD-composition, SdrE-composition, IsdA-composition, IsdB-composition, or any other sortase processed peptide or protein. It is expected that the treatment cycles would be repeated as necessary. It also is contemplated that various standard therapies, such as hydration, may be applied in combination with the described therapy.

D. General Pharmaceutical Compositions

In some embodiments, pharmaceutical compositions are administered to a subject. Different aspects of the present invention involve administering an effective amount of a composition to a subject. In some embodiments of the present invention, members of the Ess pathway and including

polypeptides or peptides of the Esa or Esx class, and/or members of sortase substrates may be administered to the patient to protect against infection by one or more *staphylococcus* pathogens. Alternatively, an expression vector encoding one or more such polypeptides or peptides may be given to a patient as a preventative treatment. Additionally, such compounds can be administered in combination with an antibiotic. Such compositions will generally be dissolved or dispersed in a pharmaceutically acceptable carrier or aqueous medium.

The phrases "pharmaceutically acceptable" or "pharmacologically acceptable" refer to molecular entities and compositions that do not produce an adverse, allergic, or other untoward reaction when administered to an animal, or human. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredients, its use in immunogenic and therapeutic compositions is contemplated. Supplementary active ingredients, such as other anti-cancer agents, can also be incorporated into the compositions.

In addition to the compounds formulated for parenteral administration, such as those for intravenous or intramuscular injection, other pharmaceutically acceptable forms include, e.g., tablets or other solids for oral administration; time release capsules; and any other form currently used, including creams, lotions, mouthwashes, inhalants and the like.

The active compounds of the present invention can be formulated for parenteral administration, e.g., formulated for injection via the intravenous, intramuscular, sub-cutaneous, or even intraperitoneal routes. The preparation of an aqueous composition that contains a compound or compounds that increase the expression of an MHC class 1 molecule will be known to those of skill in the art in light of the present disclosure. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for use to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and, the preparations can also be emulsified.

Solutions of the active compounds as free base or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil, or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that it may be easily injected. It also should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

The proteinaceous compositions may be formulated into a neutral or salt form. Pharmaceutically acceptable salts, include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example,

sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

The carrier also can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion, and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques, which yield a powder of the active ingredient, plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Administration of the compositions according to the present invention will typically be via any common route. This includes, but is not limited to oral, nasal, or buccal administration. Alternatively, administration may be by orthotopic, intradermal, subcutaneous, intramuscular, intraperitoneal, intranasal, or intravenous injection. In certain embodiments, a vaccine composition may be inhaled (e.g., U.S. Pat. No. 6,651,655, which is specifically incorporated by reference). Such compositions would normally be administered as pharmaceutically acceptable compositions that include physiologically acceptable carriers, buffers or other excipients. As used herein, the term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem complications commensurate with a reasonable benefit/risk ratio. The term "pharmaceutically acceptable carrier," means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a chemical agent.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous, and intraperitoneal administration. In this connection, sterile aqueous media which can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage could be dissolved in isotonic NaCl solution and either added to hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, Remington's Pharmaceutical Sciences, 1990). Some variation in dos-

age will necessarily occur depending on the condition of the subject. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

An effective amount of therapeutic or prophylactic composition is determined based on the intended goal. The term "unit dose" or "dosage" refers to physically discrete units suitable for use in a subject, each unit containing a predetermined quantity of the composition calculated to produce the desired responses discussed above in association with its administration, i.e., the appropriate route and regimen. The quantity to be administered, both according to number of treatments and unit dose, depends on the protection desired.

Precise amounts of the composition also depend on the judgment of the practitioner and are peculiar to each individual. Factors affecting dose include physical and clinical state of the subject, route of administration, intended goal of treatment (alleviation of symptoms versus cure), and potency, stability, and toxicity of the particular composition.

Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically or prophylactically effective. The formulations are easily administered in a variety of dosage forms, such as the type of injectable solutions described above.

E. In Vitro, Ex Vivo, or In Vivo Administration

As used herein, the term in vitro administration refers to manipulations performed on cells removed from or outside of an animal, including, but not limited to cells in culture. The term ex vivo administration refers to cells which have been manipulated in vitro, and are subsequently administered to a living animal. The term in vivo administration includes all manipulations performed within an animal.

In certain aspects of the present invention, the compositions may be administered either in vitro, ex vivo, or in vivo. In certain in vitro embodiments, autologous B-lymphocyte cell lines are incubated with a virus vector of the instant invention for 24 to 48 hours or with EsaC, EsxA, EsxB, and/or any other secreted virulence factor or polypeptide transported by the Ess pathway (or any combination thereof) and/or any cell surface proteins, such as SdrC, SdrD, SdrE, IsdA, IsdB, Spa, ClfA, ClfB, IsdC and/or SasF proteins for two hours. The transduced cells can then be used for in vitro analysis, or alternatively for ex vivo administration.

U.S. Pat. Nos. 4,690,915 and 5,199,942, both incorporated herein by reference, disclose methods for ex vivo manipulation of blood mononuclear cells and bone marrow cells for use in therapeutic applications.

F. Antibodies And Passive Immunization

Another aspect of the invention is a method of preparing an immune globulin for use in prevention or treatment of staphylococcal infection comprising the steps of immunizing a recipient with the vaccine of the invention and isolating immune globulin from the recipient. An immune globulin prepared by this method is a further aspect of the invention. A pharmaceutical composition comprising the immune globulin of the invention and a pharmaceutically acceptable carrier is a further aspect of the invention which could be used in the manufacture of a medicament for the treatment or prevention of staphylococcal disease. A method for treatment or prevention of staphylococcal infection comprising a step of administering to a patient an effective amount of the pharmaceutical preparation of the invention is a further aspect of the invention.

Inocula for polyclonal antibody production are typically prepared by dispersing the antigenic composition in a physiologically tolerable diluent such as saline or other adjuvants

suitable for human use to form an aqueous composition. An immunostimulatory amount of inoculum is administered to a mammal and the inoculated mammal is then maintained for a time sufficient for the antigenic composition to induce protective antibodies.

The antibodies can be isolated to the extent desired by well known techniques such as affinity chromatography (Harlow and Lane, *Antibodies: A Laboratory Manual* 1988).

Antibodies can include antiserum preparations from a variety of commonly used animals e.g. goats, primates, donkeys, swine, horses, guinea pigs, rats or man. The animals are bled and serum recovered.

An immune globulin produced in accordance with the present invention can include whole antibodies, antibody fragments or subfragments. Antibodies can be whole immunoglobulins of any class e.g. IgG, IgM, IgA, IgD or IgE, chimeric antibodies or hybrid antibodies with dual specificity to two or more antigens of the invention. They may also be fragments e.g. F(ab')₂, Fab', Fab, Fv and the like including hybrid fragments. An immune globulin also includes natural, synthetic or genetically engineered proteins that act like an antibody by binding to specific antigens to form a complex.

A vaccine of the present invention can be administered to a recipient who then acts as a source of immune globulin, produced in response to challenge from the specific vaccine. A subject thus treated would donate plasma from which hyperimmune globulin would be obtained via conventional plasma fractionation methodology. The hyperimmune globulin would be administered to another subject in order to impart resistance against or treat staphylococcal infection. Hyperimmune globulins of the invention are particularly useful for treatment or prevention of staphylococcal disease in infants, immune compromised individuals or where treatment is required and there is no time for the individual to produce antibodies in response to vaccination.

An additional aspect of the invention is a pharmaceutical composition comprising two or more monoclonal antibodies (or fragments thereof; preferably human or humanized) reactive against at least two constituents of the immunogenic composition of the invention, which could be used to treat or prevent infection by Gram positive bacteria, preferably staphylococci, more preferably *S. aureus* or *S. epidermidis*. Such pharmaceutical compositions comprise monoclonal antibodies that can be whole immunoglobulins of any class e.g. IgG, IgM, IgA, IgD or IgE, chimeric antibodies or hybrid antibodies with specificity to two or more antigens of the invention. They may also be fragments e.g. F(ab')₂, Fab', Fab, Fv and the like including hybrid fragments.

Methods of making monoclonal antibodies are well known in the art and can include the fusion of splenocytes with myeloma cells (Kohler and Milstein, 1975; Harlow and Lane, 1988). Alternatively, monoclonal Fv fragments can be obtained by screening a suitable phage display library (Vaughan et al., 1998). Monoclonal antibodies may be humanized or part humanized by known methods.

VI. EXAMPLES

The following examples are given for the purpose of illustrating various embodiments of the invention and are not meant to limit the present invention in any fashion. One skilled in the art will appreciate readily that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those objects, ends and advantages inherent herein. The present examples, along with the methods described herein are presently representative of preferred embodiments, are exemplary, and are not

intended as limitations on the scope of the invention. Changes therein and other uses which are encompassed within the spirit of the invention as defined by the scope of the claims will occur to those skilled in the art.

Example 1

EsaC and its Role in *Staphylococcus* Infection

Sequence analysis of EsaB and EsaC. esaB encodes an 80 amino acid protein that is conserved in the genome of many Gram-positive bacteria. Further, esaB-like genes are always found closely associated on the chromosome of Gram-positive bacteria with esxA- and essC-like genes (FIG. 1). The crystal structure of *B. subtilis* YukD (EsaB homologue) was recently solved and shown to adopt a fold that is closely related to ubiquitin. YukD lacks the C-terminal peptide that is crucial for the activity of ubiquitin, suggesting that YukD is unlikely to modify other polypeptides by covalent linkage (van den Ent and Lowe, 2005). EsaB is a predicted soluble protein without a canonical signal peptide. esaC encodes a predicted soluble 130 amino acid protein that is conserved in the genomes of staphylococci, but absent from the genomes of other bacteria. In all staphylococcal genomes sequenced thus far, esaC is located between essC and esxB on the staphylococcal chromosome, with the exception of USA200, a strain that harbors an inversion of esaC and esxB. An unrelated gene, also of unknown function, occupies the position analogous to that of EsaC in the genomes of other Gram-positive bacteria (FIG. 1). Although these genes share no homology with staphylococcal EsaC, they are of similar size and their individual products also lack amino acid sequence homology. Together these data indicate that a species specific gene occupies the position between essC- and esxB-homologues of Gram-positive Ess clusters, while esaB is conserved amongst these species (FIG. 1).

EsaC protein production is tightly controlled. Using EsaC specific rabbit antiserum for immunoblotting experiments, the inventors failed to detect EsaC in total extracts of *S. aureus* strain Newman. The inventors wondered whether EsaC may be produced in mutants of the Ess cluster and found that only the esaB mutant produced EsaC, whereas mutations in all other genes had no effect (FIG. 2A). The esaB phenotype was complemented by providing wild type esaB on a plasmid (FIG. 2B). EsaB was produced constitutively (FIG. 2A). The inventors examined whether the expression of esaC was negatively controlled in strain Newman. A quantitative RT-PCR analysis was used to compare esaC transcript levels in wild type Newman as well as an isogenic variant with transposon insertion in the esaB gene. This analysis revealed that esaC transcripts are increased 3-fold in an esaB mutant as compared to wild type *S. aureus* Newman (FIG. 2C). As a control, transcripts were analyzed from a strain lacking the complete open reading frame encoding EsaC. Neither the transposon insertion in esaB nor the deletion of esaC had polar effects on the expression of downstream genes essB and esxB, as verified by RT-PCR and immunoblot analyses (data not shown). Pulse labeling of staphylococci with [³⁵S]-methionine was used to identify newly synthesized EsaC species via immunoprecipitation and autoradiography of proteins separated on SDS-PAGE. While esaC transcripts are observed both in wild type and isogenic esaB Newman strains, the EsaC polypeptide was only detected in a strain lacking esaB, but not in the wild type parent strain Newman (FIG. 2D). This result suggests that esaC regulation occurs by a post-transcriptional mechanism and can be relieved by mutations in esaB. When the minimal coding sequence of esaC was expressed under

the control of the constitutive hprK gene promoter (pOS-esaC), a protein product could readily be detected by immunoblot with anti-EsaC antibodies (FIG. 3; TSB grown bacteria), implying that untranslated esaC sequences are required for EsaB-mediated regulation. An attempt to establish whether EsaB may interact with coding or untranslated esaC DNA and RNA sequences was unsuccessful. Further, purified EsaB was not found to interact with purified EsaC or stimulate EsaC hydrolysis when mixed with soluble crude extracts of staphylococci. Hence the mechanism whereby EsaB controls esaC expression or production remains unclear.

Serum grown staphylococci produce EsaC. The inventors examined whether EsaB-mediated repression of EsaC might be relieved when staphylococci are grown under conditions that mimic infection. Production of EsaC in *S. aureus* Newman was compared when bacteria were grown in tryptic soy broth (TSB) or serum by immunoblot analysis of whole culture lysates (FIG. 3). *S. aureus* Newman indeed produced EsaC when grown in human serum, suggesting that EsaB-mediated repression is reversible and may be modulated in response to host environmental factors. As noted above, when esaC was cloned on plasmid pOS1 and its expression driven by the hprK promoter (pOS-esaC), production of EsaC appeared to be constitutive (FIG. 3). Thus, production of EsaC is controlled by cis acting nucleic acid sequence elements, by EsaB and by host factors that must be present in human serum.

Clinical isolates grown in broth produce EsaC. The inventors examined whether EsaC production is also regulated in other staphylococcal strains and examined several isolates, including USA100, USA200, USA300, USA700, MW2, Mu50, and N315, all of which were grown to mid-log phase in TSB. Whole culture lysates (WC) were generated by lyso-staphin digestion, normalized for total protein concentration, and examined by immunoblot using EsaC or ribosomal protein L6 specific antiserum. EsaC was readily detected in extracts of some staphylococcal strains, in particular strains USA300 and USA700 as shown in FIG. 4A (WC; left panel). Interestingly, DeLeo and colleagues reported that strain USA300 expressed greater amounts of various toxins and in particular exoproteins such as α -toxin, a phenomenon that could in part account for the increased virulence of the strain (Burlak et al., 2007). Unlike *S. aureus* Newman, USA300 strain LAC produced EsaC under normal growth conditions in TSB. The inventors therefore sought to determine whether EsaC production was regulated by EsaB in *S. aureus* USA300. The genome sequences for *S. aureus* Newman and USA300 have been determined, and are closely related in overall sequence and structure (Baba et al., 2008; Diep et al., 2006b). Hence, (p85 was used to transduce the esaB::erm allele into strain USA300. USA300 carrying the esaB::erm allele and its isogenic parent were grown to mid-log phase in TSB. Whole bacterial culture extracts were generated with lysostaphin digestion, and examined by immunoblot with EsaC or L6 specific antisera. EsaC was detected with increased abundance in the esaB variant of *S. aureus* USA300 (FIG. 4A). Thus, even though the more virulent *S. aureus* USA300 can produce EsaC when grown in TSB, disruption of esaB causes a similar increase in EsaC production as observed for *S. aureus* Newman.

EsaC is a secreted factor. Cultures of wild type *S. aureus* strains USA300 and USA700 were grown to mid-log phase and proteins in the medium were separated from staphylococci by removing intact cells by centrifugation. Proteins in the supernatants were concentrated ~125 fold and separated on SDS-PAGE. The samples were subjected to immunoblotting and probed with anti-EsaC or anti-L6 (for cell lysis

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control) antibodies. Data in FIG. 4A (right panel) indicate that EsaC is indeed secreted into the medium of *S. aureus* strains USA300 and USA700. Since EsaC does not carry a canonical signal sequence, the inventors examined whether it may represent a substrate of the Ess pathway. Plasmid pOS-
5 esaC which leads to constitutive EsaC production in *S. aureus* Newman was electroporated in an isogenic variant that cannot express *essC*. *EssC* is an essential component of the ESAT-6 secretion system. Disruption of the *essC* gene indeed
10 abolished secretion of EsaC and the protein accumulated in the cytoplasm of staphylococci (FIG. 4B). In sum, EsaC appears to be a novel substrate for the non-canonical Ess secretion pathway.

To examine the subcellular localization and efficiency of secretion of EsaC, the inventors took advantage of strain Newman lacking *esaB* and strain USA300, both of which
15 produce EsaC from the chromosomal locus. Cultures of *S. aureus* were separated into cytoplasm, membrane, cell wall, and medium (FIG. 4C; fractions C, M, W, MD, respectively). A whole culture extract was added as control (FIG. 4C; WC).
20 Proteins in all fractions were revealed by immunoblotting with specific antibodies. Strain Newman did not produce EsaC. However, EsaC was found in the culture medium of strains Newman lacking *esaB* and USA300 but not in the cytoplasm, membrane or cell wall, a distribution previously
25 reported for *EsxA* and *EsxB* (Burts et al., 2005). EsaC could not be detected in strain USA300 lacking *esxB* (FIG. 4C). Upon extended exposure of the immunoblot, a weak immuno-reactive EsaC species could be detected in the total culture sample but not in the conditioned medium (not
30 shown), suggesting that *EsxB* is required for EsaC secretion (FIG. 4B). As a control, protein A (*Spa*) was detected in the cell wall fraction, whereas ribosomal protein L6 and membrane bound sortase A (*SrtA*) resided in the cytoplasm and the plasma membrane, as expected (FIG. 4C). Together, these
35 results demonstrate that EsaC is secreted across the bacterial envelope into the culture medium in a manner requiring an intact type VII secretion system.

EsaC is produced during infection. The inventors examined whether EsaC is produced during infection. Mice were
40 infected with *S. aureus* Newman. Blood was collected from infected and control (mock infected) animals on days 0 and 30. The presence of anti-EsaC IgG in serum samples was tested in an ELISA using purified EsaC as immobilized antigen. Data in FIG. 5A show that animals infected with *S.*
45 *aureus* Newman developed IgG type antibodies against EsaC, suggesting that the protein is synthesized by wild type Newman during infection and presented to the immune system. Further, human sera were collected from two patients that had been diagnosed with *S. aureus* infection and two healthy
50 individuals. An ELISA revealed elevated anti-EsaC IgG in sera of acutely infected patients as compared to healthy individuals (FIG. 5B).

To further evaluate the ubiquitous nature of this host response, it was asked whether EsaC antibodies were produced upon infection of mice with *S. aureus* USA100,
55 USA200, USA300, USA700, MW2, Mu50, or N315. Staphylococci were grown to mid-log phase and $\sim 10^6$ bacteria were used to infect groups of five three-week old mice. Blood was collected via retro-orbital bleeds on days 0 and 30. The presence of α -EsaC IgG was examined in an ELISA using purified
60 EsaC as antigen (FIG. 5C; only data for day 30 are shown). Mice infected with *S. aureus* produced IgG antibodies against EsaC (FIG. 5C) but not against *SrtA*, the transmembrane protein responsible for protein sorting in the bacterial envelope (FIG. 5D). In sum, EsaC is encoded by all
65 staphylococcal strains examined thus far and appears to be

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produced during host infection. Further, infected hosts develop an antibody response toward EsaC but not *SrtA*, suggesting that the EsaC antigen must be presented to the host's immune system during infection and may be a secreted
5 antigen in agreement with the general hypothesis that EsaC may be secreted during infection.

EsaB and EsaC are required for persistent infection. An intact type VII secretion system is required for host pathogen
10 interaction both in staphylococci and pathogenic mycobacteria. The inventors examined whether the accessory factors EsaB and EsaC are also required for staphylococcal replication in infected hosts. To test this possibility, groups of
15 3-week old mice were challenged with 10^6 colony forming units (CFU) of wild type *S. aureus* Newman or isogenic variants lacking *esaB* or *esaC*. Animals (groups of 10-12) were killed five and thirty-six days after infection. Kidneys were removed post mortem. Tissue homogenate derived from the right kidney was spread on agar for colony formation and
20 enumeration of staphylococcal load (FIG. 6), whereas the left kidney was fixed in formalin, thin sectioned and stained with hematoxylin and eosin for histopathology (FIG. 7). As compared to animals inoculated with wild-type *S. aureus* Newman, bacterial load five days following infection was reduced
25 by 1.5 and 0.8 logs in abscesses of animals infected with *esaB* and *esaC* variants, respectively (FIG. 6). Histopathology of kidney tissue at the same time interval revealed that the total number of abscesses was reduced in organs from animals
30 infected with *esaB* (2.1 ± 1.7) or *esaC* (1.5 ± 1.0) variants as compared to the wild-type parent (4.9 ± 2.2) (FIG. 7). Thus, although both *esaB* and *esaC* mutants appear to display virulence defects, these variants retain the ability of forming
abscesses in infected host tissues.

Earlier work suggested that virulent *S. aureus* strains may persist in tissues of infected mice for a prolonged period of
35 time (Xu et al., 2004), similar to the clinicopathological features observed with human diseases caused by *S. aureus* (Musher et al., 1994). If so, chronic-persistent features of staphylococcal infections may resemble those observed for tuberculosis, where ESAT-6 secretion is a reported virulence
40 factor for acute infection (Pym et al., 2003; Stanley et al., 2003). To test whether the accessory genes of the staphylococcal Ess pathway contribute to pathogen persistence, animals were infected with wild-type *S. aureus* Newman; bacterial load as well as histopathology were examined 36 days
45 following inoculation (FIG. 6 and FIG. 7). The average number of abscesses indeed increased from 4.9 (± 2.2) on day five to 6.9 (± 2.4) on day thirty-six, and the size of abscesses increased over time, whereas bacterial load remained persistently high at $2-3 \times 10^6$ cfu. In contrast to wild-type staphylococci, the bacterial load for animals infected with the *esaB*
50 mutant dropped from 5×10^4 cfu on day five to 1.5×10^1 cfu on day thirty-six, while abscesses were either not detectable or were found to occur at reduced frequency and size. Similar to *esaB* variants, deletion of *esaC* also reduced the bacterial load from 2.5×10^5 cfu on day five to 1×10^3 cfu on day thirty-six,
55 with a concomitant reduction in abscess number to 1.8 (± 1.5) and in abscess size. Of note, *esaC* mutants formed more abscesses and persisted at a higher bacterial load than *esaB* mutants. This observation is in agreement with the conjecture that EsaB may regulate not only *esaC* but also additional
60 staphylococcal genes during infection.

Example 2

Experimental Procedures

Bacterial strains, plasmids and growth conditions. *S. aureus* cells were grown in tryptic soy broth at 37° C., respec-

tively. Chloramphenicol and erythromycin were used at 10 mg/L, for plasmid and allele selection, respectively, when necessary. *S. aureus* strains MW2, Mu50, N315, USA100, USA200, USA300, and USA700, were obtained through the Network on Antimicrobial Resistance in *S. aureus* (NARSA, NIAID). All mutants used in this study with the exception of *esaC* were obtained from the Phoenix (Φ NE) library (Bae et al., 2004). Each *Phoenix* isolate is a derivative of the clinical isolate Newman (Bae et al., 2004; Duthie and Lorenz, 1952). All *bursa aurealis* insertions were transduced into wild-type *S. aureus* Newman or USA300 using bacteriophage ϕ 85 and verified by PCR analysis using flanking primers. For deletion of *esaC*, a 2-kbp DNA fragment flanking the *esaC* gene but carrying only the first and last four codons of *esaC* gene was amplified by PCR, with abutted BamHI-EcoRI restriction sites. The DNA fragment was cloned into pKOR1 for allelic replacement performed as described earlier (Bae and Schneewind, 2006). A second *esaC* allele was constructed by cloning a 2-kbp DNA fragment containing *esaC* and 1-kbp nucleotide sequence upstream and downstream of *esaC* respectively, into plasmid pTS1. In this case, a stop codon was introduced at position four of the *esaC* coding sequence. pTS1 carries a mutation that renders its DNA replication in staphylococci sensitive to temperature shift at 43° C. Allelic replacement was performed as described earlier (Burts et al., 2005). Both *esaC* mutant alleles behaved identically and did not prevent production and secretion of *EsxB* encoded by the gene immediately downstream of *esaC*. All data shown in this study use the mutant carrying the entire deletion of the *esaC* gene.

The *E. coli-S. aureus* shuttle vector pOS1 that carries the *hprK* promoter and Shine Dalgarno sequence (275 bp upstream of the *hprK* *lgt yvoF yvcD* translational start site) and three cloning sites *NdeI*, *XhoI*, *BamHI*, as described earlier (Bubeck-Wardenburg et al., 2006) was used for complementation studies. All cloning procedures were carried out in *E. coli* and ampicillin was used at 100 mg/L for plasmid selection. The complementation plasmids pOS-*esaB* and pOS-*esaC* were generated by amplifying the minimal coding sequence of each gene using primer pairs *EsaB-XhoI-F* aactcgagatgaatcagcagctaaaagt (SEQ ID NO:35) and *EsaB-BamHI-R* aaggatccctatagtaactcaaaatat (SEQ ID NO:36) for *esaB* and *EsaC-NdeI-F* aacatgatatttaatatgatattga (SEQ ID NO:37) and *EsaC-XhoI-R* aactcgagtaattcatgctttatataaat (SEQ ID NO:38) for *esaC*.

Culture Fractionation and Western blot experiments. Bacterial cells were grown at 37° C. to an optical density of 0.8 at 660 nm (OD_{660nm}) in tryptic soy broth. 1.5 ml of culture was spun (10,000×g for 4 min), and supernatants (1 ml) were transferred to a fresh tube. Proteins in the supernatant were precipitated with 7.5% trichloroacetic acid (TCA), and sedimented by centrifugation (10,000×g for 10 min) (MD, medium fraction). For whole culture lysates (WC), cultures (1.5 ml) were incubated in the presence of lysostaphin (100 μ g/ml) for 30 min at 37° C. and a 1-ml aliquot was precipitated with TCA.

For studies using serum, colony forming units were counted and approximately 2×10^4 bacteria were added to 1.5 ml freshly drawn human blood placed in a sterile polystyrene round bottom tube. The samples were allowed to incubate with shaking at 37° C. for 5 h and spun at 10,000×g for 4 min. Bacteria in the cell pellet were washed with TSM to remove any proteins in the serum that would interfere with western blotting analysis and suspended in 1.5 ml Tris-HCl buffer 0.05 M, pH 8.0 containing 100 μ g/ml lysostaphin. 1 ml of the cell lysate was removed and precipitated with 7.5% TCA.

All TCA precipitates were washed with ice-cold acetone, solubilized in 50 μ l of 0.5 M Tris-HCl (pH 8.0)/4% SDS and

heated at 90° C. for 10 min. Proteins were separated on SDS/PAGE and transferred to poly(vinylidene difluoride) membrane for immunoblot analysis with appropriate polyclonal antibodies. Immunoreactive signals were revealed by using a secondary antibody coupled to horseradish peroxidase and chemiluminescence.

Staphylococcal fractionation. Cultures were centrifuged as described above and supernatants TCA precipitated in the presence of deoxycholic acid (MD, medium fraction of a 5 ml culture). Cell pellets of a 5 ml culture were washed with TSM buffer, suspended in 5 ml TSM buffer containing 100 μ g/ml lysostaphin and incubated at 37° C. for 30 min. Protoplasts were collected by centrifugation at 10,000×g for 10 min, and the supernatant (W, cell wall fraction) was precipitated with TCA. The protoplasts were suspended in 5 ml membrane buffer (0.1 M Tris-HCl, pH 7.5/0.1 M NaCl/10 mM $MgCl_2$) and subjected to five rounds of freeze-thaw in a dry ice ethanol bath. Soluble proteins (C, cytoplasmic fraction) were separated from insoluble materials and membranes (M, membrane fraction) by centrifugation at 100,000×g for 30 min. All samples were TCA-precipitated before immunoblotting.

Labeling experiments and immunoprecipitation. Staphylococcal cultures were grown overnight in minimal medium, diluted 1:100 into minimal medium to OD_{660nm} 0.8 and metabolically labeled with 100 μ Ci [^{35} S]methionine for 2 min. TCA (5% final concentration) was added to stop all biological processes. All precipitates were washed with cold acetone and digested with lysostaphin in a 1 ml reaction volume of Tris-HCl buffer 0.5 M, pH 8.0 containing 100 μ g/ml of enzyme for 2 hours at 37° C. Digests were precipitated with TCA, washed with acetone and the samples were boiled in SDS (50 μ A 4% SDS, 0.5 M Tris-HCl, pH 8.0). Insoluble materials were removed by sedimentation. Total radioactive counts were measured using 5 μ A of each sample in a scintillation counter. The incorporation of radiolabeled amino acids was found to be similar between all the samples examined (~20 cpm/ μ l). Twenty μ l of each sample were immunoprecipitated with protein-specific antiserum and protein A beads. The beads were washed five times in RIPA buffer (50 mM Tris-HCl, 150 mM NaCl, 1% Triton X-100, 0.5% deoxycholate, 0.1% SDS, pH 7.5) and boiled in sample buffer prior to separation on SDS-PAGE. The gels were dried for visualization of radiolabeled polypeptides by autoradiography.

Transcriptional analysis of *esaC*. RNA from approximately 5×10^7 cells grown in tryptic soy broth was isolated using the RNeasy Midi Kit (Qiagen). The RNA was used to generate cDNA with random oligos (Promega). The relative abundance of *esaC* transcripts detected in Newman, *esaB* and *esaC* strains was measured qualitatively by PCR, using TaqDNA polymerase (Promega) with primers *EsaC-NdeI-F* and *EsaC-XhoI-R* and *sdrE130F* (tcgatttttagtgtagtcagac (SEQ ID NO:39)) and *sdrE640R* (tctacttttgaaggcgttgg (SEQ ID NO:40)) for amplification of *esaC* and *sdrE* specific DNA fragments, respectively. Real-time PCR (RT-PCR) was performed using the 7300 Real time PCR System (Applied Biosystems) and data analyzed and interpreted using Relative quantification study (Sequence Detection 1.3.1).

Renal abscess. Overnight cultures of *S. aureus* strains were diluted 1:100 into fresh tryptic soy broth and grown for 3 h at 37° C. Staphylococci were centrifuged, washed twice, and diluted in PBS to yield an OD_{660nm} of 0.4 ($3-5 \times 10^7$ cfu per ml). Viable staphylococci were enumerated by colony formation on tryptic soy agar plates to quantify the infectious dose. Mice were anesthetized by intraperitoneal injection of 80-120 mg of ketamine and 3-6 mg of xylazine per kilogram of body weight. One hundred μ l of bacterial suspension (0.5×10^6 colony forming units) was administered intravenously via

retro-orbital injection into BALB/c mice (24-day-old female, 10 mice per group, Charles River Laboratories, Wilmington, Mass.). On days 5 and 36, groups of ten mice were euthanized by compressed CO₂ inhalation. Kidneys were removed and homogenized in PBS containing 1% Triton X-100. Aliquots of homogenates were diluted and plated on agar medium for triplicate determination of CFU. Student's t-test was performed for statistical analysis using the software Analyse-it™. For histology, kidney tissue was incubated at room temperature in 10% formalin for 24 h. Tissues were embedded in paraffin, thin-sectioned, stained with hematoxylin/eosin, and examined by microscopy.

ELISA. Sera from infected individuals were obtained from the University of Chicago Hospitals Clinical Laboratory. These studies were carried out in accordance with an IRB protocol approved for the collection of sera from infected and healthy individuals. BALB/c mice were infected with one hundred µl of bacterial suspension (0.5×10^6 colony forming units) as described above. Blood samples were drawn by retro-orbital bleeding on days 0 and 30. Sera were examined by ELISA for IgG titers with specific antigen-binding activity. Animal experiments were performed in accordance with institutional guidelines following experimental protocol review and approval by the Institutional Animal Care and Use Committee.

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The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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att aaa aag cat gct gaa gag att gcg cat gaa att gaa gtt cgt tct      96
Ile Lys Lys His Ala Glu Glu Ile Ala His Glu Ile Glu Val Arg Ser
20            25            30

gga tat tta aga aaa gct gaa caa tat aag cga tta gaa ttt aat ttg      144
Gly Tyr Leu Arg Lys Ala Glu Gln Tyr Lys Arg Leu Glu Phe Asn Leu
35            40            45

agt ttt gca cta gat gat att gaa agc aca gca aag gac gta caa act      192
Ser Phe Ala Leu Asp Asp Ile Glu Ser Thr Ala Lys Asp Val Gln Thr
50            55            60

gca aaa tct agt gct aat aag gac agt gta act gtt aag gga aag gcg      240
Ala Lys Ser Ser Ala Asn Lys Asp Ser Val Thr Val Lys Gly Lys Ala
65            70            75            80

ccc aat acg tta tat att gaa aaa aga aat ttg atg aaa caa aag ctt      288
Pro Asn Thr Leu Tyr Ile Glu Lys Arg Asn Leu Met Lys Gln Lys Leu
85            90            95

gaa atg ttg ggt gaa gat atc gat aaa aat aaa gaa tcc ctc caa aaa      336
Glu Met Leu Gly Glu Asp Ile Asp Lys Asn Lys Glu Ser Leu Gln Lys
100           105           110

gct aag gaa att gct ggc gaa aag gca agt gaa tat ttt aat aaa gca      384
Ala Lys Glu Ile Ala Gly Glu Lys Ala Ser Glu Tyr Phe Asn Lys Ala
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Met Asn
130

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Ala Lys Ser Ser Ala Asn Lys Asp Ser Val Thr Val Lys Gly Lys Ala			
65	70	75	80
Pro Asn Thr Leu Tyr Ile Glu Lys Arg Asn Leu Met Lys Gln Lys Leu			
85	90	95	
Glu Met Leu Gly Glu Asp Ile Asp Lys Asn Lys Glu Ser Leu Gln Lys			
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1	5	10	15
tct tac ggg caa ggt tca gac caa atc cgt caa att tta tct gat tta			96
Ser Tyr Gly Gln Gly Ser Asp Gln Ile Arg Gln Ile Leu Ser Asp Leu			
20	25	30	
aca cgt gca caa ggt gaa att gca gcg aac tgg gaa ggt caa gct ttc			144
Thr Arg Ala Gln Gly Glu Ile Ala Ala Asn Trp Glu Gly Gln Ala Phe			
35	40	45	
agc cgt ttc gaa gag caa ttc caa caa ctt agt cct aaa gta gaa aaa			192
Ser Arg Phe Glu Glu Gln Phe Gln Gln Leu Ser Pro Lys Val Glu Lys			
50	55	60	
ttt gca caa tta tta gaa gaa att aaa caa caa ttg aat agc act gct			240
Phe Ala Gln Leu Leu Glu Glu Ile Lys Gln Gln Leu Asn Ser Thr Ala			
65	70	75	80
gat gcc gtt caa gaa caa gac caa caa ctt tct aat aat ttc ggt ttg			288
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Gln			
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20	25	30	
Thr Arg Ala Gln Gly Glu Ile Ala Ala Asn Trp Glu Gly Gln Ala Phe			
35	40	45	
Ser Arg Phe Glu Glu Gln Phe Gln Gln Leu Ser Pro Lys Val Glu Lys			

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50	55	60	
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1	5	10	15
gcg aaa caa tta gcg gca aaa ata gct aaa gat att gaa gca tgt caa			96
Ala Lys Gln Leu Ala Ala Lys Ile Ala Lys Asp Ile Glu Ala Cys Gln			
	20	25	30
aag caa acg caa cag ctc gct gag tat atc gaa ggt agt gat tgg gaa			144
Lys Gln Thr Gln Gln Leu Ala Glu Tyr Ile Glu Gly Ser Asp Trp Glu			
	35	40	45
gga cag ttc gcc aat aag gtg aaa gat gtg tta ctt att atg gca aag			192
Gly Gln Phe Ala Asn Lys Val Lys Asp Val Leu Leu Ile Met Ala Lys			
	50	55	60
ttt caa gaa gaa tta gta caa ccg atg gct gac cat caa aaa gca att			240
Phe Gln Glu Glu Leu Val Gln Pro Met Ala Asp His Gln Lys Ala Ile			
65	70	75	80
gat aac tta agt caa aat cta gcg aaa tac gat aca tta tca att aag			288
Asp Asn Leu Ser Gln Asn Leu Ala Lys Tyr Asp Thr Leu Ser Ile Lys			
	85	90	95
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Gln Gly Leu Asp Arg Val			
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	20	25	30
Lys Gln Thr Gln Gln Leu Ala Glu Tyr Ile Glu Gly Ser Asp Trp Glu			
	35	40	45
Gly Gln Phe Ala Asn Lys Val Lys Asp Val Leu Leu Ile Met Ala Lys			
	50	55	60
Phe Gln Glu Glu Leu Val Gln Pro Met Ala Asp His Gln Lys Ala Ile			
65	70	75	80
Asp Asn Leu Ser Gln Asn Leu Ala Lys Tyr Asp Thr Leu Ser Ile Lys			
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tcc aat cga tta aat aaa ttt tcg att aga aag tac aca gtg gga aca      96
Ser Asn Arg Leu Asn Lys Phe Ser Ile Arg Lys Tyr Thr Val Gly Thr
          20          25          30

gca tca att tta gta ggt aca aca tta att ttt ggt ctg ggg aac caa     144
Ala Ser Ile Leu Val Gly Thr Thr Leu Ile Phe Gly Leu Gly Asn Gln
          35          40          45

gaa gca aag gct gca gaa agt act aat aaa gaa ttg aac gaa gcg aca     192
Glu Ala Lys Ala Ala Glu Ser Thr Asn Lys Glu Leu Asn Glu Ala Thr
          50          55          60

act tca gca agt gat aat caa tcg agt gat aaa gtt gat atg cag caa     240
Thr Ser Ala Ser Asp Asn Gln Ser Ser Asp Lys Val Asp Met Gln Gln
        65          70          75          80

cta aat caa gaa gac aat act aaa aat gat aat caa aaa gaa atg gta     288
Leu Asn Gln Glu Asp Asn Thr Lys Asn Asp Asn Gln Lys Glu Met Val
          85          90          95

tca tct caa ggt aat gaa acg act tca aat ggg aat aaa tca ata gaa     336
Ser Ser Gln Gly Asn Glu Thr Thr Ser Asn Gly Asn Lys Ser Ile Glu
          100          105          110

aaa gaa agt gta caa tct acc act gga aat aaa gtt gaa gtt tca act     384
Lys Glu Ser Val Gln Ser Thr Thr Gly Asn Lys Val Glu Val Ser Thr
          115          120          125

gcc aaa tca gat gag caa gct tca cca aaa tct acg aat gaa gat tta     432
Ala Lys Ser Asp Glu Gln Ala Ser Pro Lys Ser Thr Asn Glu Asp Leu
          130          135          140

aac act aaa caa act ata agt aat caa gaa ggg tta caa cct gat ttg     480
Asn Thr Lys Gln Thr Ile Ser Asn Gln Glu Gly Leu Gln Pro Asp Leu
          145          150          155          160

cta gag aat aaa tca gtg gta aat gtt caa cca act aat gag gaa aac     528
Leu Glu Asn Lys Ser Val Val Asn Val Gln Pro Thr Asn Glu Glu Asn
          165          170          175

aaa aag gta gat gcg aaa act gaa tca act aca tta aat gtt aaa agt     576
Lys Lys Val Asp Ala Lys Thr Glu Ser Thr Thr Leu Asn Val Lys Ser
          180          185          190

gat gct atc aag agt aat gct gaa act ctt gtt gat aac aat agt aat     624
Asp Ala Ile Lys Ser Asn Ala Glu Thr Leu Val Asp Asn Asn Ser Asn
          195          200          205

tca aat aat gaa aat aat gca gat atc att ttg cca aaa agt aca gca     672
Ser Asn Asn Glu Asn Asn Ala Asp Ile Ile Leu Pro Lys Ser Thr Ala
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cct aaa agt ttg aat aca aga atg cgt atg gca gca ata caa cca aac     720
Pro Lys Ser Leu Asn Thr Arg Met Arg Met Ala Ala Ile Gln Pro Asn
          225          230          235          240

tca aca gat tct aaa aat gtt aat gat tta atc aca tca aat aca aca     768
Ser Thr Asp Ser Lys Asn Val Asn Asp Leu Ile Thr Ser Asn Thr Thr
          245          250          255

tta act gtc gtt gat gca gat aat agc aaa acg att gta cca gcc caa     816
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gat tat tta tca tta aaa tca caa att aca gtt gat gac aaa gtt aaa     864

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305 310 315 320	
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Asn Asn Gly Glu Thr Ile Ala Thr Ala Lys His Asp Thr Ala Asn Asn	
325 330 335	
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Leu Ile Thr Tyr Thr Phe Thr Asp Tyr Val Asp Arg Phe Asn Ser Val	
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Lys Met Gly Ile Asn Tyr Ser Ile Tyr Met Asp Ala Asp Thr Ile Pro	
355 360 365	
gtt gac aag aaa gat gtt cct ttt agt gta act att gga aat caa att	1152
Val Asp Lys Lys Asp Val Pro Phe Ser Val Thr Ile Gly Asn Gln Ile	
370 375 380	
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Gln Ser Gly Gly Ala Gly Gln Glu Val Tyr Lys Ile Gly Asn Tyr Val	
565 570 575	
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755 760 765	
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Leu Thr Thr Thr Gly Val Ile Asn Gly Ala Asp Asn Met Thr Leu Asp	
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tat aaa aca cca aaa tat agt tta ggt gat tat gtt tgg tac gac agt Tyr Lys Thr Pro Lys Tyr Ser Leu Gly Asp Tyr Val Trp Tyr Asp Ser 1010 1015 1020	3072
aat aaa gac ggc aaa caa gat tca act gaa aaa ggt atc aaa gat gtt Asn Lys Asp Gly Lys Gln Asp Ser Thr Glu Lys Gly Ile Lys Asp Val 1025 1030 1035 1040	3120
aaa gtt att tta tta aat gaa aaa ggc gaa gta att gga aca act aaa Lys Val Ile Leu Leu Asn Glu Lys Gly Glu Val Ile Gly Thr Thr Lys 1045 1050 1055	3168
aca gat gaa aat ggt aaa tac cgc ttt gat aat tta gat agc ggt aaa Thr Asp Glu Asn Gly Lys Tyr Arg Phe Asp Asn Leu Asp Ser Gly Lys 1060 1065 1070	3216
tac aaa gtt att ttt gaa aag cct act ggc tta aca caa aca ggt aca Tyr Lys Val Ile Phe Glu Lys Pro Thr Gly Leu Thr Gln Thr Gly Thr 1075 1080 1085	3264
aat aca act gaa gat gat aaa gat gcc gat ggt ggc gaa gtt gat gta Asn Thr Thr Glu Asp Asp Lys Asp Ala Asp Gly Gly Glu Val Asp Val 1090 1095 1100	3312
aca att acg gat cat gat gat ttc aca ctt gat aat ggc tac tac gaa Thr Ile Thr Asp His Asp Asp Phe Thr Leu Asp Asn Gly Tyr Tyr Glu 1105 1110 1115 1120	3360
gaa gaa aca tca gat agc gac tca gat tcg gac agc gat tca gac tca Glu Glu Thr Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 1125 1130 1135	3408
gac agc gat tca gac tca gat agt gat tca gat tca gat agt gat tca Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 1140 1145 1150	3456
gat tca gat agt gat tca gat tca gac agc gac tca gac tca gat agt Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 1155 1160 1165	3504
gac tca gac tca gat agc gat tca gat tca gat agc gat tca gac tca Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 1170 1175 1180	3552
gac agc gat tca gat tca gac agc gac tca gac tca gat agc gac tca Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 1185 1190 1195 1200	3600
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gat tca gac tca gat agc gac tca gac tca gat agc gat tca gat tca Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 1215 1220 1225	3696

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1235	1240	1245	
gat tca gat agc gat tca gac tca gac tca gat agc gat tca gat tca			3792
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser			
1250	1255	1260	
gac agc gac tca gat tcg gac agc gac tca gac tca gac agt gat tca			3840
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser			
1265	1270	1275	1280
gat tca gat agc gac tca gac tca gat agc gac tca gat tca gac agc			3888
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser			
1285	1290	1295	
gat tca gac tca gat agt gac tca gat tcg gac agc gat tca gac tca			3936
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser			
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gat agc gac tca gat tca gac agt gat tca gac tca gat gca ggt aag			3984
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ala Gly Lys			
1315	1320	1325	
cac aca cct gtt aaa cca atg agt act act aaa gac cat cac aat aaa			4032
His Thr Pro Val Lys Pro Met Ser Thr Thr Lys Asp His His Asn Lys			
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gca aaa gca tta cca gaa aca ggt aat gaa aat agt ggc tca aat aac			4080
Ala Lys Ala Leu Pro Glu Thr Gly Asn Glu Asn Ser Gly Ser Asn Asn			
1345	1350	1355	1360
gca acg tta ttt ggc gga tta ttc gca gca tta gga tca tta ttg tta			4128
Ala Thr Leu Phe Gly Gly Leu Phe Ala Ala Leu Gly Ser Leu Leu Leu			
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Phe Gly Arg Arg Lys Lys Gln Asn Lys			
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<211> LENGTH: 1385			
<212> TYPE: PRT			
<213> ORGANISM: Staphylococcus sp.			
<400> SEQUENCE: 8			
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Ala Ser Ile Leu Val Gly Thr Thr Leu Ile Phe Gly Leu Gly Asn Gln			
35 40 45			
Glu Ala Lys Ala Ala Glu Ser Thr Asn Lys Glu Leu Asn Glu Ala Thr			
50 55 60			
Thr Ser Ala Ser Asp Asn Gln Ser Ser Asp Lys Val Asp Met Gln Gln			
65 70 75 80			
Leu Asn Gln Glu Asp Asn Thr Lys Asn Asp Asn Gln Lys Glu Met Val			
85 90 95			
Ser Ser Gln Gly Asn Glu Thr Thr Ser Asn Gly Asn Lys Ser Ile Glu			
100 105 110			
Lys Glu Ser Val Gln Ser Thr Thr Gly Asn Lys Val Glu Val Ser Thr			
115 120 125			
Ala Lys Ser Asp Glu Gln Ala Ser Pro Lys Ser Thr Asn Glu Asp Leu			
130 135 140			
Asn Thr Lys Gln Thr Ile Ser Asn Gln Glu Gly Leu Gln Pro Asp Leu			
145 150 155 160			

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Leu Glu Asn Lys Ser Val Val Asn Val Gln Pro Thr Asn Glu Glu Asn
 165 170 175
 Lys Lys Val Asp Ala Lys Thr Glu Ser Thr Thr Leu Asn Val Lys Ser
 180 185 190
 Asp Ala Ile Lys Ser Asn Ala Glu Thr Leu Val Asp Asn Asn Ser Asn
 195 200 205
 Ser Asn Asn Glu Asn Asn Ala Asp Ile Ile Leu Pro Lys Ser Thr Ala
 210 215 220
 Pro Lys Ser Leu Asn Thr Arg Met Arg Met Ala Ala Ile Gln Pro Asn
 225 230 235 240
 Ser Thr Asp Ser Lys Asn Val Asn Asp Leu Ile Thr Ser Asn Thr Thr
 245 250 255
 Leu Thr Val Val Asp Ala Asp Asn Ser Lys Thr Ile Val Pro Ala Gln
 260 265 270
 Asp Tyr Leu Ser Leu Lys Ser Gln Ile Thr Val Asp Asp Lys Val Lys
 275 280 285
 Ser Gly Asp Tyr Phe Thr Ile Lys Tyr Ser Asp Thr Val Gln Val Tyr
 290 295 300
 Gly Leu Asn Pro Glu Asp Ile Lys Asn Ile Gly Asp Ile Lys Asp Pro
 305 310 315 320
 Asn Asn Gly Glu Thr Ile Ala Thr Ala Lys His Asp Thr Ala Asn Asn
 325 330 335
 Leu Ile Thr Tyr Thr Phe Thr Asp Tyr Val Asp Arg Phe Asn Ser Val
 340 345 350
 Lys Met Gly Ile Asn Tyr Ser Ile Tyr Met Asp Ala Asp Thr Ile Pro
 355 360 365
 Val Asp Lys Lys Asp Val Pro Phe Ser Val Thr Ile Gly Asn Gln Ile
 370 375 380
 Thr Thr Thr Thr Ala Asp Ile Thr Tyr Pro Ala Tyr Lys Glu Ala Asp
 385 390 395 400
 Asn Asn Ser Ile Gly Ser Ala Phe Thr Glu Thr Val Ser His Val Gly
 405 410 415
 Asn Val Glu Asp Pro Gly Tyr Tyr Asn Gln Val Val Tyr Val Asn Pro
 420 425 430
 Met Asp Lys Asp Leu Lys Gly Ala Lys Leu Lys Val Glu Ala Tyr His
 435 440 445
 Pro Lys Tyr Pro Thr Asn Ile Gly Gln Ile Asn Gln Asn Val Thr Asn
 450 455 460
 Ile Lys Ile Tyr Arg Val Pro Glu Gly Tyr Thr Leu Asn Lys Gly Tyr
 465 470 475 480
 Asp Val Asn Thr Asn Asp Leu Val Asp Val Thr Asp Glu Phe Lys Asn
 485 490 495
 Lys Met Thr Tyr Gly Ser Asn Gln Ser Val Asn Leu Asp Phe Gly Asp
 500 505 510
 Ile Thr Ser Ala Tyr Val Val Met Val Asn Thr Lys Phe Gln Tyr Thr
 515 520 525
 Asn Ser Glu Ser Pro Thr Leu Val Gln Met Ala Thr Leu Ser Ser Thr
 530 535 540
 Gly Asn Lys Ser Val Ser Thr Gly Asn Ala Leu Gly Phe Thr Asn Asn
 545 550 555 560
 Gln Ser Gly Gly Ala Gly Gln Glu Val Tyr Lys Ile Gly Asn Tyr Val
 565 570 575

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Trp	Glu	Asp	Thr	Asn	Lys	Asn	Gly	Val	Gln	Glu	Leu	Gly	Glu	Lys	Gly	
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Val	Gly	Asn	Val	Thr	Val	Thr	Val	Phe	Asp	Asn	Asn	Thr	Asn	Thr	Lys	
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Leu	Pro	Asn	Gly	Asp	Tyr	Arg	Val	Glu	Phe	Ser	Asn	Leu	Pro	Lys	Gly	
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Tyr	Glu	Val	Thr	Pro	Ser	Lys	Gln	Gly	Asn	Asn	Glu	Glu	Leu	Asp	Ser	
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Asn	Gly	Leu	Ser	Ser	Val	Ile	Thr	Val	Asn	Gly	Lys	Asp	Asn	Leu	Ser	
			660					665					670			
Ala	Asp	Leu	Gly	Ile	Tyr	Lys	Pro	Lys	Tyr	Asn	Leu	Gly	Asp	Tyr	Val	
	675						680					685				
Trp	Glu	Asp	Thr	Asn	Lys	Asn	Gly	Ile	Gln	Asp	Gln	Asp	Glu	Lys	Gly	
	690					695					700					
Ile	Ser	Gly	Val	Thr	Val	Thr	Leu	Lys	Asp	Glu	Asn	Gly	Asn	Val	Leu	
705					710					715					720	
Lys	Thr	Val	Thr	Thr	Asp	Ala	Asp	Gly	Lys	Tyr	Lys	Phe	Thr	Asp	Leu	
				725					730					735		
Asp	Asn	Gly	Asn	Tyr	Lys	Val	Glu	Phe	Thr	Thr	Pro	Glu	Gly	Tyr	Thr	
			740					745					750			
Pro	Thr	Thr	Val	Thr	Ser	Gly	Ser	Asp	Ile	Glu	Lys	Asp	Ser	Asn	Gly	
		755					760					765				
Leu	Thr	Thr	Thr	Gly	Val	Ile	Asn	Gly	Ala	Asp	Asn	Met	Thr	Leu	Asp	
	770					775					780					
Ser	Gly	Phe	Tyr	Lys	Thr	Pro	Lys	Tyr	Asn	Leu	Gly	Asn	Tyr	Val	Trp	
785					790					795					800	
Glu	Asp	Thr	Asn	Lys	Asp	Gly	Lys	Gln	Asp	Ser	Thr	Glu	Lys	Gly	Ile	
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Ser	Gly	Val	Thr	Val	Thr	Leu	Lys	Asn	Glu	Asn	Gly	Glu	Val	Leu	Gln	
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Thr	Thr	Lys	Thr	Asp	Lys	Asp	Gly	Lys	Tyr	Gln	Phe	Thr	Gly	Leu	Glu	
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Asn	Gly	Thr	Tyr	Lys	Val	Glu	Phe	Glu	Thr	Pro	Ser	Gly	Tyr	Thr	Pro	
	850					855					860					
Thr	Gln	Val	Gly	Ser	Gly	Thr	Asp	Glu	Gly	Ile	Asp	Ser	Asn	Gly	Thr	
865					870					875					880	
Ser	Thr	Thr	Gly	Val	Ile	Lys	Asp	Lys	Asp	Asn	Asp	Thr	Ile	Asp	Ser	
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Gly	Phe	Tyr	Lys	Pro	Thr	Tyr	Asn	Leu	Gly	Asp	Tyr	Val	Trp	Glu	Asp	
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Thr	Asn	Lys	Asn	Gly	Val	Gln	Asp	Lys	Asp	Glu	Lys	Gly	Ile	Ser	Gly	
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Val	Thr	Val	Thr	Leu	Lys	Asp	Glu	Asn	Asp	Lys	Val	Leu	Lys	Thr	Val	
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945					950					955					960	
Thr	Tyr	Lys	Val	Glu	Phe	Glu	Thr	Pro	Ser	Gly	Tyr	Thr	Pro	Thr	Ser	
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Val	Thr	Ser	Gly	Asn	Asp	Thr	Glu	Lys	Asp	Ser	Asn	Gly	Leu	Thr	Thr	
			980					985					990			
Thr	Gly	Val	Ile	Lys	Asp	Ala	Asp	Asn	Met	Thr	Leu	Asp	Ser	Gly	Phe	

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995	1000	1005
Tyr Lys Thr Pro Lys Tyr Ser Leu Gly Asp Tyr Val Trp Tyr Asp Ser 1010 1015 1020		
Asn Lys Asp Gly Lys Gln Asp Ser Thr Glu Lys Gly Ile Lys Asp Val 1025 1030 1035 1040		
Lys Val Ile Leu Leu Asn Glu Lys Gly Glu Val Ile Gly Thr Thr Lys 1045 1050 1055		
Thr Asp Glu Asn Gly Lys Tyr Arg Phe Asp Asn Leu Asp Ser Gly Lys 1060 1065 1070		
Tyr Lys Val Ile Phe Glu Lys Pro Thr Gly Leu Thr Gln Thr Gly Thr 1075 1080 1085		
Asn Thr Thr Glu Asp Asp Lys Asp Ala Asp Gly Gly Glu Val Asp Val 1090 1095 1100		
Thr Ile Thr Asp His Asp Asp Phe Thr Leu Asp Asn Gly Tyr Tyr Glu 1105 1110 1115 1120		
Glu Glu Thr Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 1125 1130 1135		
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 1140 1145 1150		
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Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 1205 1210 1215		
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Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ala Gly Lys 1315 1320 1325		
His Thr Pro Val Lys Pro Met Ser Thr Thr Lys Asp His His Asn Lys 1330 1335 1340		
Ala Lys Ala Leu Pro Glu Thr Gly Asn Glu Asn Ser Gly Ser Asn Asn 1345 1350 1355 1360		
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<210> SEQ ID NO 9

<211> LENGTH: 3426

<212> TYPE: DNA

<213> ORGANISM: Staphylococcus sp.

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<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (1) .. (3426)

<400> SEQUENCE: 9

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tca aat cgc tta aac aaa ttt tcg att aga aag tat act gta gga act	96
Ser Asn Arg Leu Asn Lys Phe Ser Ile Arg Lys Tyr Thr Val Gly Thr	
20 25 30	
gca tcg att tta gta ggt acg aca ttg att ttt ggt cta ggg aac caa	144
Ala Ser Ile Leu Val Gly Thr Thr Leu Ile Phe Gly Leu Gly Asn Gln	
35 40 45	
gaa gct aaa gct gct gaa aac act agt aca gaa aat gcg aaa caa gat	192
Glu Ala Lys Ala Ala Glu Asn Thr Ser Thr Glu Asn Ala Lys Gln Asp	
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gat gca acg act agt gat aat aaa gaa gta gtg tcg gaa act gaa aat	240
Asp Ala Thr Thr Ser Asp Asn Lys Glu Val Val Ser Glu Thr Glu Asn	
65 70 75 80	
aat tcg aca aca gaa aat gat tca aca aat cca att aag aaa gaa aca	288
Asn Ser Thr Thr Glu Asn Asp Ser Thr Asn Pro Ile Lys Lys Glu Thr	
85 90 95	
aat act gat tca caa cca gaa gct aaa gaa gaa tca act aca tca agt	336
Asn Thr Asp Ser Gln Pro Glu Ala Lys Glu Glu Ser Thr Thr Ser Ser	
100 105 110	
act caa caa cag caa aat aac gtt aca gct aca act gaa act aag cct	384
Thr Gln Gln Gln Gln Asn Asn Val Thr Ala Thr Thr Glu Thr Lys Pro	
115 120 125	
caa aac att gaa aaa gaa aat gtt aaa cct tca act gat aaa act gcg	432
Gln Asn Ile Glu Lys Glu Asn Val Lys Pro Ser Thr Asp Lys Thr Ala	
130 135 140	
aca gaa gat aca tct gtt att tta gaa gag aag aaa gca cca aat tat	480
Thr Glu Asp Thr Ser Val Ile Leu Glu Glu Lys Lys Ala Pro Asn Tyr	
145 150 155 160	
aca aat aac gat gta act aca aaa cca tct aca agt gaa att caa aca	528
Thr Asn Asn Asp Val Thr Thr Lys Pro Ser Thr Ser Glu Ile Gln Thr	
165 170 175	
aaa cca act aca cct caa gaa tct aca aat att gaa aat tca caa ccg	576
Lys Pro Thr Thr Pro Gln Glu Ser Thr Asn Ile Glu Asn Ser Gln Pro	
180 185 190	
caa cca acg cct tca aaa gta gac aat caa gtt aca gat gca act aat	624
Gln Pro Thr Pro Ser Lys Val Asp Asn Gln Val Thr Asp Ala Thr Asn	
195 200 205	
cca aaa gaa cca gta aat gtg tca aaa gaa gaa ctt aaa aat aat cct	672
Pro Lys Glu Pro Val Asn Val Ser Lys Glu Glu Leu Lys Asn Asn Pro	
210 215 220	
gag aaa tta aaa gaa tta gtt aga aat gat aac aat aca gat cgt tca	720
Glu Lys Leu Lys Glu Leu Val Arg Asn Asp Asn Asn Thr Asp Arg Ser	
225 230 235 240	
act aaa cca gtt gct aca gct cca aca agt gtt gca cca aaa cga tta	768
Thr Lys Pro Val Ala Thr Ala Pro Thr Ser Val Ala Pro Lys Arg Leu	
245 250 255	
aat gcg aaa atg cgt ttt gca gtt gca caa cca gca gca gtt gct tca	816
Asn Ala Lys Met Arg Phe Ala Val Ala Gln Pro Ala Ala Val Ala Ser	
260 265 270	
aat aat gta aat gac tta att aca gtt acg aaa cag acg atc aaa gtt	864
Asn Asn Val Asn Asp Leu Ile Thr Val Thr Lys Gln Thr Ile Lys Val	
275 280 285	
ggc gat ggt aaa gat aat gtg gca gca gcg cat gac ggt aaa gat att	912

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Gly	Asp	Gly	Lys	Asp	Asn	Val	Ala	Ala	Ala	His	Asp	Gly	Lys	Asp	Ile	
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Glu	Tyr	Asp	Thr	Glu	Phe	Thr	Ile	Asp	Asn	Lys	Val	Lys	Lys	Gly	Asp	
305					310					315					320	
aca	atg	acg	att	aat	tat	gat	aag	aat	gta	att	cct	tcg	gat	tta	aca	1008
Thr	Met	Thr	Ile	Asn	Tyr	Asp	Lys	Asn	Val	Ile	Pro	Ser	Asp	Leu	Thr	
				325					330					335		
gat	aaa	aat	gat	cct	atc	gat	att	act	gat	cca	tca	gga	gag	gtc	att	1056
Asp	Lys	Asn	Asp	Pro	Ile	Asp	Ile	Thr	Asp	Pro	Ser	Gly	Glu	Val	Ile	
				340				345					350			
gcc	aaa	gga	aca	ttt	gat	aaa	gcg	act	aag	caa	atc	aca	tat	aca	ttt	1104
Ala	Lys	Gly	Thr	Phe	Asp	Lys	Ala	Thr	Lys	Gln	Ile	Thr	Tyr	Thr	Phe	
		355					360					365				
aca	gat	tat	gta	gat	aaa	tat	gaa	gat	ata	aaa	gca	cgt	tta	act	tta	1152
Thr	Asp	Tyr	Val	Asp	Lys	Tyr	Glu	Asp	Ile	Lys	Ala	Arg	Leu	Thr	Leu	
	370					375					380					
tac	tca	tat	att	gat	aag	caa	gca	gta	cct	aat	gaa	act	agt	ttg	aat	1200
Tyr	Ser	Tyr	Ile	Asp	Lys	Gln	Ala	Val	Pro	Asn	Glu	Thr	Ser	Leu	Asn	
385					390					395					400	
tta	acg	ttt	gca	aca	gca	ggg	aaa	gaa	act	agc	caa	aac	gtt	tct	gtt	1248
Leu	Thr	Phe	Ala	Thr	Ala	Gly	Lys	Glu	Thr	Ser	Gln	Asn	Val	Ser	Val	
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gat	tat	caa	gac	cca	atg	gtt	cat	ggg	gat	tca	aac	att	caa	tct	atc	1296
Asp	Tyr	Gln	Asp	Pro	Met	Val	His	Gly	Asp	Ser	Asn	Ile	Gln	Ser	Ile	
			420					425					430			
ttt	aca	aag	tta	gat	gaa	aac	aaa	caa	act	att	gaa	caa	caa	att	tat	1344
Phe	Thr	Lys	Leu	Asp	Glu	Asn	Lys	Gln	Thr	Ile	Glu	Gln	Gln	Ile	Tyr	
		435				440						445				
gtt	aat	cct	ttg	aaa	aaa	aca	gca	act	aac	act	aaa	gtt	gat	ata	gct	1392
Val	Asn	Pro	Leu	Lys	Lys	Thr	Ala	Thr	Asn	Thr	Lys	Val	Asp	Ile	Ala	
	450					455					460					
ggg	agt	caa	gta	gat	gat	tat	gga	aat	att	aaa	cta	gga	aat	ggg	agt	1440
Gly	Ser	Gln	Val	Asp	Asp	Tyr	Gly	Asn	Ile	Lys	Leu	Gly	Asn	Gly	Ser	
465					470				475					480		
acc	att	att	gac	caa	aat	aca	gaa	ata	aaa	gtt	tat	aaa	gtt	aac	cct	1488
Thr	Ile	Ile	Asp	Gln	Asn	Thr	Glu	Ile	Lys	Val	Tyr	Lys	Val	Asn	Pro	
			485						490				495			
aat	caa	caa	ttg	cct	caa	agt	aat	aga	atc	tat	gat	ttt	agt	caa	tac	1536
Asn	Gln	Gln	Leu	Pro	Gln	Ser	Asn	Arg	Ile	Tyr	Asp	Phe	Ser	Gln	Tyr	
			500					505					510			
gaa	gat	gta	aca	agt	caa	ttt	gat	aat	aaa	aaa	tca	ttt	agt	aat	aat	1584
Glu	Asp	Val	Thr	Ser	Gln	Phe	Asp	Asn	Lys	Lys	Ser	Phe	Ser	Asn	Asn	
		515				520						525				
gta	gca	aca	ttg	gat	ttt	ggg	gat	att	aat	tca	gcc	tat	att	atc	aaa	1632
Val	Ala	Thr	Leu	Asp	Phe	Gly	Asp	Ile	Asn	Ser	Ala	Tyr	Ile	Ile	Lys	
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gtt	gtt	agt	aaa	tat	aca	cct	aca	tca	gat	ggc	gaa	cta	gat	att	gct	1680
Val	Val	Ser	Lys	Tyr	Thr	Pro	Thr	Ser	Asp	Gly	Glu	Leu	Asp	Ile	Ala	
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caa	ggg	act	agt	atg	aga	aca	act	gat	aaa	tat	ggg	tat	tat	aat	tat	1728
Gln	Gly	Thr	Ser	Met	Arg	Thr	Thr	Asp	Lys	Tyr	Gly	Tyr	Tyr	Asn	Tyr	
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gca	gga	tat	tca	aac	ttc	atc	gta	act	tct	aat	gac	act	ggc	ggg	ggc	1776
Ala	Gly	Tyr	Ser	Asn	Phe	Ile	Val	Thr	Ser	Asn	Asp	Thr	Gly	Gly	Gly	
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gac	ggg	act	gtt	aaa	cct	gaa	gaa	aag	tta	tac	aaa	att	ggg	gac	tat	1824
Asp	Gly	Thr	Val	Lys	Pro	Glu	Glu	Lys	Leu	Tyr	Lys	Ile	Gly	Asp	Tyr	
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gaa aag cca atg gca aac gtt tta gtt aca tta act tac ccg gac ggt	1920
Glu Lys Pro Met Ala Asn Val Leu Val Thr Leu Thr Tyr Pro Asp Gly	
625 630 635 640	
act aca aaa tca gta aga aca gat gct aac ggt cat tat gaa ttc ggt	1968
Thr Thr Lys Ser Val Arg Thr Asp Ala Asn Gly His Tyr Glu Phe Gly	
645 650 655	
ggt ttg aaa gac gga gaa act tat aca gtt aaa ttc gaa acg cca gct	2016
Gly Leu Lys Asp Gly Glu Thr Tyr Thr Val Lys Phe Glu Thr Pro Ala	
660 665 670	
gga tat ctt cca aca aaa gta aat gga aca act gat ggt gaa aaa gac	2064
Gly Tyr Leu Pro Thr Lys Val Asn Gly Thr Thr Asp Gly Glu Lys Asp	
675 680 685	
tca aat ggt agt tct ata act gtt aaa att aat ggt aaa gat gat atg	2112
Ser Asn Gly Ser Ser Ile Thr Val Lys Ile Asn Gly Lys Asp Asp Met	
690 695 700	
tct tta gac act ggt ttt tat aaa gaa cct aaa tat aat ctt ggt gac	2160
Ser Leu Asp Thr Gly Phe Tyr Lys Glu Pro Lys Tyr Asn Leu Gly Asp	
705 710 715 720	
tat gta tgg gaa gat aca aat aaa gat ggt atc caa gat gct aat gaa	2208
Tyr Val Trp Glu Asp Thr Asn Lys Asp Gly Ile Gln Asp Ala Asn Glu	
725 730 735	
cct ggt atc aaa gat gtt aag gtt aca tta aaa gat agt act gga aaa	2256
Pro Gly Ile Lys Asp Val Lys Val Thr Leu Lys Asp Ser Thr Gly Lys	
740 745 750	
ggt att ggt aca act act act gat gcc tcg ggt aaa tat aaa ttt aca	2304
Val Ile Gly Thr Thr Thr Thr Asp Ala Ser Gly Lys Tyr Lys Phe Thr	
755 760 765	
gat tta gat aat ggt aac tat aca gta gaa ttt gaa aca cca gca ggt	2352
Asp Leu Asp Asn Gly Asn Tyr Thr Val Glu Phe Glu Thr Pro Ala Gly	
770 775 780	
tac acg cca acg gtt aaa aat act aca gct gaa gat aaa gat tct aat	2400
Tyr Thr Pro Thr Val Lys Asn Thr Thr Ala Glu Asp Lys Asp Ser Asn	
785 790 795 800	
ggt tta aca aca aca ggt gtc att aaa gat gca gat aat atg aca tta	2448
Gly Leu Thr Thr Thr Gly Val Ile Lys Asp Ala Asp Asn Met Thr Leu	
805 810 815	
gac agt ggt ttc tat aaa aca cca aaa tac agt tta ggt gat tat gtt	2496
Asp Ser Gly Phe Tyr Lys Thr Pro Lys Tyr Ser Leu Gly Asp Tyr Val	
820 825 830	
tgg tac gac agt aat aaa gac ggt aaa caa gat tca act gaa aaa ggt	2544
Trp Tyr Asp Ser Asn Lys Asp Gly Lys Gln Asp Ser Thr Glu Lys Gly	
835 840 845	
atc aaa gat gtt aaa gtt act tta tta aat gaa aaa ggc gaa gta att	2592
Ile Lys Asp Val Lys Val Thr Leu Leu Asn Glu Lys Gly Glu Val Ile	
850 855 860	
gga aca act aaa aca gat gaa aat ggt aaa tat cgt ttc gat aat tta	2640
Gly Thr Thr Lys Thr Asp Glu Asn Gly Lys Tyr Arg Phe Asp Asn Leu	
865 870 875 880	
gat agc ggt aaa tac aaa gtt att ttt gaa aag cct gct ggc tta aca	2688
Asp Ser Gly Lys Tyr Lys Val Ile Phe Glu Lys Pro Ala Gly Leu Thr	
885 890 895	
caa aca gtt aca aat aca act gaa gat gat aaa gat gcc gat ggt ggc	2736
Gln Thr Val Thr Asn Thr Thr Glu Asp Asp Lys Asp Ala Asp Gly Gly	
900 905 910	
gaa gtt gac gta aca att acg gat cat gat gat ttc aca ctt gat aac	2784
Glu Val Asp Val Thr Ile Thr Asp His Asp Asp Phe Thr Leu Asp Asn	
915 920 925	

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gga tac ttc gaa gaa gat aca tca gac agt gat tca gac tca gac agt Gly Tyr Phe Glu Glu Asp Thr Ser Asp Ser Asp Ser Asp Ser Asp Ser 930 935 940	2832
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gat agc gat tca gat tca gac agc gac tca gac tca gat agc gac tca Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 965 970 975	2928
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gac tca gat tcg gac agt gat tca gac tca gat agc gac tca gat tca Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 1045 1050 1055	3168
gac agc gac tca gac tca gat agc gac tca gac tca gac agt gat tca Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 1060 1065 1070	3216
gac tca gat agc gat tcg gac tcg gat gca gga aaa cat aca cct gtt Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Ala Gly Lys His Thr Pro Val 1075 1080 1085	3264
aaa cca atg agt act act aaa gac cat cac aat aaa gca aaa gca tta Lys Pro Met Ser Thr Thr Lys Asp His His Asn Lys Ala Lys Ala Leu 1090 1095 1100	3312
cca gaa aca ggt agt gaa aat aac ggc tca aat aac gca acg tta ttt Pro Glu Thr Gly Ser Glu Asn Asn Gly Ser Asn Asn Ala Thr Leu Phe 1105 1110 1115 1120	3360
ggt gga tta ttt gca gca tta ggt tca tta ttg tta ttc ggt cgt cgc Gly Gly Leu Phe Ala Ala Leu Gly Ser Leu Leu Leu Phe Gly Arg Arg 1125 1130 1135	3408
aaa aaa caa aac aaa taa Lys Lys Gln Asn Lys 1140	3426

<210> SEQ ID NO 10

<211> LENGTH: 1141

<212> TYPE: PRT

<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 10

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Ala Ser Ile Leu Val Gly Thr Thr Leu Ile Phe Gly Leu Gly Asn Gln 35 40 45
Glu Ala Lys Ala Ala Glu Asn Thr Ser Thr Glu Asn Ala Lys Gln Asp 50 55 60
Asp Ala Thr Thr Ser Asp Asn Lys Glu Val Val Ser Glu Thr Glu Asn 65 70 75 80

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Asn	Gln	Gln	Leu	Pro	Gln	Ser	Asn	Arg	Ile	Tyr	Asp	Phe	Ser	Gln	Tyr
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Glu	Asp	Val	Thr	Ser	Gln	Phe	Asp	Asn	Lys	Lys	Ser	Phe	Ser	Asn	Asn
			515				520					525			
Val	Ala	Thr	Leu	Asp	Phe	Gly	Asp	Ile	Asn	Ser	Ala	Tyr	Ile	Ile	Lys
			530			535				540					
Val	Val	Ser	Lys	Tyr	Thr	Pro	Thr	Ser	Asp	Gly	Glu	Leu	Asp	Ile	Ala
			545		550				555						560
Gln	Gly	Thr	Ser	Met	Arg	Thr	Thr	Asp	Lys	Tyr	Gly	Tyr	Tyr	Asn	Tyr
				565					570					575	
Ala	Gly	Tyr	Ser	Asn	Phe	Ile	Val	Thr	Ser	Asn	Asp	Thr	Gly	Gly	Gly
			580					585					590		
Asp	Gly	Thr	Val	Lys	Pro	Glu	Glu	Lys	Leu	Tyr	Lys	Ile	Gly	Asp	Tyr
			595				600					605			
Val	Trp	Glu	Asp	Val	Asp	Lys	Asp	Gly	Val	Gln	Gly	Thr	Asp	Ser	Lys
			610			615					620				
Glu	Lys	Pro	Met	Ala	Asn	Val	Leu	Val	Thr	Leu	Thr	Tyr	Pro	Asp	Gly
			625		630					635					640
Thr	Thr	Lys	Ser	Val	Arg	Thr	Asp	Ala	Asn	Gly	His	Tyr	Glu	Phe	Gly
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Gly	Leu	Lys	Asp	Gly	Glu	Thr	Tyr	Thr	Val	Lys	Phe	Glu	Thr	Pro	Ala
			660					665					670		
Gly	Tyr	Leu	Pro	Thr	Lys	Val	Asn	Gly	Thr	Thr	Asp	Gly	Glu	Lys	Asp
			675				680					685			
Ser	Asn	Gly	Ser	Ser	Ile	Thr	Val	Lys	Ile	Asn	Gly	Lys	Asp	Asp	Met
			690			695					700				
Ser	Leu	Asp	Thr	Gly	Phe	Tyr	Lys	Glu	Pro	Lys	Tyr	Asn	Leu	Gly	Asp
			705		710					715					720
Tyr	Val	Trp	Glu	Asp	Thr	Asn	Lys	Asp	Gly	Ile	Gln	Asp	Ala	Asn	Glu
				725					730					735	
Pro	Gly	Ile	Lys	Asp	Val	Lys	Val	Thr	Leu	Lys	Asp	Ser	Thr	Gly	Lys
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Val	Ile	Gly	Thr	Thr	Thr	Thr	Asp	Ala	Ser	Gly	Lys	Tyr	Lys	Phe	Thr
			755				760					765			
Asp	Leu	Asp	Asn	Gly	Asn	Tyr	Thr	Val	Glu	Phe	Glu	Thr	Pro	Ala	Gly
			770			775					780				
Tyr	Thr	Pro	Thr	Val	Lys	Asn	Thr	Thr	Ala	Glu	Asp	Lys	Asp	Ser	Asn
			785		790					795					800
Gly	Leu	Thr	Thr	Thr	Gly	Val	Ile	Lys	Asp	Ala	Asp	Asn	Met	Thr	Leu
				805					810					815	
Asp	Ser	Gly	Phe	Tyr	Lys	Thr	Pro	Lys	Tyr	Ser	Leu	Gly	Asp	Tyr	Val
			820					825					830		
Trp	Tyr	Asp	Ser	Asn	Lys	Asp	Gly	Lys	Gln	Asp	Ser	Thr	Glu	Lys	Gly
			835				840						845		
Ile	Lys	Asp	Val	Lys	Val	Thr	Leu	Leu	Asn	Glu	Lys	Gly	Glu	Val	Ile
			850			855	</								

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915					920					925									
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Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser				
945					950					955					960				
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser				
965					970					975									
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser				
980					985					990									
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser				
995					1000					1005									
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser				
1010					1015					1020									
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser				
1025					1030					1035					1040				
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser				
1045					1050					1055									
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser				
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Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ala	Gly	Lys	His	Thr	Pro	Val				
1075					1080					1085									
Lys	Pro	Met	Ser	Thr	Thr	Lys	Asp	His	His	Asn	Lys	Ala	Lys	Ala	Leu				
1090					1095					1100									
Pro	Glu	Thr	Gly	Ser	Glu	Asn	Asn	Gly	Ser	Asn	Asn	Ala	Thr	Leu	Phe				
1105					1110					1115					1120				
Gly	Gly	Leu	Phe	Ala	Ala	Leu	Gly	Ser	Leu	Leu	Leu	Phe	Gly	Arg	Arg				
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1140																			
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<212> TYPE: DNA																			
<213> ORGANISM: Staphylococcus sp.																			
<220> FEATURE:																			
<221> NAME/KEY: CDS																			
<222> LOCATION: (1)..(1050)																			
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1					5				10					15					
tca	gct	atg	aaa	aag	att	aca	atg	ggg	aca	gca	tct	atc	att	tta	ggg				
Ser	Ala	Met	Lys	Lys	Ile	Thr	Met	Gly	Thr	Ala	Ser	Ile	Ile	Leu	Gly				
			20					25					30						
tcc	ctt	gta	tac	ata	ggc	gca	gac	agc	caa	caa	gtc	aat	gcg	gca	aca				
Ser	Leu	Val	Tyr	Ile	Gly	Ala	Asp	Ser	Gln	Gln	Val	Asn	Ala	Ala	Thr				
		35				40						45							
gaa	gct	acg	aac	gca	act	aat	aat	caa	agc	aca	caa	ggt	tct	caa	gca				
Glu	Ala	Thr	Asn	Ala	Thr	Asn	Asn	Gln	Ser	Thr	Gln	Val	Ser	Gln	Ala				
		50				55					60								
aca	tca	caa	cca	att	aat	ttc	caa	gtg	caa	aaa	gat	ggc	tct	tca	gag				
Thr	Ser	Gln	Pro	Ile	Asn	Phe	Gln	Val	Gln	Lys	Asp	Gly	Ser	Ser	Glu				
		65			70				75					80					
aag	tca	cac	atg	gat	gac	tat	atg	caa	cac	cct	ggg	aaa	gta	att	aaa				
Lys	Ser	His	Met	Asp	Asp	Tyr	Met	Gln	His	Pro	Gly	Lys	Val	Ile	Lys				
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Gln Asn Asn Lys Tyr Tyr Phe Gln Thr Val Leu Asn Asn Ala Ser Phe	
100 105 110	
tggtgg aaa gaa tac aaa ttt tac aat gca aac aat caa gaa tta gca aca	384
Trp Lys Glu Tyr Lys Phe Tyr Asn Ala Asn Asn Gln Glu Leu Ala Thr	
115 120 125	
act gtt gtt aac gat aat aaa aaa gcg gat act aga aca atc aat gtt	432
Thr Val Val Asn Asp Asn Lys Lys Ala Asp Thr Arg Thr Ile Asn Val	
130 135 140	
gca gtt gaa cct gga tat aag agc tta act act aaa gta cat att gtc	480
Ala Val Glu Pro Gly Tyr Lys Ser Leu Thr Thr Lys Val His Ile Val	
145 150 155 160	
gtg cca caa att aat tac aat cat aga tat act acg cat ttg gaa ttt	528
Val Pro Gln Ile Asn Tyr Asn His Arg Tyr Thr Thr His Leu Glu Phe	
165 170 175	
gaa aaa gca att cct aca tta gct gac gca gca aaa cca aac aat gtt	576
Glu Lys Ala Ile Pro Thr Leu Ala Asp Ala Ala Lys Pro Asn Asn Val	
180 185 190	
aaa ccg gtt caa cca aaa cca gct caa cct aaa aca cct act gag caa	624
Lys Pro Val Gln Pro Lys Pro Ala Gln Pro Lys Thr Pro Thr Glu Gln	
195 200 205	
act aaa cca gtt caa cct aaa gtt gaa aaa gtt aaa cct act gta act	672
Thr Lys Pro Val Gln Pro Lys Val Glu Lys Val Lys Pro Thr Val Thr	
210 215 220	
aca aca agc aaa gtt gaa gac aat cac tct act aaa gtt gta agt act	720
Thr Thr Ser Lys Val Glu Asp Asn His Ser Thr Lys Val Val Ser Thr	
225 230 235 240	
gac aca aca aaa gat caa act aaa aca caa act gct cat aca gtt aaa	768
Asp Thr Thr Lys Asp Gln Thr Lys Thr Gln Thr Ala His Thr Val Lys	
245 250 255	
aca gca caa act gct caa gaa caa aat aaa gtt caa aca cct gtt aaa	816
Thr Ala Gln Thr Ala Gln Glu Gln Asn Lys Val Gln Thr Pro Val Lys	
260 265 270	
gat gtt gca aca gcg aaa tct gaa agc aac aat caa gct gta agt gat	864
Asp Val Ala Thr Ala Lys Ser Glu Ser Asn Asn Gln Ala Val Ser Asp	
275 280 285	
aat aaa tca caa caa act aac aaa gtt aca aaa cat aac gaa acg cct	912
Asn Lys Ser Gln Gln Thr Asn Lys Val Thr Lys His Asn Glu Thr Pro	
290 295 300	
aaa caa gca tct aaa gct aaa gaa tta cca aaa act ggt tta act tca	960
Lys Gln Ala Ser Lys Ala Lys Glu Leu Pro Lys Thr Gly Leu Thr Ser	
305 310 315 320	
gtt gat aac ttt att agc aca gtt gcc ttc gca aca ctt gcc ctt tta	1008
Val Asp Asn Phe Ile Ser Thr Val Ala Phe Ala Thr Leu Ala Leu Leu	
325 330 335	
ggt tca tta tct tta tta ctt ttc aaa aga aaa gaa tct aaa ta	1052
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340 345 350	

<210> SEQ ID NO 12

<211> LENGTH: 350

<212> TYPE: PRT

<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 12

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20 25 30

Ser Leu Val Tyr Ile Gly Ala Asp Ser Gln Gln Val Asn Ala Ala Thr

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

<210> SEQ ID NO 13

<211> LENGTH: 1938

<212> TYPE: DNA

<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 13

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tttattttct tgtgtatttt tattgttttg gctttgagtg tgtccatcat ttgtgttttt      180
aatgtttgct ttttgaatg gagcactatc ttttgcttcg ctagaacctg ctgaagtgtg      240
aacaacatct tttgtgtgtt ttgatgaagc agttgttggt tttgcaacat tttgagtcgt      300
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agcaggcggt ttgtctttac ctgactcact agatgcgtea tttcttttt caacacttgg 420
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tggtgttggt ttgctaggcg tagctggagt agcttccttc ttagctgagt tatcttggtg 540
ttcttttttg ttagatttat cggatttggc ttttgtaaat gcttctttat caacgattct 600
gacatgggat tgtccatcat aatcaatcgt ttttacgtga actttaacga tagcatcata 660
tagagtttta ccttcaacat atgggaaaat aattgttcta gtattatttt tagcatcttt 720
gcttatagtt ctaacacggt gaccttcaac catgaaatct ttccagtaat cgtcattagt 780
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acctgtttct tcagctgctg cttgtgcttc gccatttgac attaataata aaagtgtact 1860
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<210> SEQ ID NO 14

<211> LENGTH: 645

<212> TYPE: PRT

<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 14

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20          25          30
Met Ser Asn Gly Glu Ala Gln Ala Ala Glu Glu Thr Gly Gly Thr
35          40          45
Asn Thr Glu Ala Gln Pro Lys Thr Glu Ala Val Ala Ser Pro Thr Thr
50          55          60
Thr Ser Glu Lys Ala Pro Glu Thr Lys Pro Val Ala Asn Ala Val Ser
65          70          75          80
Val Ser Asn Lys Glu Val Glu Ala Pro Thr Ser Glu Thr Lys Glu Ala
85          90          95

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Lys 100	Glu	Val	Lys	Glu	Val	Lys	Ala	Pro	Lys	Glu	Thr	Lys	Ala	Val	Lys
Pro 115	Ala	Ala	Lys	Ala	Thr	Asn	Asn	Thr	Tyr	Pro	Ile	Leu	Asn	Gln	Glu
Leu 130	Arg	Glu	Ala	Ile	Lys	Asn	Pro	Ala	Ile	Lys	Asp	Lys	Asp	His	Ser
Ala 145	Pro	Asn	Ser	Arg	Pro	Ile	Asp	Phe	Glu	Met	Lys	Lys	Glu	Asn	Gly
Glu	Gln	Gln	Phe	Tyr	His	Tyr	Ala	Ser	Ser	Val	Lys	Pro	Ala	Arg	Val
Ile	Phe	Thr	Asp	Ser	Lys	Pro	Glu	Ile	Glu	Leu	Gly	Leu	Gln	Ser	Gly
Gln	Phe	Trp	Arg	Lys	Phe	Glu	Val	Tyr	Glu	Gly	Asp	Lys	Lys	Leu	Pro
Ile	Lys	Leu	Val	Ser	Tyr	Asp	Thr	Val	Lys	Asp	Tyr	Ala	Tyr	Ile	Arg
Phe 225	Ser	Val	Ser	Asn	Gly	Thr	Lys	Ala	Val	Lys	Ile	Val	Ser	Ser	Thr
His	Phe	Asn	Asn	Lys	Glu	Glu	Lys	Tyr	Asp	Tyr	Thr	Leu	Met	Glu	Phe
Ala	Gln	Pro	Ile	Tyr	Asn	Ser	Ala	Asp	Lys	Phe	Lys	Thr	Glu	Glu	Asp
Tyr	Lys	Ala	Glu	Lys	Leu	Leu	Ala	Pro	Tyr	Lys	Lys	Ala	Lys	Thr	Leu
Glu	Arg	Gln	Val	Tyr	Glu	Leu	Asn	Lys	Ile	Gln	Asp	Lys	Leu	Pro	Glu
Lys 305	Leu	Lys	Ala	Glu	Tyr	Lys	Lys	Lys	Leu	Glu	Asp	Thr	Lys	Lys	Ala
Leu	Asp	Glu	Gln	Val	Lys	Ser	Ala	Ile	Thr	Glu	Phe	Gln	Asn	Val	Gln
Pro	Thr	Asn	Glu	Lys	Met	Thr	Asp	Leu	Gln	Asp	Thr	Lys	Tyr	Val	Val
Tyr	Glu	Ser	Val	Glu	Asn	Asn	Glu	Ser	Met	Met	Asp	Thr	Phe	Val	Lys
His	Pro	Ile	Lys	Thr	Gly	Met	Leu	Asn	Gly	Lys	Lys	Tyr	Met	Val	Met
Glu 385	Thr	Thr	Asn	Asp	Asp	Tyr	Trp	Lys	Asp	Phe	Met	Val	Glu	Gly	Gln
Arg	Val	Arg	Thr	Ile	Ser	Lys	Asp	Ala	Lys	Asn	Asn	Thr	Arg	Thr	Ile
Ile	Phe	Pro	Tyr	Val	Glu	Gly	Lys	Thr	Leu	Tyr	Asp	Ala	Ile	Val	Lys
Val	His	Val	Lys	Thr	Ile	Asp	Tyr	Asp	Gly	Gln	Tyr	His	Val	Arg	Ile
Val	Asp	Lys	Glu	Ala	Phe	Thr	Lys	Ala	Asn	Thr	Asp	Lys	Ser	Asn	Lys
Lys 465	Glu	Gln	Gln	Asp	Asn	Ser	Ala	Lys	Lys	Glu	Ala	Thr	Pro	Ala	Thr
Pro	Ser	Lys	Pro	Thr	Pro	Ser	Pro	Val	Glu	Lys	Glu	Ser	Gln	Lys	Gln
Asp	Ser	Gln	Lys	Asp	Asp	Asn	Lys	Gln	Leu	Pro	Ser	Val	Glu	Lys	Glu

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Asn Asp Ala Ser Ser Glu Ser Gly Lys Asp Lys Thr Pro Ala Thr Lys
 515 520 525
 Pro Thr Lys Gly Glu Val Glu Ser Ser Ser Thr Thr Pro Thr Lys Val
 530 535 540
 Val Ser Thr Thr Gln Asn Val Ala Lys Pro Thr Thr Ala Ser Ser Lys
 545 550 555 560
 Thr Thr Lys Asp Val Val Gln Thr Ser Ala Gly Ser Ser Glu Ala Lys
 565 570 575
 Asp Ser Ala Pro Leu Gln Lys Ala Asn Ile Lys Asn Thr Asn Asp Gly
 580 585 590
 His Thr Gln Ser Gln Asn Asn Lys Asn Thr Gln Glu Asn Lys Ala Lys
 595 600 605
 Ser Leu Pro Gln Thr Gly Glu Glu Ser Asn Lys Asp Met Thr Leu Pro
 610 615 620
 Leu Met Ala Leu Leu Ala Leu Ser Ser Ile Val Ala Phe Val Leu Pro
 625 630 635 640
 Arg Lys Arg Lys Asn
 645

<210> SEQ ID NO 15
 <211> LENGTH: 1353
 <212> TYPE: DNA
 <213> ORGANISM: Staphylococcus sp.
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (1) .. (1353)

<400> SEQUENCE: 15

ttg aaa aag aaa aac att tat tca att cgt aaa cta ggt gta ggt att	48
Met Lys Lys Lys Asn Ile Tyr Ser Ile Arg Lys Leu Gly Val Gly Ile	
1 5 10 15	
gca tct gta act tta ggt aca tta ctt ata tct ggt ggc gta aca cct	96
Ala Ser Val Thr Leu Gly Thr Leu Leu Ile Ser Gly Gly Val Thr Pro	
20 25 30	
gct gca aat gct gcg caa cac gat gaa gct caa caa aat gct ttt tat	144
Ala Ala Asn Ala Ala Gln His Asp Glu Ala Gln Gln Asn Ala Phe Tyr	
35 40 45	
caa gtg tta aat atg cct aac tta aac gct gat caa cgt aat ggt ttt	192
Gln Val Leu Asn Met Pro Asn Leu Asn Ala Asp Gln Arg Asn Gly Phe	
50 55 60	
atc caa agc ctt aaa gat gat cca agc caa agt gct aac gtt tta ggt	240
Ile Gln Ser Leu Lys Asp Asp Pro Ser Gln Ser Ala Asn Val Leu Gly	
65 70 75 80	
gaa gct caa aaa ctt aat gac tct caa gct cca aaa gct gat gcg caa	288
Glu Ala Gln Lys Leu Asn Asp Ser Gln Ala Pro Lys Ala Asp Ala Gln	
85 90 95	
caa aat aac ttc aac aaa gat caa caa agc gcc ttc tat gaa atc ttg	336
Gln Asn Asn Phe Asn Lys Asp Gln Gln Ser Ala Phe Tyr Glu Ile Leu	
100 105 110	
aac atg cct aac tta aac gaa gcg caa cgt aac ggc ttc att caa agt	384
Asn Met Pro Asn Leu Asn Glu Ala Gln Arg Asn Gly Phe Ile Gln Ser	
115 120 125	
ctt aaa gac gac cca agc caa agc act aat gtt tta ggt gaa gct aaa	432
Leu Lys Asp Asp Pro Ser Gln Ser Thr Asn Val Leu Gly Glu Ala Lys	
130 135 140	
aaa tta aac gaa tct caa gca ccg aaa gct gat aac aat ttc aac aaa	480
Lys Leu Asn Glu Ser Gln Ala Pro Lys Ala Asp Asn Asn Phe Asn Lys	
145 150 155 160	
gaa caa caa aat gct ttc tat gaa atc ttg aat atg cct aac tta aac	528

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Glu	Gln	Gln	Asn	Ala	Phe	Tyr	Glu	Ile	Leu	Asn	Met	Pro	Asn	Leu	Asn	
			165						170					175		
gaa	gaa	caa	cgc	aat	ggc	ttc	atc	caa	agc	tta	aaa	gat	gac	cca	agc	576
Glu	Glu	Gln	Arg	Asn	Gly	Phe	Ile	Gln	Ser	Leu	Lys	Asp	Asp	Pro	Ser	
			180					185					190			
caa	agt	gct	aac	cta	ttg	tca	gaa	gct	aaa	aag	tta	aat	gaa	tct	caa	624
Gln	Ser	Ala	Asn	Leu	Leu	Ser	Glu	Ala	Lys	Lys	Leu	Asn	Glu	Ser	Gln	
			195				200					205				
gca	ccg	aaa	gcg	gat	aac	aaa	ttc	aac	aaa	gaa	caa	caa	aat	gct	ttc	672
Ala	Pro	Lys	Ala	Asp	Asn	Lys	Phe	Asn	Lys	Glu	Gln	Gln	Asn	Ala	Phe	
			210				215					220				
tat	gaa	atc	tta	cat	tta	cct	aac	tta	aac	gaa	gaa	caa	cgt	aac	ggc	720
Tyr	Glu	Ile	Leu	His	Leu	Pro	Asn	Leu	Asn	Glu	Glu	Gln	Arg	Asn	Gly	
							230					235			240	
ttc	atc	caa	agc	ctt	aaa	gac	gat	cct	tca	gtg	agc	aaa	gaa	att	tta	768
Phe	Ile	Gln	Ser	Leu	Lys	Asp	Asp	Pro	Ser	Val	Ser	Lys	Glu	Ile	Leu	
							245								255	
gca	gaa	gct	aaa	aag	cta	aac	gat	gct	caa	gca	cca	aaa	gag	gaa	gac	816
Ala	Glu	Ala	Lys	Lys	Leu	Asn	Asp	Ala	Gln	Ala	Pro	Lys	Glu	Glu	Asp	
							260								270	
aac	aaa	aaa	cct	ggc	aaa	gaa	gac	ggc	aac	aaa	cct	ggc	aaa	gaa	gac	864
Asn	Lys	Lys	Pro	Gly	Lys	Glu	Asp	Gly	Asn	Lys	Pro	Gly	Lys	Glu	Asp	
							280								285	
ggc	aac	aag	cct	ggc	aaa	gaa	gac	aac	aaa	aaa	cct	ggc	aaa	gaa	gac	912
Gly	Asn	Lys	Pro	Gly	Lys	Glu	Asp	Asn	Lys	Lys	Pro	Gly	Lys	Glu	Asp	
							295								300	
ggc	aac	aag	cct	ggc	aaa	gaa	gac	aac	aac	aaa	cct	ggc	aaa	gaa	gac	960
Gly	Asn	Lys	Pro	Gly	Lys	Glu	Asp	Asn	Asn	Lys	Pro	Gly	Lys	Glu	Asp	
							310								320	
ggc	aac	aag	cct	ggc	aaa	gaa	gac	aac	aac	aag	cct	ggc	aaa	gaa	gac	1008
Gly	Asn	Lys	Pro	Gly	Lys	Glu	Asp	Asn	Asn	Lys	Pro	Gly	Lys	Glu	Asp	
							325								335	
ggc	aac	aag	cct	ggc	aaa	gaa	gac	ggc	aac	aaa	cct	ggc	aaa	gaa	gac	1056
Gly	Asn	Lys	Pro	Gly	Lys	Glu	Asp	Gly	Asn	Lys	Pro	Gly	Lys	Glu	Asp	
							340								350	
ggc	aac	gga	gta	cat	gtc	gtt	aaa	cct	ggc	gat	aca	gta	aat	gac	att	1104
Gly	Asn	Gly	Val	His	Val	Val	Lys	Pro	Gly	Asp	Thr	Val	Asn	Asp	Ile	
							355								365	
gca	aaa	gca	aac	ggc	act	act	gct	gac	aaa	att	gct	gca	gat	aac	aaa	1152
Ala	Lys	Ala	Asn	Gly	Thr	Thr	Ala	Asp	Lys	Ile	Ala	Ala	Asp	Asn	Lys	
							370								380	
tta	gct	gat	aaa	aac	atg	atc	aaa	cct	ggc	caa	gaa	ctt	gtt	gtt	gat	1200
Leu	Ala	Asp	Lys	Asn	Met	Ile	Lys	Pro	Gly	Gln	Glu	Leu	Val	Val	Asp	
							385								400	
aag	aag	caa	cca	gca	aac	cat	gca	gat	gct	aac	aaa	gct	caa	gca	tta	1248
Lys	Lys	Gln	Pro	Ala	Asn	His	Ala	Asp	Ala	Asn	Lys	Ala	Gln	Ala	Leu	
							405								415	
cca	gaa	act	ggc	gaa	gaa	aat	cca	ttc	atc	ggc	aca	act	gta	ttt	ggc	1296
Pro	Glu	Thr	Gly	Glu	Glu	Asn	Pro	Phe	Ile	Gly	Thr	Thr	Val	Phe	Gly	
							420								430	
gga	tta	tca	tta	gcc	tta	ggc	gca	gcg	tta	tta	gct	gga	cgt	cgt	cgc	1344
Gly	Leu	Ser	Leu	Ala	Leu	Gly	Ala	Ala	Leu	Leu	Ala	Gly	Arg	Arg	Arg	
							435								445	
gaa	cta	taa														1353
Glu	Leu															
							450									

<210> SEQ ID NO 16

<211> LENGTH: 450

<212> TYPE: PRT

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<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 16

Met Lys Lys Lys Asn Ile Tyr Ser Ile Arg Lys Leu Gly Val Gly Ile
1 5 10 15

Ala Ser Val Thr Leu Gly Thr Leu Leu Ile Ser Gly Gly Val Thr Pro
20 25 30

Ala Ala Asn Ala Ala Gln His Asp Glu Ala Gln Gln Asn Ala Phe Tyr
35 40 45

Gln Val Leu Asn Met Pro Asn Leu Asn Ala Asp Gln Arg Asn Gly Phe
50 55 60

Ile Gln Ser Leu Lys Asp Asp Pro Ser Gln Ser Ala Asn Val Leu Gly
65 70 75 80

Glu Ala Gln Lys Leu Asn Asp Ser Gln Ala Pro Lys Ala Asp Ala Gln
85 90 95

Gln Asn Asn Phe Asn Lys Asp Gln Gln Ser Ala Phe Tyr Glu Ile Leu
100 105 110

Asn Met Pro Asn Leu Asn Glu Ala Gln Arg Asn Gly Phe Ile Gln Ser
115 120 125

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

Lys Leu Asn Glu Ser Gln Ala Pro Lys Ala Asp Asn Asn Phe Asn Lys
145 150 155 160

Glu Gln Gln Asn Ala Phe Tyr Glu Ile Leu Asn Met Pro Asn Leu Asn
165 170 175

Glu Glu Gln Arg Asn Gly Phe Ile Gln Ser Leu Lys Asp Asp Pro Ser
180 185 190

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

Ala Pro Lys Ala Asp Asn Lys Phe Asn Lys Glu Gln Gln Asn Ala Phe
210 215 220

Tyr Glu Ile Leu His Leu Pro Asn Leu Asn Glu Glu Gln Arg Asn Gly
225 230 235 240

Phe Ile Gln Ser Leu Lys Asp Asp Pro Ser Val Ser Lys Glu Ile Leu
245 250 255

Ala Glu Ala Lys Lys Leu Asn Asp Ala Gln Ala Pro Lys Glu Glu Asp
260 265 270

Asn Lys Lys Pro Gly Lys Glu Asp Gly Asn Lys Pro Gly Lys Glu Asp
275 280 285

Gly Asn Lys Pro Gly Lys Glu Asp Asn Lys Lys Pro Gly Lys Glu Asp
290 295 300

Gly Asn Lys Pro Gly Lys Glu Asp Asn Asn Lys Pro Gly Lys Glu Asp
305 310 315 320

Gly Asn Lys Pro Gly Lys Glu Asp Asn Asn Lys Pro Gly Lys Glu Asp
325 330 335

Gly Asn Lys Pro Gly Lys Glu Asp Gly Asn Lys Pro Gly Lys Glu Asp
340 345 350

Gly Asn Gly Val His Val Val Lys Pro Gly Asp Thr Val Asn Asp Ile
355 360 365

Ala Lys Ala Asn Gly Thr Thr Ala Asp Lys Ile Ala Ala Asp Asn Lys
370 375 380

Leu Ala Asp Lys Asn Met Ile Lys Pro Gly Gln Glu Leu Val Val Asp
385 390 395 400

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aag Lys 225	tta Leu	gaa Glu	aag Lys	act Thr	aca Thr 230	ttt Phe	gac Asp	cct Pro	aat Asn	caa Gln 235	agt Ser	ggt Gly	aac Asn	aca Thr 240	ttt Phe 240	720
atg Met	gcg Ala	gca Ala	aat Asn	ttt Phe 245	aca Thr	gtg Val	aca Thr	gat Asp	aaa Lys 250	gtg Val	aaa Lys	tca Ser	ggg Gly	gat Asp 255	tat Tyr 255	768
ttt Phe	aca Thr	gcg Ala	aag Lys 260	tta Leu	cca Pro	gat Asp	agt Ser	tta Leu 265	act Thr	ggt Gly	aat Asn	gga Gly	gac Asp 270	gtg Val	gat Asp	816
tat Tyr	tct Ser	aat Asn 275	tca Ser	aat Asn	aat Asn	acg Thr	atg Met 280	cca Pro	att Ile	gca Ala	gac Asp 285	att Ile	aaa Lys	agt Ser	acg Thr	864
aat Asn 290	ggc Gly	gat Asp	gtt Val	gta Val	gct Ala	aaa Lys 295	gca Ala	aca Thr	tat Tyr	gat Asp	atc Ile 300	ttg Leu	act Thr	aag Lys	acg Thr	912
tat Tyr 305	aca Thr	ttt Phe	gtc Val	ttt Phe	aca Thr 310	gat Asp	tat Tyr	gta Val	aat Asn	aat Asn 315	aaa Lys	gaa Glu	aat Asn	att Ile	aac Asn 320	960
gga Gly	caa Gln	ttt Phe	tca Ser 325	tta Leu	cct Pro	tta Leu	ttt Phe	aca Thr	gac Asp 330	cga Arg	gca Ala	aag Lys	gca Ala	cct Pro 335	aaa Lys	1008
tca Ser	gga Gly	aca Thr	tat Tyr 340	gat Asp	gcg Ala	aat Asn	att Ile	aat Asn 345	att Ile	gcg Ala	gat Asp	gaa Glu	atg Met 350	ttt Phe	aat Asn	1056
aat Asn	aaa Lys	att Ile 355	act Thr	tat Tyr	aac Asn	tat Tyr	agt Ser 360	tcg Ser	cca Pro	att Ile	gca Ala	gga Gly	att Ile 365	gat Asp	aaa Lys	1104
cca Pro 370	aat Asn	ggc Gly	gcg Ala	aac Asn	att Ile 375	tct Ser 375	tct Ser	caa Gln	att Ile	att Ile 380	ggt Gly	gta Val	gat Asp	aca Thr	gct Ala	1152
tca Ser 385	ggt Gly	caa Gln	aac Asn	aca Thr	tac Tyr 390	aag Lys	caa Gln	aca Thr	gta Val	ttt Phe 395	ggt Val	aac Asn	cct Pro	aag Lys	caa Gln 400	1200
cga Arg	gtt Val	tta Leu	ggt Gly	aat Asn 405	acg Thr	tgg Trp	gtg Val	tat Tyr	att Ile 410	aaa Lys	ggc Gly	tac Tyr	caa Gln	gat Asp 415	aaa Lys	1248
atc Ile	gaa Glu	gaa Glu	agt Ser 420	agc Ser	ggt Gly	aaa Lys	gta Val	agt Ser 425	gct Ala	aca Thr	gat Asp	aca Thr	aaa Lys 430	ctg Leu	aga Arg	1296
att Ile	ttt Phe	gaa Glu 435	gtg Val	aat Asn	gat Asp	aca Thr	tct Ser 440	aaa Lys	tta Leu	tca Ser	gat Asp	agc Tyr 445	tac Tyr	tat Tyr	gca Ala	1344
gat Asp 450	cca Pro	aat Asn	gac Asp	tct Ser	aac Asn	ctt Leu 455	aaa Lys	gaa Glu	gta Val	aca Thr	gac Asp 460	caa Gln	ttt Phe	aaa Lys	aat Asn	1392
aga Arg 465	atc Ile	tat Tyr	tat Tyr	gag Glu	cat His 470	cca Pro	aat Asn	gta Val	gct Ala	agt Ser 475	att Ile	aaa Lys	ttt Phe	ggt Gly	gat Asp 480	1440
att Ile	act Thr	aaa Lys	aca Thr	tat Tyr 485	gta Val	gta Val	tta Leu	gta Val	gaa Glu 490	ggg Gly	cat His	tac Tyr	gac Asp	aat Asn 495	aca Thr	1488
ggt Gly	aag Lys	aac Asn	tta Leu 500	aaa Lys	act Thr	cag Gln	gtt Val	att Ile 505	caa Gln	gaa Glu	aat Asn	gtt Val	gat Asp 510	cct Pro	gta Val	1536
aca Thr	aat Asn	aga Arg	gac Asp	tac Tyr	agt Ser	att Ile	ttc Phe 520	ggt Gly	tgg Trp	aat Asn	aat Asn	gag Glu 525	aat Asn	gtt Val	gta Val	1584
cgt Arg	tat Tyr 530	ggt Gly	ggt Gly	gga Gly	agt Ser	gct Ala 535	gat Asp	ggt Gly	gat Asp	tca Ser	gca Ala 540	gta Val	aat Asn	ccg Pro	aaa Lys	1632

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gac cca act cca ggg ccg ccg gtt gac cca gaa cca agt cca gac cca Asp Pro Thr Pro Gly Pro Pro Val Asp Pro Glu Pro Ser Pro Asp Pro 545 550 555 560	1680
gaa cca gaa cca acg cca gat cca gaa cca agt cca gac cca gaa ccg Glu Pro Glu Pro Thr Pro Asp Pro Glu Pro Ser Pro Asp Pro Glu Pro 565 570 575	1728
gaa cca agc cca gac ccg gat ccg gat tcg gat tca gac agt gac tca Glu Pro Ser Pro Asp Pro Asp Pro Asp Ser Asp Ser Asp Ser Asp Ser 580 585 590	1776
ggc tca gac agc gac tca ggt tca gat agc gac tca gaa tca gat agc Gly Ser Asp Ser Asp Ser Gly Ser Asp Ser Asp Ser Glu Ser Asp Ser 595 600 605	1824
gat tcg gat tca gac agt gat tca gat tca gac agc gac tca gaa tca Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Glu Ser 610 615 620	1872
gat agc gat tca gaa tca gat agc gac tca gat tca gat agc gat tca Asp Ser Asp Ser Glu Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 625 630 635 640	1920
gat tca gat agc gat tca gaa tca gat agc gat tcg gat tca gac agt Asp Ser Asp Ser Asp Ser Glu Ser Asp Ser Asp Ser Asp Ser Asp Ser 645 650 655	1968
gat tca gat tca gac agc gac tca gaa tca gat agc gac tca gaa tca Asp Ser Asp Ser Asp Ser Asp Ser Glu Ser Asp Ser Asp Ser Glu Ser 660 665 670	2016
gat agt gag tca gat tca gac agt gac tcg gac tca gac agt gat tca Asp Ser Glu Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 675 680 685	2064
gac tca gat agc gat tca gac tca gat agc gat tca gac tca gac agc Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 690 695 700	2112
gat tca gat tca gac agc gac tca gaa tca gac agc gac tca gac tca Asp Ser Asp Ser Asp Ser Asp Ser Glu Ser Asp Ser Asp Ser Asp Ser 705 710 715 720	2160
gat agc gac tca gac tca gac agc gac tca gat tca gat agc gat tca Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 725 730 735	2208
gac tca gac agc gac tca gac tca gac agc gac tca gac tca gat agc Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 740 745 750	2256
gat tca gac tca gac agc gac tca gat tca gat agc gat tcg gac tca Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 755 760 765	2304
gac agc gat tca gat tca gac agc gac tca gac tcg gat agc gat tca Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 770 775 780	2352
gat tca gac agc gac tca gac tcg gat agc gac tcg gat tca gat agt Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser 785 790 795 800	2400
gac tcc gat tca aga gtt aca cca cca aat aat gaa cag aaa gca cca Asp Ser Asp Ser Arg Val Thr Pro Pro Asn Asn Glu Gln Lys Ala Pro 805 810 815	2448
tca aat cct aaa ggt gaa gta aac cat tct aat aag gta tca aaa caa Ser Asn Pro Lys Gly Glu Val Asn His Ser Asn Lys Val Ser Lys Gln 820 825 830	2496
cac aaa act gat gct tta cca gaa aca gga gat aag agc gaa aac aca His Lys Thr Asp Ala Leu Pro Glu Thr Gly Asp Lys Ser Glu Asn Thr 835 840 845	2544
aat gca act tta ttt ggt gca atg atg gca tta tta gga tca tta cta Asn Ala Thr Leu Phe Gly Ala Met Met Ala Leu Leu Gly Ser Leu Leu	2592

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850	855	860	
ttg ttt aga aaa cgc aag caa gat cat aaa gaa aaa gcg taa			2634
Leu Phe Arg Lys Arg Lys Gln Asp His Lys Glu Lys Ala			
865	870	875	

<210> SEQ ID NO 18
 <211> LENGTH: 877
 <212> TYPE: PRT
 <213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 18

Met	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				
Arg	Val	Leu	Gly	Asn	Thr	Trp	Val	Tyr	Ile	Lys	Gly	Tyr	Gln	Asp	Lys	
							405					410				
Ile	Glu	Glu	Ser	Ser	Gly	Lys	Val	Ser	Ala	Thr	Asp	Thr	Lys	Leu	Arg	
							420					425				
Ile	Phe	Glu	Val	Asn	Asp	Thr	Ser	Lys	Leu	Ser	Asp	Ser	Tyr	Tyr	Ala	
							435					440				
Asp	Pro	Asn	Asp	Ser	Asn	Leu	Lys	Glu	Val	Thr	Asp	Gln	Phe	Lys	Asn	
							450					455				
Arg	Ile	Tyr	Tyr	Glu	His	Pro	Asn	Val	Ala	Ser	Ile	Lys	Phe	Gly	Asp	
							465					470				
Ile	Thr	Lys	Thr	Tyr	Val	Val	Leu	Val	Glu	Gly	His	Tyr	Asp	Asn	Thr	
							485					490				
Gly	Lys	Asn	Leu	Lys	Thr	Gln	Val	Ile	Gln	Glu	Asn	Val	Asp	Pro	Val	
							500					505				
Thr	Asn	Arg	Asp	Tyr	Ser	Ile	Phe	Gly	Trp	Asn	Asn	Glu	Asn	Val	Val	
							515					520				
Arg	Tyr	Gly	Gly	Gly	Ser	Ala	Asp	Gly	Asp	Ser	Ala	Val	Asn	Pro	Lys	
							530					535				
Asp	Pro	Thr	Pro	Gly	Pro	Pro	Val	Asp	Pro	Glu	Pro	Ser	Pro	Asp	Pro	
							545					550				
Glu	Pro	Glu	Pro	Thr	Pro	Asp	Pro	Glu	Pro	Ser	Pro	Asp	Pro	Glu	Pro	
							565					570				
Glu	Pro	Ser	Pro	Asp	Pro	Asp	Pro	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	
							580					585				
Gly	Ser	Asp	Ser	Asp	Ser	Gly	Ser	Asp	Ser	Asp	Ser	Glu	Ser	Asp	Ser	
							595					600				
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Glu	Ser	
							610					615				
Asp	Ser	Asp	Ser	Glu	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	
							625					630				
Asp	Ser	Asp	Ser	Asp	Ser	Glu	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	
							645					650				
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Glu	Ser	Asp	Ser	Asp	Ser	Asp	Ser	
							660					665				
Asp	Ser	Glu	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	
							675					680				
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	
							690					695				
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Glu	Ser	Asp	Ser	Asp	Ser	Asp	Ser	
							705					710				
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	
							725					730				
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	
							740					745				
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	
							755					760</				

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Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
 770 775 780
 Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
 785 790 795 800
 Asp Ser Asp Ser Arg Val Thr Pro Pro Asn Asn Glu Gln Lys Ala Pro
 805 810 815
 Ser Asn Pro Lys Gly Glu Val Asn His Ser Asn Lys Val Ser Lys Gln
 820 825 830
 His Lys Thr Asp Ala Leu Pro Glu Thr Gly Asp Lys Ser Glu Asn Thr
 835 840 845
 Asn Ala Thr Leu Phe Gly Ala Met Met Ala Leu Leu Gly Ser Leu Leu
 850 855 860
 Leu Phe Arg Lys Arg Lys Gln Asp His Lys Glu Lys Ala
 865 870 875

<210> SEQ ID NO 19
 <211> LENGTH: 684
 <212> TYPE: DNA
 <213> ORGANISM: Staphylococcus sp.
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (1)..(684)

<400> SEQUENCE: 19

ttg aaa aat att tta aaa gtt ttt aat aca acg att tta gcg tta att	48
Met Lys Asn Ile Leu Lys Val Phe Asn Thr Thr Ile Leu Ala Leu Ile	
1 5 10 15	
atc atc atc gcg aca ttc agt aat tct gca aat gcc gca gat agc ggt	96
Ile Ile Ile Ala Thr Phe Ser Asn Ser Ala Asn Ala Ala Asp Ser Gly	
20 25 30	
act ttg aat tat gag gtt tac aaa tac aat acc aat gac acg tca att	144
Thr Leu Asn Tyr Glu Val Tyr Lys Tyr Asn Thr Asn Asp Thr Ser Ile	
35 40 45	
gct aat gac tat ttt aat aaa ccg gca aag tac att aag aaa aat ggt	192
Ala Asn Asp Tyr Phe Asn Lys Pro Ala Lys Tyr Ile Lys Lys Asn Gly	
50 55 60	
aaa ttg tat gtt caa ata act gtc aac cac agt cat tgg att act gga	240
Lys Leu Tyr Val Gln Ile Thr Val Asn His Ser His Trp Ile Thr Gly	
65 70 75 80	
atg agt atc gaa gga cat aaa gaa aat att att agt aaa aac act gcc	288
Met Ser Ile Glu Gly His Lys Glu Asn Ile Ile Ser Lys Asn Thr Ala	
85 90 95	
aaa gat gaa cgc act tct gaa ttt gaa gta agt aag ttg aac ggt aaa	336
Lys Asp Glu Arg Thr Ser Glu Phe Glu Val Ser Lys Leu Asn Gly Lys	
100 105 110	
ata gat gga aaa att gac gtt tat atc gat gaa aaa gta aat gga aag	384
Ile Asp Gly Lys Ile Asp Val Tyr Ile Asp Glu Lys Val Asn Gly Lys	
115 120 125	
cca ttc aaa tat gac cat cat tac aac att aca tat aaa ttt aat gga	432
Pro Phe Lys Tyr Asp His His Tyr Asn Ile Thr Tyr Lys Phe Asn Gly	
130 135 140	
cca act gat gta gca ggt gct aat gca cca ggt aaa gat gat aaa aat	480
Pro Thr Asp Val Ala Gly Ala Asn Ala Pro Gly Lys Asp Asp Lys Asn	
145 150 155 160	
tct gct tca ggt agt gac aaa gga tct gat gga acg act act ggt caa	528
Ser Ala Ser Gly Ser Asp Lys Gly Ser Asp Gly Thr Thr Thr Gly Gln	
165 170 175	
agt gaa tct aat agt tcg aat aaa gac aaa gta gaa aat cca caa aca	576
Ser Glu Ser Asn Ser Ser Asn Lys Asp Lys Val Glu Asn Pro Gln Thr	
180 185 190	

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aat gct ggt aca cct gca tat ata tat gca ata cca gtt gca tcc tta      624
Asn Ala Gly Thr Pro Ala Tyr Ile Tyr Ala Ile Pro Val Ala Ser Leu
      195                      200                      205

gca tta tta atc gca atc aca ttg ttt gtt aga aaa aaa tct aaa ggc      672
Ala Leu Leu Ile Ala Ile Thr Leu Phe Val Arg Lys Lys Ser Lys Gly
      210                      215                      220

aat gtg gaa taa      684
Asn Val Glu
225

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<210> SEQ ID NO 20
<211> LENGTH: 227
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

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<400> SEQUENCE: 20

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Met Lys Asn Ile Leu Lys Val Phe Asn Thr Thr Ile Leu Ala Leu Ile
1                      5                      10                      15

Ile Ile Ile Ala Thr Phe Ser Asn Ser Ala Asn Ala Ala Asp Ser Gly
      20                      25                      30

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

Ala Asn Asp Tyr Phe Asn Lys Pro Ala Lys Tyr Ile Lys Lys Asn Gly
      50                      55                      60

Lys Leu Tyr Val Gln Ile Thr Val Asn His Ser His Trp Ile Thr Gly
      65                      70                      75                      80

Met Ser Ile Glu Gly His Lys Glu Asn Ile Ile Ser Lys Asn Thr Ala
      85                      90                      95

Lys Asp Glu Arg Thr Ser Glu Phe Glu Val Ser Lys Leu Asn Gly Lys
      100                     105                     110

Ile Asp Gly Lys Ile Asp Val Tyr Ile Asp Glu Lys Val Asn Gly Lys
      115                     120                     125

Pro Phe Lys Tyr Asp His His Tyr Asn Ile Thr Tyr Lys Phe Asn Gly
      130                     135                     140

Pro Thr Asp Val Ala Gly Ala Asn Ala Pro Gly Lys Asp Asp Lys Asn
      145                     150                     155                     160

Ser Ala Ser Gly Ser Asp Lys Gly Ser Asp Gly Thr Thr Thr Gly Gln
      165                     170                     175

Ser Glu Ser Asn Ser Ser Asn Lys Asp Lys Val Glu Asn Pro Gln Thr
      180                     185                     190

Asn Ala Gly Thr Pro Ala Tyr Ile Tyr Ala Ile Pro Val Ala Ser Leu
      195                     200                     205

Ala Leu Leu Ile Ala Ile Thr Leu Phe Val Arg Lys Lys Ser Lys Gly
      210                     215                     220

Asn Val Glu
225

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<210> SEQ ID NO 21
<211> LENGTH: 1908
<212> TYPE: DNA
<213> ORGANISM: Staphylococcus sp.
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(1908)

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<400> SEQUENCE: 21

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atg gct aaa tat cga ggg aaa ccg ttt caa tta tat gta aag tta tcg      48
Met Ala Lys Tyr Arg Gly Lys Pro Phe Gln Leu Tyr Val Lys Leu Ser

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1	5	10	15	
tgt tcg aca atg atg gcg tca agt atc att tta acg aat atc ttg ccg				96
Cys Ser Thr Met Met Ala Ser Ser Ile Ile Leu Thr Asn Ile Leu Pro				
	20	25	30	
tac gat gcc caa gct gca tct gaa aag gat act gaa att tca aaa gag				144
Tyr Asp Ala Gln Ala Ala Ser Glu Lys Asp Thr Glu Ile Ser Lys Glu				
	35	40	45	
ata tta tct aag caa gat tta tta gac aaa gtt gac aaa gca att cgt				192
Ile Leu Ser Lys Gln Asp Leu Leu Asp Lys Val Asp Lys Ala Ile Arg				
	50	55	60	
caa att gag caa tta aaa cag tta tcg gct tca tct aaa gca cat tat				240
Gln Ile Glu Gln Leu Lys Gln Leu Ser Ala Ser Ser Lys Ala His Tyr				
	65	70	75	80
aaa gca caa cta aat gaa gcg aaa aca gca tcg caa ata gat gaa atc				288
Lys Ala Gln Leu Asn Glu Ala Lys Thr Ala Ser Gln Ile Asp Glu Ile				
	85	90	95	
ata aaa cga gct aat gag ttg gat agc aaa gaa aat aaa agt tct cac				336
Ile Lys Arg Ala Asn Glu Leu Asp Ser Lys Glu Asn Lys Ser Ser His				
	100	105	110	
act gaa atg aac ggt caa agt gat ata gac agt aaa tta gat caa ttg				384
Thr Glu Met Asn Gly Gln Ser Asp Ile Asp Ser Lys Leu Asp Gln Leu				
	115	120	125	
ctt aaa gat tta aat gag gtt tct tca aat gtt gat agg ggt caa caa				432
Leu Lys Asp Leu Asn Glu Val Ser Ser Asn Val Asp Arg Gly Gln Gln				
	130	135	140	
agt gcc gag gac gat ctt aat gca atg aaa aat gat atg tca caa acg				480
Ser Gly Glu Asp Asp Leu Asn Ala Met Lys Asn Asp Met Ser Gln Thr				
	145	150	155	160
gct aca aca aaa tat gga gaa aaa gat gat aaa aat gat gaa gca atg				528
Ala Thr Thr Lys Tyr Gly Glu Lys Asp Asp Lys Asn Asp Glu Ala Met				
	165	170	175	
gta aat aag gcg tta gaa gac cta gac cat ttg aat cag caa ata cac				576
Val Asn Lys Ala Leu Glu Asp Leu Asp His Leu Asn Gln Gln Ile His				
	180	185	190	
aaa tcg aaa gat gca ttg aaa gat gca tcg aaa gat ccg gca gtg tct				624
Lys Ser Lys Asp Ala Leu Lys Asp Ala Ser Lys Asp Pro Ala Val Ser				
	195	200	205	
aca aca gat agt aat cat gaa gta gct aaa acg cca aat aat gat ggt				672
Thr Thr Asp Ser Asn His Glu Val Ala Lys Thr Pro Asn Asn Asp Gly				
	210	215	220	
tct gga cat gtt gtg tta aat aaa ttt ctt tca aat gaa gag aat caa				720
Ser Gly His Val Val Leu Asn Lys Phe Leu Ser Asn Glu Glu Asn Gln				
	225	230	235	240
agc cat agt aat caa ctc act gat aaa tta caa gga agc gat aaa att				768
Ser His Ser Asn Gln Leu Thr Asp Lys Leu Gln Gly Ser Asp Lys Ile				
	245	250	255	
aat cat gct atg att gaa aaa ttg gct aaa agt aat gcc tca acg caa				816
Asn His Ala Met Ile Glu Lys Leu Ala Lys Ser Asn Ala Ser Thr Gln				
	260	265	270	
cat tac aca tat cat aaa ctg aat acg tta caa tct tta gat caa cgt				864
His Tyr Thr Tyr His Lys Leu Asn Thr Leu Gln Ser Leu Asp Gln Arg				
	275	280	285	
att gca aat acg caa ctt cct aaa aat caa aaa tca gac tta atg agc				912
Ile Ala Asn Thr Gln Leu Pro Lys Asn Gln Lys Ser Asp Leu Met Ser				
	290	295	300	
gaa gta aat aag acg aaa gag cgt ata aaa agt caa cga aat att att				960
Glu Val Asn Lys Thr Lys Glu Arg Ile Lys Ser Gln Arg Asn Ile Ile				
	305	310	315	320
ttg gaa gaa ctt gca cgt act gat gat aaa aag tat gct aca caa agc				1008

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Leu	Glu	Glu	Leu	Ala	Arg	Thr	Asp	Asp	Lys	Lys	Tyr	Ala	Thr	Gln	Ser	
				325					330					335		
att	tta	gaa	agt	ata	ttt	aat	aaa	gac	gag	gca	gat	aaa	att	cta	aaa	1056
Ile	Leu	Glu	Ser	Ile	Phe	Asn	Lys	Asp	Glu	Ala	Asp	Lys	Ile	Leu	Lys	
			340					345					350			
gat	ata	cgt	gtt	gat	ggg	aaa	aca	gat	caa	caa	att	gca	gat	caa	att	1104
Asp	Ile	Arg	Val	Asp	Gly	Lys	Thr	Asp	Gln	Gln	Ile	Ala	Asp	Gln	Ile	
		355					360					365				
act	cgt	cat	att	gat	caa	cta	tct	ctg	aca	acg	agt	gat	gat	tta	tta	1152
Thr	Arg	His	Ile	Asp	Gln	Leu	Ser	Leu	Thr	Thr	Ser	Asp	Asp	Leu	Leu	
	370						375					380				
acg	tca	ttg	att	gat	caa	tca	caa	gat	aag	tcg	cta	ttg	att	tct	caa	1200
Thr	Ser	Leu	Ile	Asp	Gln	Ser	Gln	Asp	Lys	Ser	Leu	Leu	Ile	Ser	Gln	
	385				390					395					400	
atc	tta	caa	acg	aaa	tta	gga	aaa	gct	gaa	gca	gat	aaa	ttg	gct	aaa	1248
Ile	Leu	Gln	Thr	Lys	Leu	Gly	Lys	Ala	Glu	Ala	Asp	Lys	Leu	Ala	Lys	
			405					410						415		
gat	tggt	acg	aat	aaa	gga	tta	tca	aat	cgc	caa	atc	gtt	gac	caa	ttg	1296
Asp	Trp	Thr	Asn	Lys	Gly	Leu	Ser	Asn	Arg	Gln	Ile	Val	Asp	Gln	Leu	
			420					425					430			
aag	aaa	cat	ttt	gca	tca	act	ggc	gac	acg	tct	tca	gat	gat	ata	tta	1344
Lys	Lys	His	Phe	Ala	Ser	Thr	Gly	Asp	Thr	Ser	Ser	Asp	Asp	Ile	Leu	
		435					440					445				
aaa	gca	att	ttg	aat	aat	gcc	aaa	gat	aaa	aag	caa	gca	att	gaa	acg	1392
Lys	Ala	Ile	Leu	Asn	Asn	Ala	Lys	Asp	Lys	Lys	Gln	Ala	Ile	Glu	Thr	
		450				455					460					
att	tta	gca	aca	cgt	ata	gaa	aga	caa	aag	gca	aaa	tta	ctg	gca	gat	1440
Ile	Leu	Ala	Thr	Arg	Ile	Glu	Arg	Gln	Lys	Ala	Lys	Leu	Leu	Ala	Asp	
	465				470				475					480		
tta	att	act	aaa	ata	gaa	aca	gat	caa	aat	aaa	att	ttt	aat	tta	gtt	1488
Leu	Ile	Thr	Lys	Ile	Glu	Thr	Asp	Gln	Asn	Lys	Ile	Phe	Asn	Leu	Val	
			485					490						495		
aaa	tcg	gca	ttg	aat	ggg	aaa	gcg	gat	gat	tta	ttg	aat	tta	caa	aag	1536
Lys	Ser	Ala	Leu	Asn	Gly	Lys	Ala	Asp	Asp	Leu	Leu	Asn	Leu	Gln	Lys	
		500						505					510			
aga	ctc	aat	caa	acg	aaa	aaa	gat	ata	gac	tat	att	tta	tca	cca	ata	1584
Arg	Leu	Asn	Gln	Thr	Lys	Lys	Asp	Ile	Asp	Tyr	Ile	Leu	Ser	Pro	Ile	
		515					520					525				
gta	aat	cgt	cca	agt	tta	cta	gat	cga	ttg	aat	aaa	aat	ggg	aaa	aca	1632
Val	Asn	Arg	Pro	Ser	Leu	Leu	Asp	Arg	Leu	Asn	Lys	Asn	Gly	Lys	Thr	
		530				535					540					
acg	gat	tta	aat	aag	tta	gca	aat	tta	atg	aat	caa	gga	tca	aat	tta	1680
Thr	Asp	Leu	Asn	Lys	Leu	Ala	Asn	Leu	Met	Asn	Gln	Gly	Ser	Asn	Leu	
	545				550				555					560		
tta	gac	agt	att	cca	gat	ata	ccc	aca	cca	aag	cca	gaa	aag	acg	tta	1728
Leu	Asp	Ser	Ile	Pro	Asp	Ile	Pro	Thr	Pro	Lys	Pro	Glu	Lys	Thr	Leu	
			565					570						575		
aca	ctt	ggg	aaa	ggg	aat	gga	ttg	tta	agt	gga	tta	tta	aat	gct	gat	1776
Thr	Leu	Gly	Lys	Gly	Asn	Gly	Leu	Leu	Ser	Gly	Leu	Leu	Asn	Ala	Asp	
		580					585						590			
ggg	aat	gta	tct	ttg	cct	aaa	gcg	ggg	gaa	acg	ata	aaa	gaa	cat	tggt	1824
Gly	Asn	Val	Ser	Leu	Pro	Lys	Ala	Gly	Glu	Thr	Ile	Lys	Glu	His	Trp	
		595					600					605				
ttg	ccg	ata	tct	gta	att	gtt	ggg	gca	atg	ggg	gta	cta	atg	att	tggt	1872
Leu	Pro	Ile	Ser	Val	Ile	Val	Gly	Ala	Met	Gly	Val	Leu	Met	Ile	Trp	
	610					615					620					
tta	tca	cga	cgc	aat	aag	ttg	aaa	aat	aaa	gca	taa					1908
Leu	Ser	Arg	Arg	Asn	Lys	Leu	Lys	Asn	Lys	Ala						
		625			630				635							

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<210> SEQ ID NO 22
<211> LENGTH: 635
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 22
Met Ala Lys Tyr Arg Gly Lys Pro Phe Gln Leu Tyr Val Lys Leu Ser
1      5      10      15
Cys Ser Thr Met Met Ala Ser Ser Ile Ile Leu Thr Asn Ile Leu Pro
20      25      30
Tyr Asp Ala Gln Ala Ala Ser Glu Lys Asp Thr Glu Ile Ser Lys Glu
35      40      45
Ile Leu Ser Lys Gln Asp Leu Leu Asp Lys Val Asp Lys Ala Ile Arg
50      55      60
Gln Ile Glu Gln Leu Lys Gln Leu Ser Ala Ser Ser Lys Ala His Tyr
65      70      75      80
Lys Ala Gln Leu Asn Glu Ala Lys Thr Ala Ser Gln Ile Asp Glu Ile
85      90      95
Ile Lys Arg Ala Asn Glu Leu Asp Ser Lys Glu Asn Lys Ser Ser His
100     105     110
Thr Glu Met Asn Gly Gln Ser Asp Ile Asp Ser Lys Leu Asp Gln Leu
115     120     125
Leu Lys Asp Leu Asn Glu Val Ser Ser Asn Val Asp Arg Gly Gln Gln
130     135     140
Ser Gly Glu Asp Asp Leu Asn Ala Met Lys Asn Asp Met Ser Gln Thr
145     150     155     160
Ala Thr Thr Lys Tyr Gly Glu Lys Asp Asp Lys Asn Asp Glu Ala Met
165     170     175
Val Asn Lys Ala Leu Glu Asp Leu Asp His Leu Asn Gln Gln Ile His
180     185     190
Lys Ser Lys Asp Ala Leu Lys Asp Ala Ser Lys Asp Pro Ala Val Ser
195     200     205
Thr Thr Asp Ser Asn His Glu Val Ala Lys Thr Pro Asn Asn Asp Gly
210     215     220
Ser Gly His Val Val Leu Asn Lys Phe Leu Ser Asn Glu Glu Asn Gln
225     230     235     240
Ser His Ser Asn Gln Leu Thr Asp Lys Leu Gln Gly Ser Asp Lys Ile
245     250     255
Asn His Ala Met Ile Glu Lys Leu Ala Lys Ser Asn Ala Ser Thr Gln
260     265     270
His Tyr Thr Tyr His Lys Leu Asn Thr Leu Gln Ser Leu Asp Gln Arg
275     280     285
Ile Ala Asn Thr Gln Leu Pro Lys Asn Gln Lys Ser Asp Leu Met Ser
290     295     300
Glu Val Asn Lys Thr Lys Glu Arg Ile Lys Ser Gln Arg Asn Ile Ile
305     310     315     320
Leu Glu Glu Leu Ala Arg Thr Asp Asp Lys Lys Tyr Ala Thr Gln Ser
325     330     335
Ile Leu Glu Ser Ile Phe Asn Lys Asp Glu Ala Asp Lys Ile Leu Lys
340     345     350
Asp Ile Arg Val Asp Gly Lys Thr Asp Gln Gln Ile Ala Asp Gln Ile
355     360     365
Thr Arg His Ile Asp Gln Leu Ser Leu Thr Thr Ser Asp Asp Leu Leu
370     375     380

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Thr Ser Leu Ile Asp Gln Ser Gln Asp Lys Ser Leu Leu Ile Ser Gln
 385 390 395 400
 Ile Leu Gln Thr Lys Leu Gly Lys Ala Glu Ala Asp Lys Leu Ala Lys
 405 410 415
 Asp Trp Thr Asn Lys Gly Leu Ser Asn Arg Gln Ile Val Asp Gln Leu
 420 425 430
 Lys Lys His Phe Ala Ser Thr Gly Asp Thr Ser Ser Asp Asp Ile Leu
 435 440 445
 Lys Ala Ile Leu Asn Asn Ala Lys Asp Lys Lys Gln Ala Ile Glu Thr
 450 455 460
 Ile Leu Ala Thr Arg Ile Glu Arg Gln Lys Ala Lys Leu Leu Ala Asp
 465 470 475 480
 Leu Ile Thr Lys Ile Glu Thr Asp Gln Asn Lys Ile Phe Asn Leu Val
 485 490 495
 Lys Ser Ala Leu Asn Gly Lys Ala Asp Asp Leu Leu Asn Leu Gln Lys
 500 505 510
 Arg Leu Asn Gln Thr Lys Lys Asp Ile Asp Tyr Ile Leu Ser Pro Ile
 515 520 525
 Val Asn Arg Pro Ser Leu Leu Asp Arg Leu Asn Lys Asn Gly Lys Thr
 530 535 540
 Thr Asp Leu Asn Lys Leu Ala Asn Leu Met Asn Gln Gly Ser Asn Leu
 545 550 555 560
 Leu Asp Ser Ile Pro Asp Ile Pro Thr Pro Lys Pro Glu Lys Thr Leu
 565 570 575
 Thr Leu Gly Lys Gly Asn Gly Leu Leu Ser Gly Leu Leu Asn Ala Asp
 580 585 590
 Gly Asn Val Ser Leu Pro Lys Ala Gly Glu Thr Ile Lys Glu His Trp
 595 600 605
 Leu Pro Ile Ser Val Ile Val Gly Ala Met Gly Val Leu Met Ile Trp
 610 615 620
 Leu Ser Arg Arg Asn Lys Leu Lys Asn Lys Ala
 625 630 635

<210> SEQ ID NO 23
 <211> LENGTH: 2862
 <212> TYPE: DNA
 <213> ORGANISM: Staphylococcus sp.
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (1)..(2862)

<400> SEQUENCE: 23

atg aat aat aaa aag aca gca aca aat aga aaa ggc atg ata cca aat	48
Met Asn Asn Lys Lys Thr Ala Thr Asn Arg Lys Gly Met Ile Pro Asn	
1 5 10 15	
cga tta aac aaa ttt tcg ata aga aag tat tct gta ggt act gct tca	96
Arg Leu Asn Lys Phe Ser Ile Arg Lys Tyr Ser Val Gly Thr Ala Ser	
20 25 30	
att tta gta ggg aca aca ttg att ttt ggg tta agt ggt cat gaa gct	144
Ile Leu Val Gly Thr Thr Leu Ile Phe Gly Leu Ser Gly His Glu Ala	
35 40 45	
aaa gcg gca gaa cat acg aat gga gaa tta aat caa tca aaa aat gaa	192
Lys Ala Ala Glu His Thr Asn Gly Glu Leu Asn Gln Ser Lys Asn Glu	
50 55 60	
acg aca gcc cca agt gag aat aaa aca act gaa aaa gtt gat agt cgt	240
Thr Thr Ala Pro Ser Glu Asn Lys Thr Thr Glu Lys Val Asp Ser Arg	
65 70 75 80	

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caa cta aaa gac aat acg caa act gca act gca gat cag cct aaa gtg	288
Gln Leu Lys Asp Asn Thr Gln Thr Ala Thr Ala Asp Gln Pro Lys Val	
85 90 95	
aca atg agt gat agt gca aca gtt aaa gaa act agt agt aac atg caa	336
Thr Met Ser Asp Ser Ala Thr Val Lys Glu Thr Ser Ser Asn Met Gln	
100 105 110	
tca cca caa aac gct aca gct agt caa tct act aca caa act agc aat	384
Ser Pro Gln Asn Ala Thr Ala Ser Gln Ser Thr Thr Gln Thr Ser Asn	
115 120 125	
gta aca aca aat gat aaa tca tca act aca tat agt aat gaa act gat	432
Val Thr Thr Asn Asp Lys Ser Ser Thr Thr Tyr Ser Asn Glu Thr Asp	
130 135 140	
aaa agt aat tta aca caa gca aaa aac gtt tca act aca cct aaa aca	480
Lys Ser Asn Leu Thr Gln Ala Lys Asn Val Ser Thr Thr Pro Lys Thr	
145 150 155 160	
acg act att aaa caa aga gct tta aat cgc atg gca gtg aat act gtt	528
Thr Thr Ile Lys Gln Arg Ala Leu Asn Arg Met Ala Val Asn Thr Val	
165 170 175	
gca gct cca caa caa gga aca aat gtt aat gat aaa gta cat ttt acg	576
Ala Ala Pro Gln Gln Gly Thr Asn Val Asn Asp Lys Val His Phe Thr	
180 185 190	
aac att gat att gcg att gat aaa gga cat gtt aat aaa aca aca gga	624
Asn Ile Asp Ile Ala Ile Asp Lys Gly His Val Asn Lys Thr Thr Gly	
195 200 205	
aat act gaa ttt tgg gca act tca agt gat gtt tta aaa tta aaa gcg	672
Asn Thr Glu Phe Trp Ala Thr Ser Ser Asp Val Leu Lys Leu Lys Ala	
210 215 220	
aat tac aca atc gat gat tct gtt aaa gag ggc gat aca ttt act ttt	720
Asn Tyr Thr Ile Asp Asp Ser Val Lys Glu Gly Asp Thr Phe Thr Phe	
225 230 235 240	
aaa tat ggt caa tat ttc cgt cca ggt tct gta aga tta cct tca caa	768
Lys Tyr Gly Gln Tyr Phe Arg Pro Gly Ser Val Arg Leu Pro Ser Gln	
245 250 255	
act caa aat tta tat aat gcc caa ggt aat att att gca aaa ggt att	816
Thr Gln Asn Leu Tyr Asn Ala Gln Gly Asn Ile Ile Ala Lys Gly Ile	
260 265 270	
tac gat agt aaa aca aat aca aca acg tat act ttt acg aat tat gta	864
Tyr Asp Ser Lys Thr Asn Thr Thr Thr Tyr Thr Phe Thr Asn Tyr Val	
275 280 285	
gat caa tac aca aat gtt agc ggt agc ttt gaa caa gtc gca ttt gcg	912
Asp Gln Tyr Thr Asn Val Ser Gly Ser Phe Glu Gln Val Ala Phe Ala	
290 295 300	
aaa cgt gaa aat gca aca act gat aaa act gct tat aaa atg gaa gta	960
Lys Arg Glu Asn Ala Thr Thr Asp Lys Thr Ala Tyr Lys Met Glu Val	
305 310 315 320	
act tta ggt aat gat aca tat agt aaa gat gtc att gtc gat tat ggt	1008
Thr Leu Gly Asn Asp Thr Tyr Ser Lys Asp Val Ile Val Asp Tyr Gly	
325 330 335	
aat caa aaa ggt caa caa ctt att tcg agt aca aat tat att aat aat	1056
Asn Gln Lys Gly Gln Gln Leu Ile Ser Ser Thr Asn Tyr Ile Asn Asn	
340 345 350	
gaa gat ttg tca cgt aat atg act gtt tat gta aat caa cct aaa aag	1104
Glu Asp Leu Ser Arg Asn Met Thr Val Tyr Val Asn Gln Pro Lys Lys	
355 360 365	
acc tat aca aaa gaa aca ttt gta aca aat tta act ggt tat aaa ttt	1152
Thr Tyr Thr Lys Glu Thr Phe Val Thr Asn Leu Thr Gly Tyr Lys Phe	
370 375 380	
aat cca gat gct aaa aac ttc aaa att tac gaa gtg aca gat caa aat	1200
Asn Pro Asp Ala Lys Asn Phe Lys Ile Tyr Glu Val Thr Asp Gln Asn	

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385	390	395	400	
caa ttt gtg gat agt ttc acc cca gat act tca aaa ctt aaa gat gtt				1248
Gln Phe Val Asp Ser Phe Thr Pro Asp Thr Ser Lys Leu Lys Asp Val				
	405	410	415	
act ggt caa ttc gat gtt att tat agt aat gat aat aag acg gcg aca				1296
Thr Gly Gln Phe Asp Val Ile Tyr Ser Asn Asp Asn Lys Thr Ala Thr				
	420	425	430	
gta gat tta ttg aat ggt caa tct agt agt gat aaa cag tac atc att				1344
Val Asp Leu Leu Asn Gly Gln Ser Ser Ser Asp Lys Gln Tyr Ile Ile				
	435	440	445	
caa caa gtt gct tat cca gat aat agt tca aca gat aat ggg aaa att				1392
Gln Gln Val Ala Tyr Pro Asp Asn Ser Ser Thr Asp Asn Gly Lys Ile				
	450	455	460	
gat tat act tta gaa aca caa aat gga aaa agt agt tgg tca aac agt				1440
Asp Tyr Thr Leu Glu Thr Gln Asn Gly Lys Ser Ser Trp Ser Asn Ser				
	465	470	475	480
tat tca aat gtg aat ggc tca tca act gca aat ggc gac caa aag aaa				1488
Tyr Ser Asn Val Asn Gly Ser Ser Thr Ala Asn Gly Asp Gln Lys Lys				
	485	490	495	
tat aat cta ggt gac tat gta tgg gaa gat aca aat aaa gat ggt aaa				1536
Tyr Asn Leu Gly Asp Tyr Val Trp Glu Asp Thr Asn Lys Asp Gly Lys				
	500	505	510	
caa gat gcc aat gaa aaa ggg att aaa ggt gtt tat gtc att ctt aaa				1584
Gln Asp Ala Asn Glu Lys Gly Ile Lys Gly Val Tyr Val Ile Leu Lys				
	515	520	525	
gat agt aac ggt aaa gaa tta gat cgt acg aca aca gat gaa aat ggt				1632
Asp Ser Asn Gly Lys Glu Leu Asp Arg Thr Thr Thr Asp Glu Asn Gly				
	530	535	540	
aaa tat cag ttc act ggt tta agc aat gga act tat agt gta gag ttt				1680
Lys Tyr Gln Phe Thr Gly Leu Ser Asn Gly Thr Tyr Ser Val Glu Phe				
	545	550	555	560
tca aca cca gcc ggt tat aca ccg aca act gca aat gca ggt aca gat				1728
Ser Thr Pro Ala Gly Tyr Thr Pro Thr Thr Ala Asn Ala Gly Thr Asp				
	565	570	575	
gat gct gta gat tct gat gga cta act aca aca ggt gtc att aaa gac				1776
Asp Ala Val Asp Ser Asp Gly Leu Thr Thr Thr Gly Val Ile Lys Asp				
	580	585	590	
gct gac aac atg aca tta gat agt gga ttc tac aaa aca cca aaa tat				1824
Ala Asp Asn Met Thr Leu Asp Ser Gly Phe Tyr Lys Thr Pro Lys Tyr				
	595	600	605	
agt tta ggt gat tat gtt tgg tac gac agt aat aaa gat ggt aaa caa				1872
Ser Leu Gly Asp Tyr Val Trp Tyr Asp Ser Asn Lys Asp Gly Lys Gln				
	610	615	620	
gat tcg act gaa aaa gga att aaa ggt gtt aaa gtt act ttg caa aac				1920
Asp Ser Thr Glu Lys Gly Ile Lys Gly Val Lys Val Thr Leu Gln Asn				
	625	630	635	640
gaa aaa ggc gaa gta att ggt aca act gaa aca gat gaa aat ggt aaa				1968
Glu Lys Gly Glu Val Ile Gly Thr Thr Glu Thr Asp Glu Asn Gly Lys				
	645	650	655	
tac cgc ttt gat aat tta gat agt ggt aaa tac aaa gtt atc ttt gaa				2016
Tyr Arg Phe Asp Asn Leu Asp Ser Gly Lys Tyr Lys Val Ile Phe Glu				
	660	665	670	
aag cct gct ggt tta act caa aca ggt aca aat aca act gaa gat gat				2064
Lys Pro Ala Gly Leu Thr Gln Thr Gly Thr Asn Thr Thr Glu Asp Asp				
	675	680	685	
aaa gat gcc gat ggt ggc gaa gtt gat gta aca att acg gat cat gat				2112
Lys Asp Ala Asp Gly Gly Glu Val Asp Val Thr Ile Thr Asp His Asp				
	690	695	700	
gat ttc aca ctt gat aat ggc tac tac gaa gaa gaa aca tca gat agt				2160

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Asp Phe Thr Leu Asp Asn Gly Tyr Tyr Glu Glu Glu Thr Ser Asp Ser	
705 710 715 720	
gac tca gat tcg gac agc gat tca gac tca gat agc gac tca gat tca	2208
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser	
725 730 735	
gat agt gac tca gac tca gat agc gac tca gac tca gat agc gac tca	2256
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser	
740 745 750	
gac agc gac tca gac tca gat agt gat tca gat tcg gac agc gac tca	2304
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser	
755 760 765	
gat tca gac agc gaa tca gat tcg gat agc gac tca gac tca gat agc	2352
Asp Ser Asp Ser Glu Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser	
770 775 780	
gac tca gac agc gac tca gat tca gac agt gac tca gac tca gac agc	2400
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser	
785 790 795 800	
gac tca gat tca gac agc gat tca gat tcg gat agc gac tca gat tca	2448
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser	
805 810 815	
gat agc gat tcg gac tca gac aac gac tca gat tct gac agc gat tca	2496
Asp Ser Asp Ser Asp Ser Asp Asn Asp Ser Asp Ser Asp Ser Asp Ser	
820 825 830	
gac tca gat agc gac tca gat tca gac agc gac tca gat tca gac agc	2544
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser	
835 840 845	
gat tca gat tca gat agc gat tca gat tca gac agc gac tca gat tca	2592
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser	
850 855 860	
gat agc gac tca gac tca gac agc gat tca gac tca gat agc gac tca	2640
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser	
865 870 875 880	
gac agc gat tca gat tcg gat agc gat tca gat tca gat gca ggt aaa	2688
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ala Gly Lys	
885 890 895	
cat act ccg act aaa cca atg agt acg gtt aaa gat cag cat aaa aca	2736
His Thr Pro Thr Lys Pro Met Ser Thr Val Lys Asp Gln His Lys Thr	
900 905 910	
gct aaa gca tta cca gaa aca ggt agt gaa aat aat aat tca aat aat	2784
Ala Lys Ala Leu Pro Glu Thr Gly Ser Glu Asn Asn Asn Ser Asn Asn	
915 920 925	
ggc aca tta ttc ggt gga tta ttc gcg gca tta gga tca tta ttg tta	2832
Gly Thr Leu Phe Gly Gly Leu Phe Ala Ala Leu Gly Ser Leu Leu Leu	
930 935 940	
ttc ggt cgt cgt aaa aaa caa aat aaa taa	2862
Phe Gly Arg Arg Lys Lys Gln Asn Lys	
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<210> SEQ ID NO 24

<211> LENGTH: 953

<212> TYPE: PRT

<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 24

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Ile Leu Val Gly Thr Thr Leu Ile Phe Gly Leu Ser Gly His Glu Ala
35 40 45

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Lys Ala Ala Glu His Thr Asn Gly Glu Leu Asn Gln Ser Lys Asn Glu
 50 55 60
 Thr Thr Ala Pro Ser Glu Asn Lys Thr Thr Glu Lys Val Asp Ser Arg
 65 70 75 80
 Gln Leu Lys Asp Asn Thr Gln Thr Ala Thr Ala Asp Gln Pro Lys Val
 85 90 95
 Thr Met Ser Asp Ser Ala Thr Val Lys Glu Thr Ser Ser Asn Met Gln
 100 105 110
 Ser Pro Gln Asn Ala Thr Ala Ser Gln Ser Thr Thr Gln Thr Ser Asn
 115 120 125
 Val Thr Thr Asn Asp Lys Ser Ser Thr Thr Tyr Ser Asn Glu Thr Asp
 130 135 140
 Lys Ser Asn Leu Thr Gln Ala Lys Asn Val Ser Thr Thr Pro Lys Thr
 145 150 155 160
 Thr Thr Ile Lys Gln Arg Ala Leu Asn Arg Met Ala Val Asn Thr Val
 165 170 175
 Ala Ala Pro Gln Gln Gly Thr Asn Val Asn Asp Lys Val His Phe Thr
 180 185 190
 Asn Ile Asp Ile Ala Ile Asp Lys Gly His Val Asn Lys Thr Thr Gly
 195 200 205
 Asn Thr Glu Phe Trp Ala Thr Ser Ser Asp Val Leu Lys Leu Lys Ala
 210 215 220
 Asn Tyr Thr Ile Asp Asp Ser Val Lys Glu Gly Asp Thr Phe Thr Phe
 225 230 235 240
 Lys Tyr Gly Gln Tyr Phe Arg Pro Gly Ser Val Arg Leu Pro Ser Gln
 245 250 255
 Thr Gln Asn Leu Tyr Asn Ala Gln Gly Asn Ile Ile Ala Lys Gly Ile
 260 265 270
 Tyr Asp Ser Lys Thr Asn Thr Thr Thr Tyr Thr Phe Thr Asn Tyr Val
 275 280 285
 Asp Gln Tyr Thr Asn Val Ser Gly Ser Phe Glu Gln Val Ala Phe Ala
 290 295 300
 Lys Arg Glu Asn Ala Thr Thr Asp Lys Thr Ala Tyr Lys Met Glu Val
 305 310 315 320
 Thr Leu Gly Asn Asp Thr Tyr Ser Lys Asp Val Ile Val Asp Tyr Gly
 325 330 335
 Asn Gln Lys Gly Gln Gln Leu Ile Ser Ser Thr Asn Tyr Ile Asn Asn
 340 345 350
 Glu Asp Leu Ser Arg Asn Met Thr Val Tyr Val Asn Gln Pro Lys Lys
 355 360 365
 Thr Tyr Thr Lys Glu Thr Phe Val Thr Asn Leu Thr Gly Tyr Lys Phe
 370 375 380
 Asn Pro Asp Ala Lys Asn Phe Lys Ile Tyr Glu Val Thr Asp Gln Asn
 385 390 395 400
 Gln Phe Val Asp Ser Phe Thr Pro Asp Thr Ser Lys Leu Lys Asp Val
 405 410 415
 Thr Gly Gln Phe Asp Val Ile Tyr Ser Asn Asp Asn Lys Thr Ala Thr
 420 425 430
 Val Asp Leu Leu Asn Gly Gln Ser Ser Ser Asp Lys Gln Tyr Ile Ile
 435 440 445
 Gln Gln Val Ala Tyr Pro Asp Asn Ser Ser Thr Asp Asn Gly Lys Ile
 450 455 460

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Asp	Tyr	Thr	Leu	Glu	Thr	Gln	Asn	Gly	Lys	Ser	Ser	Trp	Ser	Asn	Ser	465	470	475	480
Tyr	Ser	Asn	Val	Asn	Gly	Ser	Ser	Thr	Ala	Asn	Gly	Asp	Gln	Lys	Lys	485	490	495	
Tyr	Asn	Leu	Gly	Asp	Tyr	Val	Trp	Glu	Asp	Thr	Asn	Lys	Asp	Gly	Lys	500	505	510	
Gln	Asp	Ala	Asn	Glu	Lys	Gly	Ile	Lys	Gly	Val	Tyr	Val	Ile	Leu	Lys	515	520	525	
Asp	Ser	Asn	Gly	Lys	Glu	Leu	Asp	Arg	Thr	Thr	Thr	Asp	Glu	Asn	Gly	530	535	540	
Lys	Tyr	Gln	Phe	Thr	Gly	Leu	Ser	Asn	Gly	Thr	Tyr	Ser	Val	Glu	Phe	545	550	555	560
Ser	Thr	Pro	Ala	Gly	Tyr	Thr	Pro	Thr	Thr	Ala	Asn	Ala	Gly	Thr	Asp	565	570	575	
Asp	Ala	Val	Asp	Ser	Asp	Gly	Leu	Thr	Thr	Gly	Val	Ile	Lys	Asp		580	585	590	
Ala	Asp	Asn	Met	Thr	Leu	Asp	Ser	Gly	Phe	Tyr	Lys	Thr	Pro	Lys	Tyr	595	600	605	
Ser	Leu	Gly	Asp	Tyr	Val	Trp	Tyr	Asp	Ser	Asn	Lys	Asp	Gly	Lys	Gln	610	615	620	
Asp	Ser	Thr	Glu	Lys	Gly	Ile	Lys	Gly	Val	Lys	Val	Thr	Leu	Gln	Asn	625	630	635	640
Glu	Lys	Gly	Glu	Val	Ile	Gly	Thr	Thr	Glu	Thr	Asp	Glu	Asn	Gly	Lys	645	650	655	
Tyr	Arg	Phe	Asp	Asn	Leu	Asp	Ser	Gly	Lys	Tyr	Lys	Val	Ile	Phe	Glu	660	665	670	
Lys	Pro	Ala	Gly	Leu	Thr	Gln	Thr	Gly	Thr	Asn	Thr	Thr	Glu	Asp	Asp	675	680	685	
Lys	Asp	Ala	Asp	Gly	Gly	Glu	Val	Asp	Val	Thr	Ile	Thr	Asp	His	Asp	690	695	700	
Asp	Phe	Thr	Leu	Asp	Asn	Gly	Tyr	Tyr	Glu	Glu	Glu	Thr	Ser	Asp	Ser	705	710	715	720
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	725	730	735	
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	740	745	750	
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	755	760	765	
Asp	Ser	Asp	Ser	Glu	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	770	775	780	
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	785	790	795	800
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	805	810	815	
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Asn	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	820	825	830	
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	835	840	845	
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	850	855	860	
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	865	870	875	880
Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ala	Gly	Lys				

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885								890				895						
His	Thr	Pro	Thr	Lys	Pro	Met	Ser	Thr	Val	Lys	Asp	Gln	His	Lys	Thr			
			900					905			910							
Ala	Lys	Ala	Leu	Pro	Glu	Thr	Gly	Ser	Glu	Asn	Asn	Asn	Ser	Asn	Asn			
			915					920			925							
Gly	Thr	Leu	Phe	Gly	Gly	Leu	Phe	Ala	Ala	Leu	Gly	Ser	Leu	Leu	Leu			
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Phe	Gly	Arg	Arg	Lys	Lys	Gln	Asn	Lys										
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Met	Asn	Met	Lys	Lys	Lys	Glu	Lys	His	Ala	Ile	Arg	Lys	Lys	Ser	Ile			
			1					10			15							
ggc	gtg	gct	tca	gtg	ctt	gta	ggt	acg	tta	atc	ggt	ttt	gga	cta	ctc	96		
Gly	Val	Ala	Ser	Val	Leu	Val	Gly	Thr	Leu	Ile	Gly	Phe	Gly	Leu	Leu			
			20					25			30							
agc	agt	aaa	gaa	gca	gat	gca	agt	gaa	aat	agt	gtt	acg	caa	tct	gat	144		
Ser	Ser	Lys	Glu	Ala	Asp	Ala	Ser	Glu	Asn	Ser	Val	Thr	Gln	Ser	Asp			
			35					40			45							
agc	gca	agt	aac	gaa	agc	aaa	agt	aat	gat	tca	agt	agc	gtt	agt	gct	192		
Ser	Ala	Ser	Asn	Glu	Ser	Lys	Ser	Asn	Asp	Ser	Ser	Ser	Val	Ser	Ala			
			50					55			60							
gca	cct	aaa	aca	gac	gac	aca	aac	gtg	agt	gat	act	aaa	aca	tcg	tca	240		
Ala	Pro	Lys	Thr	Asp	Asp	Thr	Asn	Val	Ser	Asp	Thr	Lys	Thr	Ser	Ser			
			65					70			75			80				
aac	act	aat	aat	ggc	gaa	acg	agt	gtg	gcg	caa	aat	cca	gca	caa	cag	288		
Asn	Thr	Asn	Asn	Gly	Glu	Thr	Ser	Val	Ala	Gln	Asn	Pro	Ala	Gln	Gln			
			85					90						95				
gaa	acg	aca	caa	tca	tca	tca	aca	aat	gca	act	acg	gaa	gaa	acg	ccg	336		
Glu	Thr	Thr	Gln	Ser	Ser	Ser	Thr	Asn	Ala	Thr	Thr	Glu	Glu	Thr	Pro			
			100					105			110							
gta	act	ggt	gaa	gct	act	act	acg	aca	acg	aat	caa	gct	aat	aca	ccg	384		
Val	Thr	Gly	Glu	Ala	Thr	Thr	Thr	Thr	Thr	Asn	Gln	Ala	Asn	Thr	Pro			
			115					120			125							
gca	aca	act	caa	tca	agc	aat	aca	aat	gcg	gag	gaa	tta	gtg	aat	caa	432		
Ala	Thr	Thr	Gln	Ser	Ser	Asn	Thr	Asn	Ala	Glu	Glu	Leu	Val	Asn	Gln			
			130					135			140							
aca	agt	aat	gaa	acg	act	tct	aat	gat	act	aat	aca	gta	tca	tct	gta	480		
Thr	Ser	Asn	Glu	Thr	Thr	Ser	Asn	Asp	Thr	Asn	Thr	Val	Ser	Ser	Val			
			145					150			155			160				
aat	tca	cct	caa	aat	tct	aca	aat	gcg	gaa	aat	gtt	tca	aca	acg	caa	528		
Asn	Ser	Pro	Gln	Asn	Ser	Thr	Asn	Ala	Glu	Asn	Val	Ser	Thr	Thr	Gln			
			165					170			175							
gat	act	tca	act	gaa	gca	aca	cct	tca	aac	aat	gaa	tca	gct	cca	cag	576		
Asp	Thr	Ser	Thr	Glu	Ala	Thr	Pro	Ser	Asn	Asn	Glu	Ser	Ala	Pro	Gln			
			180					185			190							
aat	aca	gat	gca	agt	aat	aaa	gat	gta	gtt	agt	caa	gcg	gtt	aat	cca	624		
Asn	Thr	Asp	Ala	Ser	Asn	Lys	Asp	Val	Val	Ser	Gln	Ala	Val	Asn	Pro			
			195					200			205							
agt	acg	cct	aga	atg	aga	gca	ttt	agt	tta	gcg	gca	gta	gct	gca	gat	672		
Ser	Thr	Pro	Arg	Met	Arg	Ala	Phe	Ser	Leu	Ala	Ala	Val	Ala	Ala	Asp			

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210	215	220	
gca ccg gca gct ggc aca gat att acg aat cag ttg aca gat gtg aaa Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asp Val Lys 225 230 235 240			720
gtt act att gac tct ggt acg act gtg tat ccg cac caa gca ggt tat Val Thr Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr 245 250 255			768
gtc aaa ctg aat tat ggt ttt tca gtg cct aat tct gct gtt aaa ggt Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly 260 265 270			816
gac aca ttc aaa ata act gta cct aaa gaa tta aac tta aat ggt gta Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val 275 280 285			864
act tca act gct aaa gtg cca cca att atg gct gga gat caa gta ttg Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu 290 295 300			912
gca aat ggt gta atc gat agt gat ggt aat gtt att tat aca ttt aca Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr 305 310 315 320			960
gac tat gtt gat aat aaa gaa aat gta aca gct aat att act atg cca Asp Tyr Val Asp Asn Lys Glu Asn Val Thr Ala Asn Ile Thr Met Pro 325 330 335			1008
gct tat att gac cct gaa aat gtt aca aag aca ggt aat gtg aca ttg Ala Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu 340 345 350			1056
aca act ggc ata gga acc aat act gct agt aag aca gta tta atc gac Thr Thr Gly Ile Gly Thr Asn Thr Ala Ser Lys Thr Val Leu Ile Asp 355 360 365			1104
tat gag aaa tat gga caa ttc cat aat tta tca att aaa ggt acg att Tyr Glu Lys Tyr Gly Gln Phe His Asn Leu Ser Ile Lys Gly Thr Ile 370 375 380			1152
gat caa atc gat aaa aca aat aat acg tat cgc caa aca att tat gtc Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val 385 390 395 400			1200
aat cca agc gga gat aac gtt gtg tta cct gcc tta aca ggt aat tta Asn Pro Ser Gly Asp Asn Val Val Leu Pro Ala Leu Thr Gly Asn Leu 405 410 415			1248
att cct aat aca aag agt aat gcg tta ata gat gca aaa aac act gat Ile Pro Asn Thr Lys Ser Asn Ala Leu Ile Asp Ala Lys Asn Thr Asp 420 425 430			1296
att aaa gtt tat aga gtc gat aat gct aat gat tta tct gaa agt tat Ile Lys Val Tyr Arg Val Asp Asn Ala Asn Asp Leu Ser Glu Ser Tyr 435 440 445			1344
tat gtg aat cct agc gat ttt gaa gat gta act aat caa gtt aga att Tyr Val Asn Pro Ser Asp Phe Glu Asp Val Thr Asn Gln Val Arg Ile 450 455 460			1392
tca ttt cca aat gct aat caa tac aaa gta gaa ttt cct acg gac gat Ser Phe Pro Asn Ala Asn Gln Tyr Lys Val Glu Phe Pro Thr Asp Asp 465 470 475 480			1440
gac caa att aca aca ccg tat att gta gtt gtt aat ggc cat att gat Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp 485 490 495			1488
cct gct agt aca ggt gat tta gca cta cgt tcg aca ttt tat ggt tat Pro Ala Ser Thr Gly Asp Leu Ala Leu Arg Ser Thr Phe Tyr Gly Tyr 500 505 510			1536
gat tct aat ttt ata tgg aga tct atg tca tgg gac aac gaa gta gca Asp Ser Asn Phe Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala 515 520 525			1584
ttt aat aac gga tca ggt tct ggt gac ggt atc gat aaa cca gtt gtt			1632

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Phe 530	Asn	Asn	Gly	Ser	Gly	Ser	Gly	Asp	Gly	Ile	Asp	Lys	Pro	Val	Val	
cct Pro 545	gaa Glu	caa Gln	cct Pro	gat Asp	gag Glu	cct Pro	ggg Gly	gaa Glu	att Ile	gaa Glu	cca Pro	att Ile	cca Pro	gag Glu	gat Asp	1680
tca Ser	gat Asp	tct Ser	gac Asp	cca Pro 565	ggg Gly	tca Ser	gat Asp	tct Ser	ggc Gly 570	agc Ser	gat Asp	tct Ser	aat Asn	tca Ser 575	gat Asp	1728
agc Ser	ggg Gly	tca Ser	gat Asp	tct Ser 580	ggc Gly	agt Ser	gat Asp	tct Ser 585	aca Thr	tca Ser	gat Asp	agt Ser	ggg Gly 590	tca Ser	gat Asp	1776
tca Ser	gcg Ala	agt Ser	gat Asp	tca Ser	gat Asp	tca Ser	gca Ala 600	agt Ser	gat Asp	tca Ser	gac Asp	tca Ser	gcg Ala	agt Ser	gat Asp	1824
tca Ser	gat Ser 610	tca Ser	gca Ala	agt Ser	gat Asp	tca Ser	gat Asp 615	tca Ser	gca Ala	agt Ser	gat Asp 620	tca Ser	gat Asp	tca Ser	gca Ala	1872
agt Ser 625	gat Asp	tca Ser	gac Asp	tca Ser	gca Ala 630	agt Ser	gat Asp	tca Ser	gat Asp	tca Ser	gca Ala 635	agt Ser	gat Asp	tca Ser	gat Asp 640	1920
tca Ser	gca Ala	agc Ser	gat Asp	tca Ser 645	gat Asp	tca Ser	gcg Ala	agc Ser	gat Asp 650	tca Ser	gat Asp	tca Ser	gcg Ala	agc Ser 655	gat Asp	1968
tca Ser	gat Asp	tca Ser	gcg Ala 660	agt Ser	gat Asp	tcc Ser	gac Asp	tca Ser	gcg Ala 665	agc Ser	gat Asp	tca Ser	gac Asp 670	tca Ser	gat Asp	2016
agt Ser	gac Asp	tca Ser	gat Asp	tcc Ser	gat Asp	agc Ser	gat Asp 680	tcc Ser	gac Asp	tca Ser	gat Asp	agc Ser	gac Asp 685	tca Ser	gat Asp	2064
tca Ser	gac Ser 690	agc Ser	gat Asp	tct Ser	gac Asp	tca Ser	gac Asp 695	agc Ser	gat Asp	tct Ser	gac Asp 700	tca Ser	gac Asp	agt Ser	gac Asp	2112
tca Ser 705	gat Asp	tcc Ser	gat Asp	agc Ser	gat Asp 710	tcc Ser	gac Asp	tca Ser	gac Asp	agt Ser	gac Asp 715	tca Ser	gat Asp	tcc Ser	gat Asp 720	2160
agc Ser	gat Asp	tcc Ser	gac Asp	tca Ser 725	gac Asp	agt Ser	gac Asp	tca Ser	gat Asp 730	tcc Ser	gat Asp	agc Ser	gat Asp	tca Ser	gat Asp 735	2208
tcc Ser	gac Asp	agt Ser	gat Asp 740	tcc Ser	gac Asp	tca Ser	gat Asp	agc Ser	gat Asp 745	tcc Ser	gac Asp	tca Ser	gat Asp 750	agc Ser	gac Asp	2256
tca Ser	gat Asp	tca Ser	gac Asp	agc Ser	gat Asp	tca Ser	gat Asp 760	tca Ser	gac Asp	agc Ser	gat Asp	tct Ser	gac Asp 765	tca Ser	gac Asp	2304
agt Ser	gac Ser 770	tca Ser	gat Asp	tcc Ser	gat Asp	agc Ser	gat Asp 775	tca Ser	gat Asp	tca Ser	gac Asp 780	agt Ser	gat Asp	tca Ser	gac Asp	2352
tca Ser 785	gat Asp	agc Ser	gat Asp	tca Ser	gat Asp 790	tcc Ser	gac Asp	agt Ser	gac Asp	tca Ser	gac Asp 795	tca Ser	gac Asp	agc Ser	gat Asp 800	2400
tca Ser	gat Asp	tcc Ser	gat Asp	agc Ser 805	gat Asp	tca Ser	gat Asp	tcc Ser	gac Asp 810	agt Ser	gac Asp	tca Ser	gat Asp	tcc Ser	gat Asp 815	2448
agt Ser	gac Asp	tcg Ser	gat Asp	tca Ser	gcg Ala	agt Ser	gat Asp	tca Ser	gat Asp 825	tca Ser	gat Asp	agc Ser	gat Asp 830	tca Ser	gaa Glu	2496
tca Ser	gat Asp	agt Ser	gac Asp	tca Ser	gac Asp	tca Ser	gac Asp 840	agt Ser	gat Asp	tca Ser	gat Asp	tca Ser	gat Asp 845	agt Ser	gac Asp	2544

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tca gac tca gac agc gat tca gaa tca gat agt gac tcc gat tca gac	2592
Ser Asp Ser Asp Ser Asp Ser Glu Ser Asp Ser Asp Ser Asp Ser Asp	
850 855 860	
agc gat tca gaa tca gat agt gac tcc gat tca gat agc gat tcg gat	2640
Ser Asp Ser Glu Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp	
865 870 875 880	
tca gcg agt gat tca gac tca ggt agt gac tcc gat tca tca agt gat	2688
Ser Ala Ser Asp Ser Asp Ser Gly Ser Asp Ser Asp Ser Ser Ser Asp	
885 890 895	
tca gat tcc gat tca acg agt gac aca gga tca gac aac gac tca gac	2736
Ser Asp Ser Asp Ser Thr Ser Asp Thr Gly Ser Asp Asn Asp Ser Asp	
900 905 910	
agt gat tca aat agc gat tcc gag tca ggt tct aac aat aat gta gtt	2784
Ser Asp Ser Asn Ser Asp Ser Glu Ser Gly Ser Asn Asn Asn Val Val	
915 920 925	
ccg cct aat tca cct aaa aat ggt act aat gct tct aat aaa aat gag	2832
Pro Pro Asn Ser Pro Lys Asn Gly Thr Asn Ala Ser Asn Lys Asn Glu	
930 935 940	
gct aaa gat agt aaa gaa cca tta cca gat aca ggt tct gaa gat gaa	2880
Ala Lys Asp Ser Lys Glu Pro Leu Pro Asp Thr Gly Ser Glu Asp Glu	
945 950 955 960	
gcg aat acg tca cta att tgg gga tta tta gca tca tta ggt tca tta	2928
Ala Asn Thr Ser Leu Ile Trp Gly Leu Leu Ala Ser Leu Gly Ser Leu	
965 970 975	
cta ctt ttc aga aga aaa aaa gaa aat aaa gat aag aaa taa	2970
Leu Leu Phe Arg Arg Lys Lys Glu Asn Lys Asp Lys Lys	
980 985	

<210> SEQ ID NO 26

<211> LENGTH: 989

<212> TYPE: PRT

<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 26

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 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	

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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 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

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Ser Asp Ser Ala Ser Asp Ser Asp Ser Ala Ser Asp Ser Asp Ser Ala
 610                               615                               620

Ser Asp Ser Asp Ser Ala Ser Asp Ser Asp Ser Ala Ser Asp Ser Asp
 625                               630                               635                               640

Ser Ala Ser Asp Ser Asp Ser Ala Ser Asp Ser Asp Ser Ala Ser Asp
                               645                               650                               655

Ser Asp Ser Ala Ser Asp Ser Asp Ser Ala 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 Asp
                               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 Asp Ser Asp Ser Asp Ser Asp Ser Asp
                               805                               810                               815

Ser Asp Ser Asp Ser Ala Ser Asp Ser Asp Ser Asp Ser Asp Ser Glu
                               820                               825                               830

Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
                               835                               840                               845

Ser Asp Ser Asp Ser Asp Ser Glu Ser Asp Ser Asp Ser Asp Ser Asp
                               850                               855                               860

Ser Asp Ser Glu Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
 865                               870                               875                               880

Ser Ala Ser Asp Ser Asp Ser Gly Ser Asp Ser Asp Ser Ser Ser Asp
                               885                               890                               895

Ser Asp Ser Asp Ser Thr Ser Asp Thr Gly Ser Asp Asn Asp Ser Asp
                               900                               905                               910

Ser Asp Ser Asn Ser Asp Ser Glu Ser Gly Ser Asn Asn Asn Val Val
                               915                               920                               925

Pro Pro Asn Ser Pro Lys Asn Gly Thr Asn Ala Ser Asn Lys Asn Glu
 930                               935                               940

Ala Lys Asp Ser Lys Glu Pro Leu Pro Asp Thr Gly Ser Glu Asp Glu
 945                               950                               955                               960

Ala Asn Thr Ser Leu Ile Trp Gly Leu Leu Ala Ser Leu Gly Ser Leu
                               965                               970                               975

Leu Leu Phe Arg Arg Lys Lys Glu Asn Lys Asp Lys Lys
                               980                               985

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<210> SEQ ID NO 27

<211> LENGTH: 54

<212> TYPE: PRT

<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 27

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Gln Gln Asn Asn Phe Asn Lys Asp Gln Gln Ser Ala Phe Tyr Glu Ile
 1 5 10 15
 Leu Asn Met Pro Asn Leu Asn Glu Ala Gln Arg Asn Gly Phe Ile Gln
 20 25 30
 Ser Leu Lys Asp Asp Pro Ser Gln Ser Thr Asn Val Leu Gly Glu Ala
 35 40 45
 Lys Lys Leu Asn Glu Ser

 <210> SEQ ID NO 28
 <211> LENGTH: 584
 <212> TYPE: PRT
 <213> ORGANISM: Staphylococcus sp.

 <400> SEQUENCE: 28
 Met Lys Phe Lys Ser Leu Ile Thr Thr Thr Leu Ala Leu Gly Val Leu
 1 5 10 15
 Ala Ser Thr Gly Ala Asn Phe Asn Asn Asn Glu Ala Ser Ala Ala Ala
 20 25 30
 Lys Pro Leu Asp Lys Ser Ser Ser Ser Leu His His Gly Tyr Ser Lys
 35 40 45
 Val His Val Pro Tyr Ala Ile Thr Val Asn Gly Thr Ser Gln Asn Ile
 50 55 60
 Leu Ser Ser Leu Thr Phe Asn Lys Asn Gln Asn Ile Ser Tyr Lys Asp
 65 70 75 80
 Leu Glu Asp Arg Val Lys Ser Val Leu Lys Ser Asp Arg Gly Ile Ser
 85 90 95
 Asp Ile Asp Leu Arg Leu Ser Lys Gln Ala Lys Tyr Thr Val Tyr Phe
 100 105 110
 Lys Asn Gly Thr Lys Lys Val Ile Asp Leu Lys Ala Gly Ile Tyr Thr
 115 120 125
 Ala Asp Leu Ile Asn Thr Ser Glu Ile Lys Ala Ile Asn Ile Asn Val
 130 135 140
 Asp Thr Lys Lys Gln Val Glu Asp Lys Lys Lys Asp Lys Ala Asn Tyr
 145 150 155 160
 Gln Val Pro Tyr Thr Ile Thr Val Asn Gly Thr Ser Gln Asn Ile Leu
 165 170 175
 Ser Asn Leu Thr Phe Asn Lys Asn Gln Asn Ile Ser Tyr Lys Asp Leu
 180 185 190
 Glu Asp Lys Val Lys Ser Val Leu Glu Ser Asn Arg Gly Ile Thr Asp
 195 200 205
 Val Asp Leu Arg Leu Ser Lys Gln Ala Lys Tyr Thr Val Asn Phe Lys
 210 215 220
 Asn Gly Thr Lys Lys Val Ile Asp Leu Lys Ser Gly Ile Tyr Thr Ala
 225 230 235 240
 Asn Leu Ile Asn Ser Ser Asp Ile Lys Ser Ile Asn Ile Asn Val Asp
 245 250 255
 Thr Lys Lys His Ile Glu Asn Lys Ala Lys Arg Asn Tyr Gln Val Pro
 260 265 270
 Tyr Ser Ile Asn Leu Asn Gly Thr Ser Thr Asn Ile Leu Ser Asn Leu
 275 280 285
 Ser Phe Ser Asn Lys Pro Trp Thr Asn Tyr Lys Asn Leu Thr Ser Gln
 290 295 300
 Ile Lys Ser Val Leu Lys His Asp Arg Gly Ile Ser Glu Gln Asp Leu
 305 310 315 320

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100							105					110				
Ser	Gln	Asn	Val	Asn	Thr	Lys	Lys	Asp	Ser	Ala	Thr	Ala	Ala	Thr	Thr	
		115					120					125				
Gln	Pro	Asp	Lys	Glu	Gln	Ser	Lys	His	Lys	Gln	Asn	Glu	Ser	Gln	Ser	
	130					135					140					
Ala	Asn	Lys	Asn	Gly	Asn	Asp	Asn	Arg	Ala	Ala	His	Val	Glu	Asn	His	
	145				150					155					160	
Glu	Ala	Asn	Val	Val	Thr	Ala	Ser	Asp	Ser	Ser	Asp	Asn	Gly	Asn	Val	
			165					170						175		
Gln	His	Asp	Arg	Asn	Glu	Leu	Gln	Ala	Phe	Phe	Asp	Ala	Asn	Tyr	His	
		180						185					190			
Asp	Tyr	Arg	Phe	Ile	Asp	Arg	Glu	Asn	Ala	Asp	Ser	Gly	Thr	Phe	Asn	
		195					200					205				
Tyr	Val	Lys	Gly	Ile	Phe	Asp	Lys	Ile	Asn	Thr	Leu	Leu	Gly	Ser	Asn	
	210					215					220					
Asp	Pro	Ile	Asn	Asn	Lys	Asp	Leu	Gln	Leu	Ala	Tyr	Lys	Glu	Leu	Glu	
	225				230					235					240	
Gln	Ala	Val	Ala	Leu	Ile	Arg	Thr	Met	Pro	Gln	Arg	Gln	Gln	Thr	Ser	
			245						250					255		
Arg	Arg	Ser	Asn	Arg	Ile	Gln	Thr	Arg	Ser	Val	Glu	Ser	Arg	Ala	Ala	
			260					265					270			
Glu	Pro	Arg	Ser	Val	Ser	Asp	Tyr	Gln	Asn	Ala	Asn	Ser	Ser	Tyr	Tyr	
		275					280					285				
Val	Glu	Asn	Ala	Asn	Asp	Gly	Ser	Gly	Tyr	Pro	Val	Gly	Thr	Tyr	Ile	
	290					295					300					
Asn	Ala	Ser	Ser	Lys	Gly	Ala	Pro	Tyr	Asn	Leu	Pro	Thr	Thr	Pro	Trp	
	305				310					315					320	
Asn	Thr	Leu	Lys	Ala	Ser	Asp	Ser	Lys	Glu	Ile	Ala	Leu	Met	Thr	Ala	
			325						330					335		
Lys	Gln	Thr	Gly	Asp	Gly	Tyr	Gln	Trp	Val	Ile	Lys	Phe	Asn	Lys	Gly	
		340						345					350			
His	Ala	Pro	His	Gln	Asn	Met	Ile	Phe	Trp	Phe	Ala	Leu	Pro	Ala	Asp	
	355					360						365				
Gln	Val	Pro	Val	Gly	Arg	Thr	Asp	Phe	Val	Thr	Val	Asn	Ser	Asp	Gly	
	370					375					380					
Thr	Asn	Val	Gln	Trp	Ser	His	Gly	Ala	Gly	Ala	Gly	Ala	Asn	Lys	Pro	
	385				390					395					400	
Leu	Gln	Gln	Met	Trp	Glu	Tyr	Gly	Val	Asn	Asp	Pro	His	Arg	Ser	His	
			405						410					415		
Asp	Phe	Lys	Ile	Arg	Asn	Arg	Ser	Gly	Gln	Val	Ile	Tyr	Asp	Trp	Pro	
		420						425					430			
Thr	Val	His	Ile	Tyr	Ser	Leu	Glu	Asp	Leu	Ser	Arg	Ala	Ser	Asp	Tyr	
	435					440						445				
Phe	Ser	Glu	Ala	Gly	Ala	Thr	Pro	Ala	Thr	Lys	Ala	Phe	Gly	Arg	Gln	
	450					455					460					
Asn	Phe	Glu	Tyr	Ile	Asn	Gly	Gln	Lys	Pro	Ala	Glu	Ser	Pro	Gly	Val	
	465				470					475					480	
Pro	Lys	Val	Tyr	Thr	Phe	Ile	Gly	Gln	Gly	Asp	Ala	Ser	Tyr	Thr	Ile	
			485						490					495		
Ser	Phe	Lys	Thr	Gln	Gly	Pro	Thr	Val	Asn	Lys	Leu	Tyr	Tyr	Ala	Ala	
		500						505					510			
Gly	Gly	Arg	Ala	Leu	Glu	Tyr	Asn	Gln	Leu	Phe	Met	Tyr	Ser	Gln	Leu	
		515					520					525				

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Tyr Val Glu Ser Thr Gln Asp His Gln Gln Arg Leu Asn Gly Leu Arg
 530 535 540
 Gln Val Val Asn Arg Thr Tyr Arg Ile Gly Thr Thr Lys Arg Val Glu
 545 550 555 560
 Val Ser Gln Gly Asn Val Gln Thr Lys Lys Val Leu Glu Ser Thr Asn
 565 570 575
 Leu Asn Ile Asp Asp Phe Val Asp Asp Pro Leu Ser Tyr Val Lys Thr
 580 585 590
 Pro Ser Asn Lys Val Leu Gly Phe Tyr Ser Asn Asn Ala Asn Thr Asn
 595 600 605
 Ala Phe Arg Pro Gly Gly Ala Gln Gln Leu Asn Glu Tyr Gln Leu Ser
 610 615 620
 Gln Leu Phe Thr Asp Gln Lys Leu Gln Glu Ala Ala Arg Thr Arg Asn
 625 630 635 640
 Pro Ile Arg Leu Met Ile Gly Phe Asp Tyr Pro Asp Ala Tyr Gly Asn
 645 650 655
 Ser Glu Thr Leu Val Pro Val Asn Leu Thr Val Leu Pro Glu Ile Gln
 660 665 670
 His Asn Ile Lys Phe Phe Lys Asn Asp Asp Thr Gln Asn Ile Ala Glu
 675 680 685
 Lys Pro Phe Ser Lys Gln Ala Gly His Pro Val Phe Tyr Val Tyr Ala
 690 695 700
 Gly Asn Gln Gly Asn Ala Ser Val Asn Leu Gly Gly Ser Val Thr Ser
 705 710 715 720
 Ile Gln Pro Leu Arg Ile Asn Leu Thr Ser Asn Glu Asn Phe Thr Asp
 725 730 735
 Lys Asp Trp Gln Ile Thr Gly Ile Pro Arg Thr Leu His Ile Glu Asn
 740 745 750
 Ser Thr Asn Arg Pro Asn Asn Ala Arg Glu Arg Asn Ile Glu Leu Val
 755 760 765
 Gly Asn Leu Leu Pro Gly Asp Tyr Phe Gly Thr Ile Arg Phe Gly Arg
 770 775 780
 Lys Glu Gln Leu Phe Glu Ile Arg Val Lys Pro His Thr Pro Thr Ile
 785 790 795 800
 Thr Thr Thr Ala Glu Gln Leu Arg Gly Thr Ala Leu Gln Lys Val Pro
 805 810 815
 Val Asn Ile Ser Gly Ile Pro Leu Asp Pro Ser Ala Leu Val Tyr Leu
 820 825 830
 Val Ala Pro Thr Asn Gln Thr Thr Asn Gly Gly Ser Glu Ala Asp Gln
 835 840 845
 Ile Pro Ser Gly Tyr Thr Ile Leu Ala Thr Gly Thr Pro Asp Gly Val
 850 855 860
 His Asn Thr Ile Thr Ile Arg Pro Gln Asp Tyr Val Val Phe Ile Pro
 865 870 875 880
 Pro Val Gly Lys Gln Ile Arg Ala Val Val Tyr Tyr Asn Lys Val Val
 885 890 895
 Ala Ser Asn Met Ser Asn Ala Val Thr Ile Leu Pro Asp Asp Ile Pro
 900 905 910
 Pro Thr Ile Asn Asn Pro Val Gly Ile Asn Ala Lys Tyr Tyr Arg Gly
 915 920 925
 Asp Glu Val Asn Phe Thr Met Gly Val Ser Asp Arg His Ser Gly Ile
 930 935 940

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Lys	Asn	Thr	Thr	Ile	Thr	Thr	Leu	Pro	Asn	Gly	Trp	Thr	Ser	Asn	Leu	945	950	955	960
Thr	Lys	Ala	Asp	Lys	Asn	Asn	Gly	Ser	Leu	Ser	Ile	Thr	Gly	Arg	Val	965	970	975	
Ser	Met	Asn	Gln	Ala	Phe	Asn	Ser	Asp	Ile	Thr	Phe	Lys	Val	Ser	Ala	980	985	990	
Thr	Asp	Asn	Val	Asn	Asn	Thr	Thr	Asn	Asp	Ser	Gln	Ser	Lys	His	Val	995	1000	1005	
Ser	Ile	His	Val	Gly	Lys	Ile	Ser	Glu	Asp	Ala	His	Pro	Ile	Val		1010	1015	1020	
Leu	Gly	Asn	Thr	Glu	Lys	Val	Val	Val	Val	Asn	Pro	Thr	Ala	Val		1025	1030	1035	
Ser	Asn	Asp	Glu	Lys	Gln	Ser	Ile	Ile	Thr	Ala	Phe	Met	Asn	Lys		1040	1045	1050	
Asn	Gln	Asn	Ile	Arg	Gly	Tyr	Leu	Ala	Ser	Thr	Asp	Pro	Val	Thr		1055	1060	1065	
Val	Asp	Asn	Asn	Gly	Asn	Val	Thr	Leu	His	Tyr	Arg	Asp	Gly	Ser		1070	1075	1080	
Ser	Thr	Thr	Leu	Asp	Ala	Thr	Asn	Val	Met	Thr	Tyr	Glu	Pro	Val		1085	1090	1095	
Val	Lys	Pro	Glu	Tyr	Gln	Thr	Val	Asn	Ala	Ala	Lys	Thr	Ala	Thr		1100	1105	1110	
Val	Thr	Ile	Ala	Lys	Gly	Gln	Ser	Phe	Ser	Ile	Gly	Asp	Ile	Lys		1115	1120	1125	
Gln	Tyr	Phe	Thr	Leu	Ser	Asn	Gly	Gln	Pro	Ile	Pro	Ser	Gly	Thr		1130	1135	1140	
Phe	Thr	Asn	Ile	Thr	Ser	Asp	Arg	Thr	Ile	Pro	Thr	Ala	Gln	Glu		1145	1150	1155	
Val	Ser	Gln	Met	Asn	Ala	Gly	Thr	Gln	Leu	Tyr	His	Ile	Thr	Ala		1160	1165	1170	
Thr	Asn	Ala	Tyr	His	Lys	Asp	Ser	Glu	Asp	Phe	Tyr	Ile	Ser	Leu		1175	1180	1185	
Lys	Ile	Ile	Asp	Val	Lys	Gln	Pro	Glu	Gly	Asp	Gln	Arg	Val	Tyr		1190	1195	1200	
Arg	Thr	Ser	Thr	Tyr	Asp	Leu	Thr	Thr	Asp	Glu	Ile	Ser	Lys	Val		1205	1210	1215	
Lys	Gln	Ala	Phe	Ile	Asn	Ala	Asn	Arg	Asp	Val	Ile	Thr	Leu	Ala		1220	1225	1230	
Glu	Gly	Asp	Ile	Ser	Val	Thr	Asn	Thr	Pro	Asn	Gly	Ala	Asn	Val		1235	1240	1245	
Ser	Thr	Ile	Thr	Val	Asn	Ile	Asn	Lys	Gly	Arg	Leu	Thr	Lys	Ser		1250	1255	1260	
Phe	Ala	Ser	Asn	Leu	Ala	Asn	Met	Asn	Phe	Leu	Arg	Trp	Val	Asn		1265	1270	1275	
Phe	Pro	Gln	Asp	Tyr	Thr	Val	Thr	Trp	Thr	Asn	Ala	Lys	Ile	Ala		1280	1285	1290	
Asn	Arg	Pro	Thr	Asp	Gly	Gly	Leu	Ser	Trp	Ser	Asp	Asp	His	Lys		1295	1300	1305	
Ser	Leu	Ile	Tyr	Arg	Tyr	Asp	Ala	Thr	Leu	Gly	Thr	Gln	Ile	Thr		1310	1315	1320	
Thr	Asn	Asp	Ile	Leu	Thr	Met	Leu	Lys	Ala	Thr	Thr	Thr	Val	Pro		1325	1330	1335	
Gly	Leu	Arg	Asn	Asn	Ile	Thr	Gly	Asn	Glu	Lys	Ser	Gln	Ala	Glu					

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1340	1345	1350
Ala Gly Gly Arg Pro Asn Phe Arg Thr Thr Gly Tyr Ser Gln Ser		
1355	1360	1365
Asn Ala Thr Thr Asp Gly Gln Arg Gln Phe Thr Leu Asn Gly Gln		
1370	1375	1380
Val Ile Gln Val Leu Asp Ile Ile Asn Pro Ser Asn Gly Tyr Gly		
1385	1390	1395
Gly Gln Pro Val Thr Asn Ser Asn Thr Arg Ala Asn His Ser Asn		
1400	1405	1410
Ser Thr Val Val Asn Val Asn Glu Pro Ala Ala Asn Gly Ala Gly		
1415	1420	1425
Ala Phe Thr Ile Asp His Val Val Lys Ser Asn Ser Thr His Asn		
1430	1435	1440
Ala Ser Asp Ala Val Tyr Lys Ala Gln Leu Tyr Leu Thr Pro Tyr		
1445	1450	1455
Gly Pro Lys Gln Tyr Val Glu His Leu Asn Gln Asn Thr Gly Asn		
1460	1465	1470
Thr Thr Asp Ala Ile Asn Ile Tyr Phe Val Pro Ser Asp Leu Val		
1475	1480	1485
Asn Pro Thr Ile Ser Val Gly Asn Tyr Thr Asn His Gln Val Phe		
1490	1495	1500
Ser Gly Glu Thr Phe Thr Asn Thr Ile Thr Ala Asn Asp Asn Phe		
1505	1510	1515
Gly Val Gln Ser Val Thr Val Pro Asn Thr Ser Gln Ile Thr Gly		
1520	1525	1530
Thr Val Asp Asn Asn His Gln His Val Ser Ala Thr Ala Pro Asn		
1535	1540	1545
Val Thr Ser Ala Thr Asn Lys Thr Ile Asn Leu Leu Ala Thr Asp		
1550	1555	1560
Thr Ser Gly Asn Thr Ala Thr Thr Ser Phe Asn Val Thr Val Lys		
1565	1570	1575
Pro Leu Arg Asp Lys Tyr Arg Val Gly Thr Ser Ser Thr Ala Ala		
1580	1585	1590
Asn Pro Val Arg Ile Ala Asn Ile Ser Asn Asn Ala Thr Val Ser		
1595	1600	1605
Gln Ala Asp Gln Thr Thr Ile Ile Asn Ser Leu Thr Phe Thr Glu		
1610	1615	1620
Thr Val Pro Asn Arg Ser Tyr Ala Arg Ala Ser Ala Asn Glu Ile		
1625	1630	1635
Thr Ser Lys Thr Val Ser Asn Val Ser Arg Thr Gly Asn Asn Ala		
1640	1645	1650
Asn Val Thr Val Thr Val Thr Tyr Gln Asp Gly Thr Thr Ser Thr		
1655	1660	1665
Val Thr Val Pro Val Lys His Val Ile Pro Glu Ile Val Ala His		
1670	1675	1680
Ser His Tyr Thr Val Gln Gly Gln Asp Phe Pro Ala Gly Asn Gly		
1685	1690	1695
Ser Ser Ala Ser Asp Tyr Phe Lys Leu Ser Asn Gly Ser Asp Ile		
1700	1705	1710
Ala Asp Ala Thr Ile Thr Trp Val Ser Gly Gln Ala Pro Asn Lys		
1715	1720	1725
Asp Asn Thr Arg Ile Gly Glu Asp Ile Thr Val Thr Ala His Ile		
1730	1735	1740

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Leu Ile Asp Gly Glu Thr Thr	Pro Ile Thr Lys Thr	Ala Thr Tyr
1745	1750	1755
Lys Val Val Arg Thr Val	Pro Lys His Val Phe Glu	Thr Ala Arg
1760	1765	1770
Gly Val Leu Tyr Pro Gly Val	Ser Asp Met Tyr Asp	Ala Lys Gln
1775	1780	1785
Tyr Val Lys Pro Val Asn Asn	Ser Trp Ser Thr Asn	Ala Gln His
1790	1795	1800
Met Asn Phe Gln Phe Val Gly	Thr Tyr Gly Pro Asn	Lys Asp Val
1805	1810	1815
Val Gly Ile Ser Thr Arg Leu	Ile Arg Val Thr Tyr	Asp Asn Arg
1820	1825	1830
Gln Thr Glu Asp Leu Thr Ile	Leu Ser Lys Val Lys	Pro Asp Pro
1835	1840	1845
Pro Arg Ile Asp Ala Asn Ser	Val Thr Tyr Lys Ala	Gly Leu Thr
1850	1855	1860
Asn Gln Glu Ile Lys Val Asn	Asn Val Leu Asn Asn	Ser Ser Val
1865	1870	1875
Lys Leu Phe Lys Ala Asp Asn	Thr Pro Leu Asn Val	Thr Asn Ile
1880	1885	1890
Thr His Gly Ser Gly Phe Ser	Ser Val Val Thr Val	Ser Asp Ala
1895	1900	1905
Leu Pro Asn Gly Gly Ile Lys	Ala Lys Ser Ser Ile	Ser Met Asn
1910	1915	1920
Asn Val Thr Tyr Thr Thr Gln	Asp Glu His Gly Gln	Val Val Thr
1925	1930	1935
Val Thr Arg Asn Glu Ser Val	Asp Ser Asn Asp Ser	Ala Thr Val
1940	1945	1950
Thr Val Thr Pro Gln Leu Gln	Ala Thr Thr Glu Gly	Ala Val Phe
1955	1960	1965
Ile Lys Gly Gly Asp Gly Phe	Asp Phe Gly His Val	Glu Arg Phe
1970	1975	1980
Ile Gln Asn Pro Pro His Gly	Ala Thr Val Ala Trp	His Asp Ser
1985	1990	1995
Pro Asp Thr Trp Lys Asn Thr	Val Gly Asn Thr His	Lys Thr Ala
2000	2005	2010
Val Val Thr Leu Pro Asn Gly	Gln Gly Thr Arg Asn	Val Glu Val
2015	2020	2025
Pro Val Lys Val Tyr Pro Val	Ala Asn Ala Lys Ala	Pro Ser Arg
2030	2035	2040
Asp Val Lys Gly Gln Asn Leu	Thr Asn Gly Thr Asp	Ala Met Asn
2045	2050	2055
Tyr Ile Thr Phe Asp Pro Asn	Thr Asn Thr Asn Gly	Ile Thr Ala
2060	2065	2070
Ala Trp Ala Asn Arg Gln Gln	Pro Asn Asn Gln Gln	Ala Gly Val
2075	2080	2085
Gln His Leu Asn Val Asp Val	Thr Tyr Pro Gly Ile	Ser Ala Ala
2090	2095	2100
Lys Arg Val Pro Val Thr Val	Asn Val Tyr Gln Phe	Glu Phe Pro
2105	2110	2115
Gln Thr Thr Tyr Thr Thr Thr	Val Gly Gly Thr Leu	Ala Ser Gly
2120	2125	2130

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Thr Gln	Ala Ser Gly Tyr	Ala	His Met Gln Asn	Ala	Thr Gly Leu
2135		2140		2145	
Pro Thr	Asp Gly Phe Thr	Tyr	Lys Trp Asn Arg	Asp	Thr Thr Gly
2150		2155		2160	
Thr Asn	Asp Ala Asn Trp	Ser	Ala Met Asn Lys	Pro	Asn Val Ala
2165		2170		2175	
Lys Val	Val Asn Ala Lys	Tyr	Asp Val Ile Tyr	Asn	Gly His Thr
2180		2185		2190	
Phe Ala	Thr Ser Leu Pro	Ala	Lys Phe Val Val	Lys	Asp Val Gln
2195		2200		2205	
Pro Ala	Lys Pro Thr Val	Thr	Glu Thr Ala Ala	Gly	Ala Ile Thr
2210		2215		2220	
Ile Ala	Pro Gly Ala Asn	Gln	Thr Val Asn Thr	His	Ala Gly Asn
2225		2230		2235	
Val Thr	Thr Tyr Ala Asp	Lys	Leu Val Ile Lys	Arg	Asn Gly Asn
2240		2245		2250	
Val Val	Thr Thr Phe Thr	Arg	Arg Asn Asn Thr	Ser	Pro Trp Val
2255		2260		2265	
Lys Glu	Ala Ser Ala Ala	Thr	Val Ala Gly Ile	Ala	Gly Thr Asn
2270		2275		2280	
Asn Gly	Ile Thr Val Ala	Ala	Gly Thr Phe Asn	Pro	Ala Asp Thr
2285		2290		2295	
Ile Gln	Val Val Ala Thr	Gln	Gly Ser Gly Glu	Thr	Val Ser Asp
2300		2305		2310	
Glu Gln	Arg Ser Asp Asp	Phe	Thr Val Val Ala	Pro	Gln Pro Asn
2315		2320		2325	
Gln Ala	Thr Thr Lys Ile	Trp	Gln Asn Gly His	Ile	Asp Ile Thr
2330		2335		2340	
Pro Asn	Asn Pro Ser Gly	His	Leu Ile Asn Pro	Thr	Gln Ala Met
2345		2350		2355	
Asp Ile	Ala Tyr Thr Glu	Lys	Val Gly Asn Gly	Ala	Glu His Ser
2360		2365		2370	
Lys Thr	Ile Asn Val Val	Arg	Gly Gln Asn Asn	Gln	Trp Thr Ile
2375		2380		2385	
Ala Asn	Lys Pro Asp Tyr	Val	Thr Leu Asp Ala	Gln	Thr Gly Lys
2390		2395		2400	
Val Thr	Phe Asn Ala Asn	Thr	Ile Lys Pro Asn	Ser	Ser Ile Thr
2405		2410		2415	
Ile Thr	Pro Lys Ala Gly	Thr	Gly His Ser Val	Ser	Ser Asn Pro
2420		2425		2430	
Ser Thr	Leu Thr Ala Pro	Ala	Ala His Thr Val	Asn	Thr Thr Glu
2435		2440		2445	
Ile Val	Lys Asp Tyr Gly	Ser	Asn Val Thr Ala	Ala	Glu Ile Asn
2450		2455		2460	
Asn Ala	Val Gln Val Ala	Asn	Lys Arg Thr Ala	Thr	Ile Lys Asn
2465		2470		2475	
Gly Thr	Ala Met Pro Thr	Asn	Leu Ala Gly Gly	Ser	Thr Thr Thr
2480		2485		2490	
Ile Pro	Val Thr Val Thr	Tyr	Asn Asp Gly Ser	Thr	Glu Glu Val
2495		2500		2505	
Gln Glu	Ser Ile Phe Thr	Lys	Ala Asp Lys Arg	Glu	Leu Ile Thr
2510		2515		2520	
Ala Lys	Asn His Leu Asp	Asp	Pro Val Ser Thr	Glu	Gly Lys Lys

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2525	2530	2535
Pro Gly Thr Ile Thr Gln Tyr Asn Asn Ala Met His Asn Ala Gln		
2540	2545	2550
Gln Gln Ile Asn Thr Ala Lys Thr Glu Ala Gln Gln Val Ile Asn		
2555	2560	2565
Asn Glu Arg Ala Thr Pro Gln Gln Val Ser Asp Ala Leu Thr Lys		
2570	2575	2580
Val Arg Ala Ala Gln Thr Lys Ile Asp Gln Ala Lys Ala Leu Leu		
2585	2590	2595
Gln Asn Lys Glu Asp Asn Ser Gln Leu Val Thr Ser Lys Asn Asn		
2600	2605	2610
Leu Gln Ser Ser Val Asn Gln Val Pro Ser Thr Ala Gly Met Thr		
2615	2620	2625
Gln Gln Ser Ile Asp Asn Tyr Asn Ala Lys Lys Arg Glu Ala Glu		
2630	2635	2640
Thr Glu Ile Thr Ala Ala Gln Arg Val Ile Asp Asn Gly Asp Ala		
2645	2650	2655
Thr Ala Gln Gln Ile Ser Asp Glu Lys His Arg Val Asp Asn Ala		
2660	2665	2670
Leu Thr Ala Leu Asn Gln Ala Lys His Asp Leu Thr Ala Asp Thr		
2675	2680	2685
His Ala Leu Glu Gln Ala Val Gln Gln Leu Asn Arg Thr Gly Thr		
2690	2695	2700
Thr Thr Gly Lys Lys Pro Ala Ser Ile Thr Ala Tyr Asn Asn Ser		
2705	2710	2715
Ile Arg Ala Leu Gln Ser Asp Leu Thr Ser Ala Lys Asn Ser Ala		
2720	2725	2730
Asn Ala Ile Ile Gln Lys Pro Ile Arg Thr Val Gln Glu Val Gln		
2735	2740	2745
Ser Ala Leu Thr Asn Val Asn Arg Val Asn Glu Arg Leu Thr Gln		
2750	2755	2760
Ala Ile Asn Gln Leu Val Pro Leu Ala Asp Asn Ser Ala Leu Lys		
2765	2770	2775
Thr Ala Lys Thr Lys Leu Asp Glu Glu Ile Asn Lys Ser Val Thr		
2780	2785	2790
Thr Asp Gly Met Thr Gln Ser Ser Ile Gln Ala Tyr Glu Asn Ala		
2795	2800	2805
Lys Arg Ala Gly Gln Thr Glu Ser Thr Asn Ala Gln Asn Val Ile		
2810	2815	2820
Asn Asn Gly Asp Ala Thr Asp Gln Gln Ile Ala Ala Glu Lys Thr		
2825	2830	2835
Lys Val Glu Glu Lys Tyr Asn Ser Leu Lys Gln Ala Ile Ala Gly		
2840	2845	2850
Leu Thr Pro Asp Leu Ala Pro Leu Gln Thr Ala Lys Thr Gln Leu		
2855	2860	2865
Gln Asn Asp Ile Asp Gln Pro Thr Ser Thr Thr Gly Met Thr Ser		
2870	2875	2880
Ala Ser Ile Ala Ala Phe Asn Glu Lys Leu Ser Ala Ala Arg Thr		
2885	2890	2895
Lys Ile Gln Glu Ile Asp Arg Val Leu Ala Ser His Pro Asp Val		
2900	2905	2910
Ala Thr Ile Arg Gln Asn Val Thr Ala Ala Asn Ala Ala Lys Ser		
2915	2920	2925

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Ala Leu Asp Gln Ala Arg Asn Gly Leu Thr Val Asp Lys Ala Pro	
2930	2935 2940
Leu Glu Asn Ala Lys Asn Gln Leu Gln His Ser Ile Asp Thr Gln	
2945	2950 2955
Thr Ser Thr Thr Gly Met Thr Gln Asp Ser Ile Asn Ala Tyr Asn	
2960	2965 2970
Ala Lys Leu Thr Ala Ala Arg Asn Lys Ile Gln Gln Ile Asn Gln	
2975	2980 2985
Val Leu Ala Gly Ser Pro Thr Val Glu Gln Ile Asn Thr Asn Thr	
2990	2995 3000
Ser Thr Ala Asn Gln Ala Lys Ser Asp Leu Asp His Ala Arg Gln	
3005	3010 3015
Ala Leu Thr Pro Asp Lys Ala Pro Leu Gln Thr Ala Lys Thr Gln	
3020	3025 3030
Leu Glu Gln Ser Ile Asn Gln Pro Thr Asp Thr Thr Gly Met Thr	
3035	3040 3045
Thr Ala Ser Leu Asn Ala Tyr Asn Gln Lys Leu Gln Ala Ala Arg	
3050	3055 3060
Gln Lys Leu Thr Glu Ile Asn Gln Val Leu Asn Gly Asn Pro Thr	
3065	3070 3075
Val Gln Asn Ile Asn Asp Lys Val Thr Glu Ala Asn Gln Ala Lys	
3080	3085 3090
Asp Gln Leu Asn Thr Ala Arg Gln Gly Leu Thr Leu Asp Arg Gln	
3095	3100 3105
Pro Ala Leu Thr Thr Leu His Gly Ala Ser Asn Leu Asn Gln Ala	
3110	3115 3120
Gln Gln Asn Asn Phe Thr Gln Gln Ile Asn Ala Ala Gln Asn His	
3125	3130 3135
Ala Ala Leu Glu Thr Ile Lys Ser Asn Ile Thr Ala Leu Asn Thr	
3140	3145 3150
Ala Met Thr Lys Leu Lys Asp Ser Val Ala Asp Asn Asn Thr Ile	
3155	3160 3165
Lys Ser Asp Gln Asn Tyr Thr Asp Ala Thr Pro Ala Asn Lys Gln	
3170	3175 3180
Ala Tyr Asp Asn Ala Val Asn Ala Ala Lys Gly Val Ile Gly Glu	
3185	3190 3195
Thr Thr Asn Pro Thr Met Asp Val Asn Thr Val Asn Gln Lys Ala	
3200	3205 3210
Ala Ser Val Lys Ser Thr Lys Asp Ala Leu Asp Gly Gln Gln Asn	
3215	3220 3225
Leu Gln Arg Ala Lys Thr Glu Ala Thr Asn Ala Ile Thr His Ala	
3230	3235 3240
Ser Asp Leu Asn Gln Ala Gln Lys Asn Ala Leu Thr Gln Gln Val	
3245	3250 3255
Asn Ser Ala Gln Asn Val Gln Ala Val Asn Asp Ile Lys Gln Thr	
3260	3265 3270
Thr Gln Ser Leu Asn Thr Ala Met Thr Gly Leu Lys Arg Gly Val	
3275	3280 3285
Ala Asn His Asn Gln Val Val Gln Ser Asp Asn Tyr Val Asn Ala	
3290	3295 3300
Asp Thr Asn Lys Lys Asn Asp Tyr Asn Asn Ala Tyr Asn His Ala	
3305	3310 3315

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Asn Asp 3320	Ile Ile Asn Gly 3325	Asn Ala Gln His 3330	Pro Val Ile Thr Pro 3330
Ser Asp 3335	Val Asn Asn Ala Leu 3340	Ser Asn Val Thr Ser 3345	Lys Glu His
Ala Leu 3350	Asn Gly Glu Ala Lys 3355	Leu Asn Ala Ala Lys 3360	Gln Glu Ala
Asn Thr 3365	Ala Leu Gly His Leu 3370	Asn Asn Leu Asn Asn 3375	Ala Gln Arg
Gln Asn 3380	Leu Gln Ser Gln Ile 3385	Asn Gly Ala His Gln 3390	Ile Asp Ala
Val Asn 3395	Thr Ile Lys Gln Asn 3400	Ala Thr Asn Leu Asn 3405	Ser Ala Met
Gly Asn 3410	Leu Arg Gln Ala Val 3415	Ala Asp Lys Asp Gln 3420	Val Lys Arg
Thr Glu 3425	Asp Tyr Ala Asp Ala 3430	Asp Thr Ala Lys Gln 3435	Asn Ala Tyr
Asn Ser 3440	Ala Val Ser Ser Ala 3445	Glu Thr Ile Ile Asn 3450	Gln Thr Thr
Asn Pro 3455	Thr Met Ser Val Asp 3460	Asp Val Asn Arg Ala 3465	Thr Ser Ala
Val Thr 3470	Ser Asn Lys Asn Ala 3475	Leu Asn Gly Tyr Glu 3480	Lys Leu Ala
Gln Ser 3485	Lys Thr Asp Ala Ala 3490	Arg Ala Ile Asp Ala 3495	Leu Pro His
Leu Asn 3500	Asn Ala Gln Lys Ala 3505	Asp Val Lys Ser Lys 3510	Ile Asn Ala
Ala Ser 3515	Asn Ile Ala Gly Val 3520	Asn Thr Val Lys Gln 3525	Gln Gly Thr
Asp Leu 3530	Asn Thr Ala Met Gly 3535	Asn Leu Gln Gly Ala 3540	Ile Asn Asp
Glu Gln 3545	Thr Thr Leu Asn Ser 3550	Gln Asn Tyr Gln Asp 3555	Ala Thr Pro
Ser Lys 3560	Lys Thr Ala Tyr Thr 3565	Asn Ala Val Gln Ala 3570	Ala Lys Asp
Ile Leu 3575	Asn Lys Ser Asn Gly 3580	Gln Asn Lys Thr Lys 3585	Asp Gln Val
Thr Glu 3590	Ala Met Asn Gln Val 3595	Asn Ser Ala Lys Asn 3600	Asn Leu Asp
Gly Thr 3605	Arg Leu Leu Asp Gln 3610	Ala Lys Gln Thr Ala 3615	Lys Gln Gln
Leu Asn 3620	Asn Met Thr His Leu 3625	Thr Thr Ala Gln Lys 3630	Thr Asn Leu
Thr Asn 3635	Gln Ile Asn Ser Gly 3640	Thr Thr Val Ala Gly 3645	Val Gln Thr
Val Gln 3650	Ser Asn Ala Asn Thr 3655	Leu Asp Gln Ala Met 3660	Asn Thr Leu
Arg Gln 3665	Ser Ile Ala Asn Lys 3670	Asp Ala Thr Lys Ala 3675	Ser Glu Asp
Tyr Val 3680	Asp Ala Asn Asn Asp 3685	Lys Gln Thr Ala Tyr 3690	Asn Asn Ala
Val Ala 3695	Ala Ala Glu Thr Ile 3700	Ile Asn Ala Asn Ser 3705	Asn Pro Glu
Met Asn	Pro Ser Thr Ile Thr	Gln Lys Ala Glu Gln	Val Asn Ser

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3710	3715	3720
Ser Lys Thr Ala Leu Asn Gly Asp Glu Asn Leu Ala Ala Ala Lys		
3725	3730	3735
Gln Asn Ala Lys Thr Tyr Leu Asn Thr Leu Thr Ser Ile Thr Asp		
3740	3745	3750
Ala Gln Lys Asn Asn Leu Ile Ser Gln Ile Thr Ser Ala Thr Arg		
3755	3760	3765
Val Ser Gly Val Asp Thr Val Lys Gln Asn Ala Gln His Leu Asp		
3770	3775	3780
Gln Ala Met Ala Ser Leu Gln Asn Gly Ile Asn Asn Glu Ser Gln		
3785	3790	3795
Val Lys Ser Ser Glu Lys Tyr Arg Asp Ala Asp Thr Asn Lys Gln		
3800	3805	3810
Gln Glu Tyr Asp Asn Ala Ile Thr Ala Ala Lys Ala Ile Leu Asn		
3815	3820	3825
Lys Ser Thr Gly Pro Asn Thr Ala Gln Asn Ala Val Glu Ala Ala		
3830	3835	3840
Leu Gln Arg Val Asn Asn Ala Lys Asp Ala Leu Asn Gly Asp Ala		
3845	3850	3855
Lys Leu Ile Ala Ala Gln Asn Ala Ala Lys Gln His Leu Gly Thr		
3860	3865	3870
Leu Thr His Ile Thr Thr Ala Gln Arg Asn Asp Leu Thr Asn Gln		
3875	3880	3885
Ile Ser Gln Ala Thr Asn Leu Ala Gly Val Glu Ser Val Lys Gln		
3890	3895	3900
Asn Ala Asn Ser Leu Asp Gly Ala Met Gly Asn Leu Gln Thr Ala		
3905	3910	3915
Ile Asn Asp Lys Ser Gly Thr Leu Ala Ser Gln Asn Phe Leu Asp		
3920	3925	3930
Ala Asp Glu Gln Lys Arg Asn Ala Tyr Asn Gln Ala Val Ser Ala		
3935	3940	3945
Ala Glu Thr Ile Leu Asn Lys Gln Thr Gly Pro Asn Thr Ala Lys		
3950	3955	3960
Thr Ala Val Glu Gln Ala Leu Asn Asn Val Asn Asn Ala Lys His		
3965	3970	3975
Ala Leu Asn Gly Thr Gln Asn Leu Asn Asn Ala Lys Gln Ala Ala		
3980	3985	3990
Ile Thr Ala Ile Asn Gly Ala Ser Asp Leu Asn Gln Lys Gln Lys		
3995	4000	4005
Asp Ala Leu Lys Ala Gln Ala Asn Gly Ala Gln Arg Val Ser Asn		
4010	4015	4020
Ala Gln Asp Val Gln His Asn Ala Thr Glu Leu Asn Thr Ala Met		
4025	4030	4035
Gly Thr Leu Lys His Ala Ile Ala Asp Lys Thr Asn Thr Leu Ala		
4040	4045	4050
Ser Ser Lys Tyr Val Asn Ala Asp Ser Thr Lys Gln Asn Ala Tyr		
4055	4060	4065
Thr Thr Lys Val Thr Asn Ala Glu His Ile Ile Ser Gly Thr Pro		
4070	4075	4080
Thr Val Val Thr Thr Pro Ser Glu Val Thr Ala Ala Ala Asn Gln		
4085	4090	4095
Val Asn Ser Ala Lys Gln Glu Leu Asn Gly Asp Glu Arg Leu Arg		
4100	4105	4110

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Glu Ala Lys Gln Asn Ala Asn Thr Ala Ile Asp Ala Leu Thr Gln 4115 4120 4125
Leu Asn Thr Pro Gln Lys Ala Lys Leu Lys Glu Gln Val Gly Gln 4130 4135 4140
Ala Asn Arg Leu Glu Asp Val Gln Thr Val Gln Thr Asn Gly Gln 4145 4150 4155
Ala Leu Asn Asn Ala Met Lys Gly Leu Arg Asp Ser Ile Ala Asn 4160 4165 4170
Glu Thr Thr Val Lys Thr Ser Gln Asn Tyr Thr Asp Ala Ser Pro 4175 4180 4185
Asn Asn Gln Ser Thr Tyr Asn Ser Ala Val Ser Asn Ala Lys Gly 4190 4195 4200
Ile Ile Asn Gln Thr Asn Asn Pro Thr Met Asp Thr Ser Ala Ile 4205 4210 4215
Thr Gln Ala Thr Thr Gln Val Asn Asn Ala Lys Asn Gly Leu Asn 4220 4225 4230
Gly Ala Glu Asn Leu Arg Asn Ala Gln Asn Thr Ala Lys Gln Asn 4235 4240 4245
Leu Asn Thr Leu Ser His Leu Thr Asn Asn Gln Lys Ser Ala Ile 4250 4255 4260
Ser Ser Gln Ile Asp Arg Ala Gly His Val Ser Glu Val Thr Ala 4265 4270 4275
Thr Lys Asn Ala Ala Thr Glu Leu Asn Thr Gln Met Gly Asn Leu 4280 4285 4290
Glu Gln Ala Ile His Asp Gln Asn Thr Val Lys Gln Ser Val Lys 4295 4300 4305
Phe Thr Asp Ala Asp Lys Ala Lys Arg Asp Ala Tyr Thr Asn Ala 4310 4315 4320
Val Ser Arg Ala Glu Ala Ile Leu Asn Lys Thr Gln Gly Ala Asn 4325 4330 4335
Thr Ser Lys Gln Asp Val Glu Ala Ala Ile Gln Asn Val Ser Ser 4340 4345 4350
Ala Lys Asn Ala Leu Asn Gly Asp Gln Asn Val Thr Asn Ala Lys 4355 4360 4365
Asn Ala Ala Lys Asn Ala Leu Asn Asn Leu Thr Ser Ile Asn Asn 4370 4375 4380
Ala Gln Lys Arg Asp Leu Thr Thr Lys Ile Asp Gln Ala Thr Thr 4385 4390 4395
Val Ala Gly Val Glu Ala Val Ser Asn Thr Ser Thr Gln Leu Asn 4400 4405 4410
Thr Ala Met Ala Asn Leu Gln Asn Gly Ile Asn Asp Lys Thr Asn 4415 4420 4425
Thr Leu Ala Ser Glu Asn Tyr His Asp Ala Asp Ser Asp Lys Lys 4430 4435 4440
Thr Ala Tyr Thr Gln Ala Val Thr Asn Ala Glu Asn Ile Leu Asn 4445 4450 4455
Lys Asn Ser Gly Ser Asn Leu Asp Lys Thr Ala Val Glu Asn Ala 4460 4465 4470
Leu Ser Gln Val Ala Asn Ala Lys Gly Ala Leu Asn Gly Asn His 4475 4480 4485
Asn Leu Glu Gln Ala Lys Ser Asn Ala Asn Thr Thr Ile Asn Gly 4490 4495 4500

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Leu	Gln	His	Leu	Thr	Thr	Ala	Gln	Lys	Asp	Lys	Leu	Lys	Gln	Gln
4505						4510					4515			
Val	Gln	Gln	Ala	Gln	Asn	Val	Ala	Gly	Val	Asp	Thr	Val	Lys	Ser
4520						4525					4530			
Ser	Ala	Asn	Thr	Leu	Asn	Gly	Ala	Met	Gly	Thr	Leu	Arg	Asn	Ser
4535						4540					4545			
Ile	Gln	Asp	Asn	Thr	Ala	Thr	Lys	Asn	Gly	Gln	Asn	Tyr	Leu	Asp
4550						4555					4560			
Ala	Thr	Glu	Arg	Asn	Lys	Thr	Asn	Tyr	Asn	Asn	Ala	Val	Asp	Ser
4565						4570					4575			
Ala	Asn	Gly	Val	Ile	Asn	Ala	Thr	Ser	Asn	Pro	Asn	Met	Asp	Ala
4580						4585					4590			
Asn	Ala	Ile	Asn	Gln	Ile	Ala	Thr	Gln	Val	Thr	Ser	Thr	Lys	Asn
4595						4600					4605			
Ala	Leu	Asp	Gly	Thr	His	Asn	Leu	Thr	Gln	Ala	Lys	Gln	Thr	Ala
4610						4615					4620			
Thr	Asn	Ala	Ile	Asp	Gly	Ala	Thr	Asn	Leu	Asn	Lys	Ala	Gln	Lys
4625						4630					4635			
Asp	Ala	Leu	Lys	Ala	Gln	Val	Thr	Ser	Ala	Gln	Arg	Val	Ala	Asn
4640						4645					4650			
Val	Thr	Ser	Ile	Gln	Gln	Thr	Ala	Asn	Glu	Leu	Asn	Thr	Ala	Met
4655						4660					4665			
Gly	Gln	Leu	Gln	His	Gly	Ile	Asp	Asp	Glu	Asn	Ala	Thr	Lys	Gln
4670						4675					4680			
Thr	Gln	Lys	Tyr	Arg	Asp	Ala	Glu	Gln	Ser	Lys	Lys	Thr	Ala	Tyr
4685						4690					4695			
Asp	Gln	Ala	Val	Ala	Ala	Ala	Lys	Ala	Ile	Leu	Asn	Lys	Gln	Thr
4700						4705					4710			
Gly	Ser	Asn	Ser	Asp	Lys	Ala	Ala	Val	Asp	Arg	Ala	Leu	Gln	Gln
4715						4720					4725			
Val	Thr	Ser	Thr	Lys	Asp	Ala	Leu	Asn	Gly	Asp	Ala	Lys	Leu	Ala
4730						4735					4740			
Glu	Ala	Lys	Ala	Ala	Ala	Lys	Gln	Asn	Leu	Gly	Thr	Leu	Asn	His
4745						4750					4755			
Ile	Thr	Asn	Ala	Gln	Arg	Thr	Asp	Leu	Glu	Gly	Gln	Ile	Asn	Gln
4760						4765					4770			
Ala	Thr	Thr	Val	Asp	Gly	Val	Asn	Thr	Val	Lys	Thr	Asn	Ala	Asn
4775						4780					4785			
Thr	Leu	Asp	Gly	Ala	Met	Asn	Ser	Leu	Gln	Gly	Ser	Ile	Asn	Asp
4790						4795					4800			
Lys	Asp	Ala	Thr	Leu	Arg	Asn	Gln	Asn	Tyr	Leu	Asp	Ala	Asp	Glu
4805						4810					4815			
Ser	Lys	Arg	Asn	Ala	Tyr	Thr	Gln	Ala	Val	Thr	Ala	Ala	Glu	Gly
4820						4825					4830			
Ile	Leu	Asn	Lys	Gln	Thr	Gly	Gly	Asn	Thr	Ser	Lys	Ala	Asp	Val
4835						4840					4845			
Asp	Asn	Ala	Leu	Asn	Ala	Val	Thr	Arg	Ala	Lys	Ala	Ala	Leu	Asn
4850						4855					4860			
Gly	Ala	Asp	Asn	Leu	Arg	Asn	Ala	Lys	Thr	Ser	Ala	Thr	Asn	Thr
4865						4870					4875			
Ile	Asp	Gly	Leu	Pro	Asn	Leu	Thr	Gln	Leu	Gln	Lys	Asp	Asn	Leu
4880						4885					4890			
Lys	His	Gln	Val	Glu	Gln	Ala	Gln	Asn	Val	Ala	Gly	Val	Asn	Gly

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4895	4900	4905
Val Lys Asp Lys Gly Asn Thr Leu Asn Thr Ala Met Gly Ala Leu		
4910	4915	4920
Arg Thr Ser Ile Gln Asn Asp Asn Thr Thr Lys Thr Ser Gln Asn		
4925	4930	4935
Tyr Leu Asp Ala Ser Asp Ser Asn Lys Asn Asn Tyr Asn Thr Ala		
4940	4945	4950
Val Asn Asn Ala Asn Gly Val Ile Asn Ala Thr Asn Asn Pro Asn		
4955	4960	4965
Met Asp Ala Asn Ala Ile Asn Gly Met Ala Asn Gln Val Asn Thr		
4970	4975	4980
Thr Lys Ala Ala Leu Asn Gly Ala Gln Asn Leu Ala Gln Ala Lys		
4985	4990	4995
Thr Asn Ala Thr Asn Thr Ile Asn Asn Ala His Asp Leu Asn Gln		
5000	5005	5010
Lys Gln Lys Asp Ala Leu Lys Thr Gln Val Asn Asn Ala Gln Arg		
5015	5020	5025
Val Ser Asp Ala Asn Asn Val Gln His Thr Ala Thr Glu Leu Asn		
5030	5035	5040
Ser Ala Met Thr Ala Leu Lys Ala Ala Ile Ala Asp Lys Glu Arg		
5045	5050	5055
Thr Lys Ala Ser Gly Asn Tyr Val Asn Ala Asp Gln Glu Lys Arg		
5060	5065	5070
Gln Ala Tyr Asp Ser Lys Val Thr Asn Ala Glu Asn Ile Ile Ser		
5075	5080	5085
Gly Thr Pro Asn Ala Thr Leu Thr Val Asn Asp Val Asn Ser Ala		
5090	5095	5100
Ala Ser Gln Val Asn Ala Ala Lys Thr Ala Leu Asn Gly Asp Asn		
5105	5110	5115
Asn Leu Arg Val Ala Lys Glu His Ala Asn Asn Thr Ile Asp Gly		
5120	5125	5130
Leu Ala Gln Leu Asn Asn Ala Gln Lys Ala Lys Leu Lys Glu Gln		
5135	5140	5145
Val Gln Ser Ala Thr Thr Leu Asp Gly Val Gln Thr Val Lys Asn		
5150	5155	5160
Ser Ser Gln Thr Leu Asn Thr Ala Met Lys Gly Leu Arg Asp Ser		
5165	5170	5175
Ile Ala Asn Glu Ala Thr Ile Lys Ala Gly Gln Asn Tyr Thr Asp		
5180	5185	5190
Ala Ser Pro Asn Asn Arg Asn Glu Tyr Asp Ser Ala Val Thr Ala		
5195	5200	5205
Ala Lys Ala Ile Ile Asn Gln Thr Ser Asn Pro Thr Met Glu Pro		
5210	5215	5220
Asn Thr Ile Thr Gln Val Thr Ser Gln Val Thr Thr Lys Glu Gln		
5225	5230	5235
Ala Leu Asn Gly Ala Arg Asn Leu Ala Gln Ala Lys Thr Thr Ala		
5240	5245	5250
Lys Asn Asn Leu Asn Asn Leu Thr Ser Ile Asn Asn Ala Gln Lys		
5255	5260	5265
Asp Ala Leu Thr Arg Ser Ile Asp Gly Ala Thr Thr Val Ala Gly		
5270	5275	5280
Val Asn Gln Glu Thr Ala Lys Ala Thr Glu Leu Asn Asn Ala Met		
5285	5290	5295

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His Ser Leu Gln Asn Gly Ile Asn Asp Glu Thr Gln Thr Lys Gln 5300 5305 5310
Thr Gln Lys Tyr Leu Asp Ala Glu Pro Ser Lys Lys Ser Ala Tyr 5315 5320 5325
Asp Gln Ala Val Asn Ala Ala Lys Ala Ile Leu Thr Lys Ala Ser 5330 5335 5340
Gly Gln Asn Val Asp Lys Ala Ala Val Glu Gln Ala Leu Gln Asn 5345 5350 5355
Val Asn Ser Thr Lys Thr Ala Leu Asn Gly Asp Ala Lys Leu Asn 5360 5365 5370
Glu Ala Lys Ala Ala Ala Lys Gln Thr Leu Gly Thr Leu Thr His 5375 5380 5385
Ile Asn Asn Ala Gln Arg Thr Ala Leu Asp Asn Glu Ile Thr Gln 5390 5395 5400
Ala Thr Asn Val Glu Gly Val Asn Thr Val Lys Ala Lys Ala Gln 5405 5410 5415
Gln Leu Asp Gly Ala Met Gly Gln Leu Glu Thr Ser Ile Arg Asp 5420 5425 5430
Lys Asp Thr Thr Leu Gln Ser Gln Asn Tyr Gln Asp Ala Asp Asp 5435 5440 5445
Ala Lys Arg Thr Ala Tyr Ser Gln Ala Val Asn Ala Ala Ala Thr 5450 5455 5460
Ile Leu Asn Lys Thr Ala Gly Gly Asn Thr Pro Lys Ala Asp Val 5465 5470 5475
Glu Arg Ala Met Gln Ala Val Thr Gln Ala Asn Thr Ala Leu Asn 5480 5485 5490
Gly Ile Gln Asn Leu Asp Arg Ala Lys Gln Ala Ala Asn Thr Ala 5495 5500 5505
Ile Thr Asn Ala Ser Asp Leu Asn Thr Lys Gln Lys Glu Ala Leu 5510 5515 5520
Lys Ala Gln Val Thr Ser Ala Gly Arg Val Ser Ala Ala Asn Gly 5525 5530 5535
Val Glu His Thr Ala Thr Glu Leu Asn Thr Ala Met Thr Ala Leu 5540 5545 5550
Lys Arg Ala Ile Ala Asp Lys Ala Glu Thr Lys Ala Ser Gly Asn 5555 5560 5565
Tyr Val Asn Ala Asp Ala Asn Lys Arg Gln Ala Tyr Asp Glu Lys 5570 5575 5580
Val Thr Ala Ala Glu Asn Ile Val Ser Gly Thr Pro Thr Pro Thr 5585 5590 5595
Leu Thr Pro Ala Asp Val Thr Asn Ala Ala Thr Gln Val Thr Asn 5600 5605 5610
Ala Lys Thr Gln Leu Asn Gly Asn His Asn Leu Glu Val Ala Lys 5615 5620 5625
Gln Asn Ala Asn Thr Ala Ile Asp Gly Leu Thr Ser Leu Asn Gly 5630 5635 5640
Pro Gln Lys Ala Lys Leu Lys Glu Gln Val Gly Gln Ala Thr Thr 5645 5650 5655
Leu Pro Asn Val Gln Thr Val Arg Asp Asn Ala Gln Thr Leu Asn 5660 5665 5670
Thr Ala Met Lys Gly Leu Arg Asp Ser Ile Ala Asn Glu Ala Thr 5675 5680 5685

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Ile Lys	Ala Gly	Gln Asn	Tyr	Thr Asp	Ala Ser	Gln	Asn Lys	Gln	
5690			5695			5700			
Thr Asp	Tyr Asn	Ser Ala	Val	Thr Ala	Ala Lys	Ala	Ile Ile	Gly	
5705			5710			5715			
Gln Thr	Thr Ser	Pro Ser	Met	Asn Ala	Gln Glu	Ile	Asn Gln	Ala	
5720			5725			5730			
Lys Asp	Gln Val	Thr Ala	Lys	Gln Gln	Ala Leu	Asn	Gly Gln	Glu	
5735			5740			5745			
Asn Leu	Arg Thr	Ala Gln	Thr	Asn Ala	Lys Gln	His	Leu Asn	Gly	
5750			5755			5760			
Leu Ser	Asp Leu	Thr Asp	Ala	Gln Lys	Asp Ala	Val	Lys Arg	Gln	
5765			5770			5775			
Ile Glu	Gly Ala	Thr His	Val	Asn Glu	Val Thr	Gln	Ala Gln	Asn	
5780			5785			5790			
Asn Ala	Asp Ala	Leu Asn	Thr	Ala Met	Thr Asn	Leu	Lys Asn	Gly	
5795			5800			5805			
Ile Gln	Asp Gln	Asn Thr	Ile	Lys Gln	Gly Val	Asn	Phe Thr	Asp	
5810			5815			5820			
Ala Asp	Glu Ala	Lys Arg	Asn	Ala Tyr	Thr Asn	Ala	Val Thr	Gln	
5825			5830			5835			
Ala Glu	Gln Ile	Leu Asn	Lys	Ala Gln	Gly Pro	Asn	Thr Ser	Lys	
5840			5845			5850			
Asp Gly	Val Glu	Thr Ala	Leu	Glu Asn	Val Gln	Arg	Ala Lys	Asn	
5855			5860			5865			
Glu Leu	Asn Gly	Asn Gln	Asn	Val Ala	Asn Ala	Lys	Thr Thr	Ala	
5870			5875			5880			
Lys Asn	Ala Leu	Asn Asn	Leu	Thr Ser	Ile Asn	Asn	Ala Gln	Lys	
5885			5890			5895			
Glu Ala	Leu Lys	Ser Gln	Ile	Glu Gly	Ala Thr	Thr	Val Ala	Gly	
5900			5905			5910			
Val Asn	Gln Val	Ser Thr	Thr	Ala Ser	Glu Leu	Asn	Thr Ala	Met	
5915			5920			5925			
Ser Asn	Leu Gln	Asn Gly	Ile	Asn Asp	Glu Ala	Ala	Thr Lys	Ala	
5930			5935			5940			
Ala Gln	Lys Tyr	Thr Asp	Ala	Asp Arg	Glu Lys	Gln	Thr Ala	Tyr	
5945			5950			5955			
Asn Asp	Ala Val	Thr Ala	Ala	Lys Thr	Leu Leu	Asp	Lys Thr	Ala	
5960			5965			5970			
Gly Ser	Asn Asp	Asn Lys	Ala	Ala Val	Glu Gln	Ala	Leu Gln	Arg	
5975			5980			5985			
Val Asn	Thr Ala	Lys Thr	Ala	Leu Asn	Gly Asp	Glu	Arg Leu	Asn	
5990			5995			6000			
Glu Ala	Lys Asn	Thr Ala	Lys	Gln Gln	Val Ala	Thr	Met Ser	His	
6005			6010			6015			
Leu Thr	Asp Ala	Gln Lys	Ala	Asn Leu	Thr Ser	Gln	Ile Glu	Ser	
6020			6025			6030			
Gly Thr	Thr Val	Ala Gly	Val	Gln Gly	Ile Gln	Ala	Asn Ala	Gly	
6035			6040			6045			
Thr Leu	Asp Gln	Ala Met	Asn	Gln Leu	Arg Gln	Ser	Ile Ala	Ser	
6050			6055			6060			
Lys Asp	Ala Thr	Lys Ser	Ser	Glu Asp	Tyr Gln	Asp	Ala Asn	Ala	
6065			6070			6075			
Asp Leu	Gln Asn	Ala Tyr	Asn	Asp Ala	Val Thr	Asn	Ala Glu	Gly	

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6080	6085	6090
Ile Ile Ser Ala Thr Asn Asn Pro Glu Met Asn Pro Asp Thr Ile		
6095	6100	6105
Asn Gln Lys Ala Ser Gln Val Asn Ser Ala Lys Ser Ala Leu Asn		
6110	6115	6120
Gly Asp Glu Lys Leu Ala Ala Ala Lys Gln Thr Ala Lys Ser Asp		
6125	6130	6135
Ile Gly Arg Leu Thr Asp Leu Asn Asn Ala Gln Arg Thr Ala Ala		
6140	6145	6150
Asn Ala Glu Val Asp Gln Ala Pro Asn Leu Ala Ala Val Thr Ala		
6155	6160	6165
Ala Lys Asn Lys Ala Thr Ser Leu Asn Thr Ala Met Gly Asn Leu		
6170	6175	6180
Lys His Ala Leu Ala Glu Lys Asp Asn Thr Lys Arg Ser Val Asn		
6185	6190	6195
Tyr Thr Asp Ala Asp Gln Pro Lys Gln Gln Ala Tyr Asp Thr Ala		
6200	6205	6210
Val Thr Gln Ala Glu Ala Ile Thr Asn Ala Asn Gly Ser Asn Ala		
6215	6220	6225
Asn Glu Thr Gln Val Gln Ala Ala Leu Asn Gln Leu Asn Gln Ala		
6230	6235	6240
Lys Asn Asp Leu Asn Gly Asp Asn Lys Val Ala Gln Ala Lys Glu		
6245	6250	6255
Ser Ala Lys Arg Ala Leu Ala Ser Tyr Ser Asn Leu Asn Asn Ala		
6260	6265	6270
Gln Ser Thr Ala Ala Ile Ser Gln Ile Asp Asn Ala Thr Thr Val		
6275	6280	6285
Ala Gly Val Thr Ala Ala Gln Asn Thr Ala Asn Glu Leu Asn Thr		
6290	6295	6300
Ala Met Gly Gln Leu Gln Asn Gly Ile Asn Asp Gln Asn Thr Val		
6305	6310	6315
Lys Gln Gln Val Asn Phe Thr Asp Ala Asp Gln Gly Lys Lys Asp		
6320	6325	6330
Ala Tyr Thr Asn Ala Val Thr Asn Ala Gln Gly Ile Leu Asp Lys		
6335	6340	6345
Ala His Gly Gln Asn Met Thr Lys Ala Gln Val Glu Ala Ala Leu		
6350	6355	6360
Asn Gln Val Thr Thr Ala Lys Asn Ala Leu Asn Gly Asp Ala Asn		
6365	6370	6375
Val Arg Gln Ala Lys Ser Asp Ala Lys Ala Asn Leu Gly Thr Leu		
6380	6385	6390
Thr His Leu Asn Asn Ala Gln Lys Gln Asp Leu Thr Ser Gln Ile		
6395	6400	6405
Glu Gly Ala Thr Thr Val Asn Gly Val Asn Gly Val Lys Thr Lys		
6410	6415	6420
Ala Gln Asp Leu Asp Gly Ala Met Gln Arg Leu Gln Ser Ala Ile		
6425	6430	6435
Ala Asn Lys Asp Gln Thr Lys Ala Ser Glu Asn Tyr Ile Asp Ala		
6440	6445	6450
Asp Pro Thr Lys Lys Thr Ala Phe Asp Asn Ala Ile Thr Gln Ala		
6455	6460	6465
Glu Ser Tyr Leu Asn Lys Asp His Gly Ala Asn Lys Asp Lys Gln		
6470	6475	6480

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Ala Val	Glu Gln Ala Ile	Gln Ser Val Thr Ser Thr	Glu Asn Ala
6485		6490	6495
Leu Asn	Gly Asp Ala Asn	Leu Gln Arg Ala Lys Thr	Glu Ala Ile
6500		6505	6510
Gln Ala	Ile Asp Asn Leu Thr	His Leu Asn Thr Pro	Gln Lys Thr
6515		6520	6525
Ala Leu	Lys Gln Gln Val Asn	Ala Ala Gln Arg Val	Ser Gly Val
6530		6535	6540
Thr Asp	Leu Lys Asn Ser Ala	Thr Ser Leu Asn Asn	Ala Met Asp
6545		6550	6555
Gln Leu	Lys Gln Ala Ile Ala	Asp His Asp Thr Ile	Val Ala Ser
6560		6565	6570
Gly Asn	Tyr Thr Asn Ala Ser	Pro Asp Lys Gln Gly	Ala Tyr Thr
6575		6580	6585
Asp Ala	Tyr Asn Ala Ala Lys	Asn Ile Val Asn Gly	Ser Pro Asn
6590		6595	6600
Val Ile	Thr Asn Ala Ala Asp	Val Thr Ala Ala Thr	Gln Arg Val
6605		6610	6615
Asn Asn	Ala Glu Thr Gly Leu	Asn Gly Asp Thr Asn	Leu Ala Thr
6620		6625	6630
Ala Lys	Gln Gln Ala Lys Asp	Ala Leu Arg Gln Met	Thr His Leu
6635		6640	6645
Ser Asp	Ala Gln Lys Gln Ser	Ile Thr Gly Gln Ile	Asp Ser Ala
6650		6655	6660
Thr Gln	Val Thr Gly Val Gln	Ser Val Lys Asp Asn	Ala Thr Asn
6665		6670	6675
Leu Asp	Asn Ala Met Asn Gln	Leu Arg Asn Ser Ile	Ala Asn Lys
6680		6685	6690
Asp Asp	Val Lys Ala Ser Gln	Pro Tyr Val Asp Ala	Asp Arg Asp
6695		6700	6705
Lys Gln	Asn Ala Tyr Asn Thr	Ala Val Thr Asn Ala	Glu Asn Ile
6710		6715	6720
Ile Asn	Ala Thr Ser Gln Pro	Thr Leu Asp Pro Ser	Ala Val Thr
6725		6730	6735
Gln Ala	Ala Asn Gln Val Ser	Thr Asn Lys Thr Ala	Leu Asn Gly
6740		6745	6750
Ala Gln	Asn Leu Ala Asn Lys	Lys Gln Glu Thr Thr	Ala Asn Ile
6755		6760	6765
Asn Gln	Leu Ser His Leu Asn	Asn Ala Gln Lys Gln	Asp Leu Asn
6770		6775	6780
Thr Gln	Val Thr Asn Ala Pro	Asn Ile Ser Thr Val	Asn Gln Val
6785		6790	6795
Lys Thr	Lys Ala Glu Gln Leu	Asp Gln Ala Met Glu	Arg Leu Ile
6800		6805	6810
Asn Gly	Ile Gln Asp Lys Asp	Gln Val Lys Gln Ser	Val Asn Phe
6815		6820	6825
Thr Asp	Ala Asp Pro Glu Lys	Gln Thr Ala Tyr Asn	Asn Ala Val
6830		6835	6840
Thr Ala	Ala Glu Asn Ile Ile	Asn Gln Ala Asn Gly	Thr Asn Ala
6845		6850	6855
Asn Gln	Ser Gln Val Glu Ala	Ala Leu Ser Thr Val	Thr Thr Thr
6860		6865	6870

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Lys 6875	Gln	Ala	Leu	Asn	Gly	Asp 6880	Arg	Lys	Val	Thr	Asp 6885	Ala	Lys	Asn
Asn 6890	Ala	Asn	Gln	Thr	Leu	Ser 6895	Thr	Leu	Asp	Asn	Leu 6900	Asn	Asn	Ala
Gln 6905	Lys	Gly	Ala	Val	Thr	Gly 6910	Asn	Ile	Asn	Gln	Ala 6915	His	Thr	Val
Ala 6920	Glu	Val	Thr	Gln	Ala	Ile 6925	Gln	Thr	Ala	Gln	Glu 6930	Leu	Asn	Thr
Ala 6935	Met	Gly	Asn	Leu	Lys	Asn 6940	Ser	Leu	Asn	Asp	Lys 6945	Asp	Thr	Thr
Leu 6950	Gly	Ser	Gln	Asn	Phe	Ala 6955	Asp	Ala	Asp	Pro	Glu 6960	Lys	Lys	Asn
Ala 6965	Tyr	Asn	Glu	Ala	Val	His 6970	Asn	Ala	Glu	Asn	Ile 6975	Leu	Asn	Lys
Ser 6980	Thr	Gly	Thr	Asn	Val	Pro 6985	Lys	Asp	Gln	Val	Glu 6990	Ala	Ala	Met
Asn 6995	Gln	Val	Asn	Ala	Thr	Lys 7000	Ala	Ala	Leu	Asn	Gly 7005	Thr	Gln	Asn
Leu 7010	Glu	Lys	Ala	Lys	Gln	His 7015	Ala	Asn	Thr	Ala	Ile 7020	Asp	Gly	Leu
Ser 7025	His	Leu	Thr	Asn	Ala	Gln 7030	Lys	Glu	Ala	Leu	Lys 7035	Gln	Leu	Val
Gln 7040	Gln	Ser	Thr	Thr	Val	Ala 7045	Glu	Ala	Gln	Gly	Asn 7050	Glu	Gln	Lys
Ala 7055	Asn	Asn	Val	Asp	Ala	Ala 7060	Met	Asp	Lys	Leu	Arg 7065	Gln	Ser	Ile
Ala 7070	Asp	Asn	Ala	Thr	Thr	Lys 7075	Gln	Asn	Gln	Asn	Tyr 7080	Thr	Asp	Ala
Ser 7085	Gln	Asn	Lys	Lys	Asp	Ala 7090	Tyr	Asn	Asn	Ala	Val 7095	Thr	Thr	Ala
Gln 7100	Gly	Ile	Ile	Asp	Gln	Thr 7105	Thr	Ser	Pro	Thr	Leu 7110	Asp	Pro	Thr
Val 7115	Ile	Asn	Gln	Ala	Ala	Gly 7120	Gln	Val	Ser	Thr	Thr 7125	Lys	Asn	Ala
Leu 7130	Asn	Gly	Asn	Glu	Asn	Leu 7135	Glu	Ala	Ala	Lys	Gln 7140	Gln	Ala	Ser
Gln 7145	Ser	Leu	Gly	Ser	Leu	Asp 7150	Asn	Leu	Asn	Asn	Ala 7155	Gln	Lys	Gln
Thr 7160	Val	Thr	Asp	Gln	Ile	Asn 7165	Gly	Ala	His	Thr	Val 7170	Asp	Glu	Ala
Asn 7175	Gln	Ile	Lys	Gln	Asn	Ala 7180	Gln	Asn	Leu	Asn	Thr 7185	Ala	Met	Gly
Asn 7190	Leu	Lys	Gln	Ala	Ile	Ala 7195	Asp	Lys	Asp	Ala	Thr 7200	Lys	Ala	Thr
Val 7205	Asn	Phe	Thr	Asp	Ala	Asp 7210	Gln	Ala	Lys	Gln	Gln 7215	Ala	Tyr	Asn
Thr 7220	Ala	Val	Thr	Asn	Ala	Glu 7225	Asn	Ile	Ser	Lys	Ala 7230	Asn	Gly	Asn
Ala 7235	Thr	Gln	Ala	Glu	Val	Glu 7240	Gln	Ala	Ile	Lys	Gln 7245	Val	Asn	Ala
Ala 7250	Lys	Gln	Ala	Leu	Asn	Gly 7255	Asn	Ala	Asn	Val	Gln 7260	His	Ala	Lys
Asp 7265	Glu	Ala	Thr	Ala	Leu	Ile	Asn	Ser	Ser	Asn	Asp	Leu	Asn	Gln

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7265	7270	7275
Ala Gln Lys Asp Ala Leu Lys Gln Gln Val Gln Asn Ala Thr Thr		
7280	7285	7290
Val Ala Gly Val Asn Asn Val Lys Gln Thr Ala Gln Glu Leu Asn		
7295	7300	7305
Asn Ala Met Thr Gln Leu Lys Gln Gly Ile Ala Asp Lys Glu Gln		
7310	7315	7320
Thr Lys Ala Asp Gly Asn Phe Val Asn Ala Asp Pro Asp Lys Gln		
7325	7330	7335
Asn Ala Tyr Asn Gln Ala Val Ala Lys Ala Glu Ala Leu Ile Ser		
7340	7345	7350
Ala Thr Pro Asp Val Val Val Thr Pro Ser Glu Ile Thr Ala Ala		
7355	7360	7365
Leu Asn Lys Val Thr Gln Ala Lys Asn Asp Leu Asn Gly Asn Thr		
7370	7375	7380
Asn Leu Ala Thr Ala Lys Gln Asn Val Gln His Ala Ile Asp Gln		
7385	7390	7395
Leu Pro Asn Leu Asn Gln Ala Gln Arg Asp Glu Tyr Ser Lys Gln		
7400	7405	7410
Ile Thr Gln Ala Thr Leu Val Pro Asn Val Asn Ala Ile Gln Gln		
7415	7420	7425
Ala Ala Thr Thr Leu Asn Asp Ala Met Thr Gln Leu Lys Gln Gly		
7430	7435	7440
Ile Ala Asn Lys Ala Gln Ile Lys Gly Ser Glu Asn Tyr His Asp		
7445	7450	7455
Ala Asp Thr Asp Lys Gln Thr Ala Tyr Asp Asn Ala Val Thr Lys		
7460	7465	7470
Ala Glu Glu Leu Leu Lys Gln Thr Thr Asn Pro Thr Met Asp Pro		
7475	7480	7485
Asn Thr Ile Gln Gln Ala Leu Thr Lys Val Asn Asp Thr Asn Gln		
7490	7495	7500
Ala Leu Asn Gly Asn Gln Lys Leu Ala Asp Ala Lys Gln Asp Ala		
7505	7510	7515
Lys Thr Thr Leu Gly Thr Leu Asp His Leu Asn Asp Ala Gln Lys		
7520	7525	7530
Gln Ala Leu Thr Thr Gln Val Glu Gln Ala Pro Asp Ile Ala Thr		
7535	7540	7545
Val Asn Asn Val Lys Gln Asn Ala Gln Asn Leu Asn Asn Ala Met		
7550	7555	7560
Thr Asn Leu Asn Asn Ala Leu Gln Asp Lys Thr Glu Thr Leu Asn		
7565	7570	7575
Ser Ile Asn Phe Thr Asp Ala Asp Gln Ala Lys Lys Asp Ala Tyr		
7580	7585	7590
Thr Asn Ala Val Ser His Ala Glu Gly Ile Leu Ser Lys Ala Asn		
7595	7600	7605
Gly Ser Asn Ala Ser Gln Thr Glu Val Glu Gln Ala Met Gln Arg		
7610	7615	7620
Val Asn Glu Ala Lys Gln Ala Leu Asn Gly Asn Asp Asn Val Gln		
7625	7630	7635
Arg Ala Lys Asp Ala Ala Lys Gln Val Ile Thr Asn Ala Asn Asp		
7640	7645	7650
Leu Asn Gln Ala Gln Lys Asp Ala Leu Lys Gln Gln Val Asp Ala		
7655	7660	7665

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Ala Gln Thr Val Ala Asn Val	Asn Thr Ile Lys Gln Thr Ala Gln
7670	7675 7680
Asp Leu Asn Gln Ala Met Thr	Gln Leu Lys Gln Gly Ile Ala Asp
7685	7690 7695
Lys Asp Gln Thr Lys Ala Asn	Gly Asn Phe Val Asn Ala Asp Thr
7700	7705 7710
Asp Lys Gln Asn Ala Tyr Asn	Asn Ala Val Ala His Ala Glu Gln
7715	7720 7725
Ile Ile Ser Gly Thr Pro Asn	Ala Asn Val Asp Pro Gln Gln Val
7730	7735 7740
Ala Gln Ala Leu Gln Gln Val	Asn Gln Ala Lys Gly Asp Leu Asn
7745	7750 7755
Gly Asn His Asn Leu Gln Val	Ala Lys Asp Asn Ala Asn Thr Ala
7760	7765 7770
Ile Asp Gln Leu Pro Asn Leu	Asn Gln Pro Gln Lys Thr Ala Leu
7775	7780 7785
Lys Asp Gln Val Ser His Ala	Glu Leu Val Thr Gly Val Asn Ala
7790	7795 7800
Ile Lys Gln Asn Ala Asp Ala	Leu Asn Asn Ala Met Gly Thr Leu
7805	7810 7815
Lys Gln Gln Ile Gln Ala Asn	Ser Gln Val Pro Gln Ser Val Asp
7820	7825 7830
Phe Thr Gln Ala Asp Gln Asp	Lys Gln Gln Ala Tyr Asn Asn Ala
7835	7840 7845
Ala Asn Gln Ala Gln Gln Ile	Ala Asn Gly Ile Pro Thr Pro Val
7850	7855 7860
Leu Thr Pro Asp Thr Val Thr	Gln Ala Val Thr Thr Met Asn Gln
7865	7870 7875
Ala Lys Asp Ala Leu Asn Gly	Asp Glu Lys Leu Ala Gln Ala Lys
7880	7885 7890
Gln Glu Ala Leu Ala Asn Leu	Asp Thr Leu Arg Asp Leu Asn Gln
7895	7900 7905
Pro Gln Arg Asp Ala Leu Arg	Asn Gln Ile Asn Gln Ala Gln Ala
7910	7915 7920
Leu Ala Thr Val Glu Gln Thr	Lys Gln Asn Ala Gln Asn Val Asn
7925	7930 7935
Thr Ala Met Ser Asn Leu Lys	Gln Gly Ile Ala Asn Lys Asp Thr
7940	7945 7950
Val Lys Ala Ser Glu Asn Tyr	His Asp Ala Asp Ala Asp Lys Gln
7955	7960 7965
Thr Ala Tyr Thr Asn Ala Val	Ser Gln Ala Glu Gly Ile Ile Asn
7970	7975 7980
Gln Thr Thr Asn Pro Thr Leu	Asn Pro Asp Glu Ile Thr Arg Ala
7985	7990 7995
Leu Thr Gln Val Thr Asp Ala	Lys Asn Gly Leu Asn Gly Glu Ala
8000	8005 8010
Lys Leu Ala Thr Glu Lys Gln	Asn Ala Lys Asp Ala Val Ser Gly
8015	8020 8025
Met Thr His Leu Asn Asp Ala	Gln Lys Gln Ala Leu Lys Gly Gln
8030	8035 8040
Ile Asp Gln Ser Pro Glu Ile	Ala Thr Val Asn Gln Val Lys Gln
8045	8050 8055

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Thr Ala 8060	Thr Ser Leu Asp 8065	Gln Ala Met Asp 8070	Gln Leu Ser Gln Ala
Ile Asn 8075	Asp Lys Ala Gln Thr 8080	Leu Ala Asp Gly Asn 8085	Tyr Leu Asn
Ala Asp 8090	Pro Asp Lys Gln Asn 8095	Ala Tyr Lys Gln Ala 8100	Val Ala Lys
Ala Glu 8105	Ala Leu Leu Asn Lys 8110	Gln Ser Gly Thr Asn 8115	Glu Val Gln
Ala Gln 8120	Val Glu Ser Ile Thr 8125	Asn Glu Val Asn Ala 8130	Ala Lys Gln
Ala Leu 8135	Asn Gly Asn Asp Asn 8140	Leu Ala Asn Ala Lys 8145	Gln Gln Ala
Lys Gln 8150	Gln Leu Ala Asn Leu 8155	Thr His Leu Asn Asp 8160	Ala Gln Lys
Gln Ser 8165	Phe Glu Ser Gln Ile 8170	Thr Gln Ala Pro Leu 8175	Val Thr Asp
Val Thr 8180	Thr Ile Asn Gln Lys 8185	Ala Gln Thr Leu Asp 8190	His Ala Met
Glu Leu 8195	Leu Arg Asn Ser Val 8200	Ala Asp Asn Gln Thr 8205	Thr Leu Ala
Ser Glu 8210	Asp Tyr His Asp Ala 8215	Thr Ala Gln Arg Gln 8220	Asn Asp Tyr
Asn Gln 8225	Ala Val Thr Ala Ala 8230	Asn Asn Ile Ile Asn 8235	Gln Thr Thr
Ser Pro 8240	Thr Met Asn Pro Asp 8245	Asp Val Asn Gly Ala 8250	Thr Thr Gln
Val Asn 8255	Asn Thr Lys Val Ala 8260	Leu Asp Gly Asp Glu 8265	Asn Leu Ala
Ala Ala 8270	Lys Gln Gln Ala Asn 8275	Asn Arg Leu Asp Gln 8280	Leu Asp His
Leu Asn 8285	Asn Ala Gln Lys Gln 8290	Gln Leu Gln Ser Gln 8295	Ile Thr Gln
Ser Ser 8300	Asp Ile Ala Ala Val 8305	Asn Gly His Lys Gln 8310	Thr Ala Glu
Ser Leu 8315	Asn Thr Ala Met Gly 8320	Asn Leu Ile Asn Ala 8325	Ile Ala Asp
His Gln 8330	Ala Val Glu Gln Arg 8335	Gly Asn Phe Ile Asn 8340	Ala Asp Thr
Asp Lys 8345	Gln Thr Ala Tyr Asn 8350	Thr Ala Val Asn Glu 8355	Ala Ala Ala
Met Ile 8360	Asn Lys Gln Thr Gly 8365	Gln Asn Ala Asn Gln 8370	Thr Glu Val
Glu Gln 8375	Ala Ile Thr Lys Val 8380	Gln Thr Thr Leu Gln 8385	Ala Leu Asn
Gly Asp 8390	His Asn Leu Gln Val 8395	Ala Lys Thr Asn Ala 8400	Thr Gln Ala
Ile Asp 8405	Ala Leu Thr Ser Leu 8410	Asn Asp Pro Gln Lys 8415	Thr Ala Leu
Lys Asp 8420	Gln Val Thr Ala Ala 8425	Thr Leu Val Thr Ala 8430	Val His Gln
Ile Glu 8435	Gln Asn Ala Asn Thr 8440	Leu Asn Gln Ala Met 8445	His Gly Leu
Arg Gln	Ser Ile Gln Asp Asn	Ala Ala Thr Lys Ala	Asn Ser Lys

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8450	8455	8460
Tyr Ile Asn Glu Asp Gln Pro Glu Gln Gln Asn Tyr Asp Gln Ala		
8465	8470	8475
Val Gln Ala Ala Asn Asn Ile Ile Asn Glu Gln Thr Ala Thr Leu		
8480	8485	8490
Asp Asn Asn Ala Ile Asn Gln Ala Ala Thr Thr Val Asn Thr Thr		
8495	8500	8505
Lys Ala Ala Leu His Gly Asp Val Lys Leu Gln Asn Asp Lys Asp		
8510	8515	8520
His Ala Lys Gln Thr Val Ser Gln Leu Ala His Leu Asn Asn Ala		
8525	8530	8535
Gln Lys His Met Glu Asp Thr Leu Ile Asp Ser Glu Thr Thr Arg		
8540	8545	8550
Thr Ala Val Lys Gln Asp Leu Thr Glu Ala Gln Ala Leu Asp Gln		
8555	8560	8565
Leu Met Asp Ala Leu Gln Gln Ser Ile Ala Asp Lys Asp Ala Thr		
8570	8575	8580
Arg Ala Ser Ser Ala Tyr Val Asn Ala Glu Pro Asn Lys Lys Gln		
8585	8590	8595
Ser Tyr Asp Glu Ala Val Gln Asn Ala Glu Ser Ile Ile Ala Gly		
8600	8605	8610
Leu Asn Asn Pro Thr Ile Asn Lys Gly Asn Val Ser Ser Ala Thr		
8615	8620	8625
Gln Ala Val Ile Ser Ser Lys Asn Ala Leu Asp Gly Val Glu Arg		
8630	8635	8640
Leu Ala Gln Asp Lys Gln Thr Ala Gly Asn Ser Leu Asn His Leu		
8645	8650	8655
Asp Gln Leu Thr Pro Ala Gln Gln Gln Ala Leu Glu Asn Gln Ile		
8660	8665	8670
Asn Asn Ala Thr Thr Arg Gly Glu Val Ala Gln Lys Leu Thr Glu		
8675	8680	8685
Ala Gln Ala Leu Asn Gln Ala Met Glu Ala Leu Arg Asn Ser Ile		
8690	8695	8700
Gln Asp Gln Gln Gln Thr Glu Ala Gly Ser Lys Phe Ile Asn Glu		
8705	8710	8715
Asp Lys Pro Gln Lys Asp Ala Tyr Gln Ala Ala Val Gln Asn Ala		
8720	8725	8730
Lys Asp Leu Ile Asn Gln Thr Asn Asn Pro Thr Leu Asp Lys Ala		
8735	8740	8745
Gln Val Glu Gln Leu Thr Gln Ala Val Asn Gln Ala Lys Asp Asn		
8750	8755	8760
Leu His Gly Asp Gln Lys Leu Ala Asp Asp Lys Gln His Ala Val		
8765	8770	8775
Thr Asp Leu Asn Gln Leu Asn Gly Leu Asn Asn Pro Gln Arg Gln		
8780	8785	8790
Ala Leu Glu Ser Gln Ile Asn Asn Ala Ala Thr Arg Gly Glu Val		
8795	8800	8805
Ala Gln Lys Leu Ala Glu Ala Lys Ala Leu Asp Gln Ala Met Gln		
8810	8815	8820
Ala Leu Arg Asn Ser Ile Gln Asp Gln Gln Gln Thr Glu Ser Gly		
8825	8830	8835
Ser Lys Phe Ile Asn Glu Asp Lys Pro Gln Lys Asp Ala Tyr Gln		
8840	8845	8850

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Ala	Ala	Val	Gln	Asn	Ala	Lys	Asp	Leu	Ile	Asn	Gln	Thr	Gly	Asn	
8855						8860					8865				
Pro	Thr	Leu	Asp	Lys	Ser	Gln	Val	Glu	Gln	Leu	Thr	Gln	Ala	Val	
8870						8875					8880				
Thr	Thr	Ala	Lys	Asp	Asn	Leu	His	Gly	Asp	Gln	Lys	Leu	Ala	Arg	
8885						8890					8895				
Asp	Gln	Gln	Gln	Ala	Val	Thr	Thr	Val	Asn	Ala	Leu	Pro	Asn	Leu	
8900						8905					8910				
Asn	His	Ala	Gln	Gln	Gln	Ala	Leu	Thr	Asp	Ala	Ile	Asn	Ala	Ala	
8915						8920					8925				
Pro	Thr	Arg	Thr	Glu	Val	Ala	Gln	His	Val	Gln	Thr	Ala	Thr	Glu	
8930						8935					8940				
Leu	Asp	His	Ala	Met	Glu	Thr	Leu	Lys	Asn	Lys	Val	Asp	Gln	Val	
8945						8950					8955				
Asn	Thr	Asp	Lys	Ala	Gln	Pro	Asn	Tyr	Thr	Glu	Ala	Ser	Thr	Asp	
8960						8965					8970				
Lys	Lys	Glu	Ala	Val	Asp	Gln	Ala	Leu	Gln	Ala	Ala	Glu	Ser	Ile	
8975						8980					8985				
Thr	Asp	Pro	Thr	Asn	Gly	Ser	Asn	Ala	Asn	Lys	Asp	Ala	Val	Asp	
8990						8995					9000				
Gln	Val	Leu	Thr	Lys	Leu	Gln	Glu	Lys	Glu	Asn	Glu	Leu	Asn	Gly	
9005						9010					9015				
Asn	Glu	Arg	Val	Ala	Glu	Ala	Lys	Thr	Gln	Ala	Lys	Gln	Thr	Ile	
9020						9025					9030				
Asp	Gln	Leu	Thr	His	Leu	Asn	Ala	Asp	Gln	Ile	Ala	Thr	Ala	Lys	
9035						9040					9045				
Gln	Asn	Ile	Asp	Gln	Ala	Thr	Lys	Leu	Gln	Pro	Ile	Ala	Glu	Leu	
9050						9055					9060				
Val	Asp	Gln	Ala	Thr	Gln	Leu	Asn	Gln	Ser	Met	Asp	Gln	Leu	Gln	
9065						9070					9075				
Gln	Ala	Val	Asn	Glu	His	Ala	Asn	Val	Glu	Gln	Thr	Val	Asp	Tyr	
9080						9085					9090				
Thr	Gln	Ala	Asp	Ser	Asp	Lys	Gln	Asn	Ala	Tyr	Lys	Gln	Ala	Ile	
9095						9100					9105				
Ala	Asp	Ala	Glu	Asn	Val	Leu	Lys	Gln	Asn	Ala	Asn	Lys	Gln	Gln	
9110						9115					9120				
Val	Asp	Gln	Ala	Leu	Gln	Asn	Ile	Leu	Asn	Ala	Lys	Gln	Ala	Leu	
9125						9130					9135				
Asn	Gly	Asp	Glu	Arg	Val	Ala	Leu	Ala	Lys	Thr	Asn	Gly	Lys	His	
9140						9145					9150				
Asp	Ile	Asp	Gln	Leu	Asn	Ala	Leu	Asn	Asn	Ala	Gln	Gln	Asp	Gly	
9155						9160					9165				
Phe	Lys	Gly	Arg	Ile	Asp	Gln	Ser	Asn	Asp	Leu	Asn	Gln	Ile	Gln	
9170						9175					9180				
Gln	Ile	Val	Asp	Glu	Ala	Lys	Ala	Leu	Asn	Arg	Ala	Met	Asp	Gln	
9185						9190					9195				
Leu	Ser	Gln	Glu	Ile	Thr	Asp	Asn	Glu	Gly	Arg	Thr	Lys	Gly	Ser	
9200						9205					9210				
Thr	Asn	Tyr	Val	Asn	Ala	Asp	Thr	Gln	Val	Lys	Gln	Val	Tyr	Asp	
9215						9220					9225				
Glu	Thr	Val	Asp	Lys	Ala	Lys	Gln	Ala	Leu	Asp	Lys	Ser	Thr	Gly	
9230						9235					9240				

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Gln Asn 9245	Leu Thr Ala Lys	Gln Val Ile Lys	Leu Asn Asp Ala Val 9255
Thr Ala 9260	Ala Lys Lys Ala	Leu Asn Gly Glu Glu Arg 9265 9270	Leu Asn Asn
Arg Lys 9275	Ala Glu Ala Leu	Gln Arg Leu Asp Gln	Leu Thr His Leu 9285
Asn Asn 9290	Ala Gln Arg Gln	Leu Ala Ile Gln Gln	Ile Asn Asn Ala 9300
Glu Thr 9305	Leu Asn Lys Ala	Ser Arg Ala Ile Asn Arg 9310 9315	Ala Thr Lys
Leu Asp 9320	Asn Ala Met Gly	Ala Val Gln Gln Tyr	Ile Asp Glu Gln 9330
His Leu 9335	Gly Val Ile Ser	Ser Thr Asn Tyr Ile	Asn Ala Asp Asp 9345
Asn Leu 9350	Lys Ala Asn Tyr	Asp Asn Ala Ile Ala	Asn Ala Ala His 9360
Glu Leu 9365	Asp Lys Val Gln	Gly Asn Ala Ile Ala	Lys Ala Glu Ala 9375
Glu Gln 9380	Leu Lys Gln Asn	Ile Ile Asp Ala Gln	Asn Ala Leu Asn 9390
Gly Asp 9395	Gln Asn Leu Ala	Asn Ala Lys Asp Lys	Ala Asn Ala Phe 9405
Val Asn 9410	Ser Leu Asn Gly	Leu Asn Gln Gln Gln	Gln Asp Leu Ala 9420
His Lys 9425	Ala Ile Asn Asn	Ala Asp Thr Val Ser	Asp Val Thr Asp 9435
Ile Val 9440	Asn Asn Gln Ile	Asp Leu Asn Asp Ala	Met Glu Thr Leu 9450
Lys His 9455	Leu Val Asp Asn	Glu Ile Pro Asn Ala	Glu Gln Thr Val 9465
Asn Tyr 9470	Gln Asn Ala Asp	Asp Asn Ala Lys Thr	Asn Phe Asp Asp 9480
Ala Lys 9485	Arg Leu Ala Asn	Thr Leu Leu Asn Ser	Asp Asn Thr Asn 9495
Val Asn 9500	Asp Ile Asn Gly	Ala Ile Gln Ala Val	Asn Asp Ala Ile 9510
His Asn 9515	Leu Asn Gly Asp	Gln Arg Leu Gln Asp	Ala Lys Asp Lys 9525
Ala Ile 9530	Gln Ser Ile Asn	Gln Ala Leu Ala Asn	Lys Leu Lys Glu 9540
Ile Glu 9545	Ala Ser Asn Ala	Thr Asp Gln Asp Lys	Leu Ile Ala Lys 9555
Asn Lys 9560	Ala Glu Glu Leu	Ala Asn Ser Ile Ile	Asn Asn Ile Asn 9570
Lys Ala 9575	Thr Ser Asn Gln	Ala Val Ser Gln Val	Gln Thr Ala Gly 9585
Asn His 9590	Ala Ile Glu Gln	Val His Ala Asn Glu	Ile Pro Lys Ala 9600
Lys Ile 9605	Asp Ala Asn Lys	Asp Val Asp Lys Gln	Val Gln Ala Leu 9615
Ile Asp 9620	Glu Ile Asp Arg	Asn Pro Asn Leu Thr	Asp Lys Glu Lys 9630
Gln Ala	Leu Lys Asp Arg	Ile Asn Gln Ile Leu	Gln Gln Gly His

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9635	9640	9645
Asn Gly Ile Asn Asn Ala Met Thr Lys Glu Glu Ile Glu Gln Ala		
9650	9655	9660
Lys Ala Gln Leu Ala Gln Ala Leu Gln Asp Ile Lys Asp Leu Val		
9665	9670	9675
Lys Ala Lys Glu Asp Ala Lys Gln Asp Val Asp Lys Gln Val Gln		
9680	9685	9690
Ala Leu Ile Asp Glu Ile Asp Gln Asn Pro Asn Leu Thr Asp Lys		
9695	9700	9705
Glu Lys Gln Ala Leu Lys Tyr Arg Ile Asn Gln Ile Leu Gln Gln		
9710	9715	9720
Gly His Asn Asp Ile Asn Asn Ala Leu Thr Lys Glu Glu Ile Glu		
9725	9730	9735
Gln Ala Lys Ala Gln Leu Ala Gln Ala Leu Gln Asp Ile Lys Asp		
9740	9745	9750
Leu Val Lys Ala Lys Glu Asp Ala Lys Asn Ala Ile Lys Ala Leu		
9755	9760	9765
Ala Asn Ala Lys Arg Asp Gln Ile Asn Ser Asn Pro Asp Leu Thr		
9770	9775	9780
Pro Glu Gln Lys Ala Lys Ala Leu Lys Glu Ile Asp Glu Ala Glu		
9785	9790	9795
Lys Arg Ala Leu Gln Asn Val Glu Asn Ala Gln Thr Ile Asp Gln		
9800	9805	9810
Leu Asn Arg Gly Leu Asn Leu Gly Leu Asp Asp Ile Arg Asn Thr		
9815	9820	9825
His Val Trp Glu Val Asp Glu Gln Pro Ala Val Asn Glu Ile Phe		
9830	9835	9840
Glu Ala Thr Pro Glu Gln Ile Leu Val Asn Gly Glu Leu Ile Val		
9845	9850	9855
His Arg Asp Asp Ile Ile Thr Glu Gln Asp Ile Leu Ala His Ile		
9860	9865	9870
Asn Leu Ile Asp Gln Leu Ser Ala Glu Val Ile Asp Thr Pro Ser		
9875	9880	9885
Thr Ala Thr Ile Ser Asp Ser Leu Thr Ala Lys Val Glu Val Thr		
9890	9895	9900
Leu Leu Asp Gly Ser Lys Val Ile Val Asn Val Pro Val Lys Val		
9905	9910	9915
Val Glu Lys Glu Leu Ser Val Val Lys Gln Gln Ala Ile Glu Ser		
9920	9925	9930
Ile Glu Asn Ala Ala Gln Gln Lys Ile Asn Glu Ile Asn Asn Ser		
9935	9940	9945
Val Thr Leu Thr Leu Glu Gln Lys Glu Ala Ala Ile Ala Glu Val		
9950	9955	9960
Asn Lys Leu Lys Gln Gln Ala Ile Asp His Val Asn Asn Ala Pro		
9965	9970	9975
Asp Val His Ser Val Glu Glu Ile Gln Gln Gln Glu Gln Ala His		
9980	9985	9990
Ile Glu Gln Phe Asn Pro Glu Gln Phe Thr Ile Glu Gln Ala Lys		
9995	10000	10005
Ser Asn Ala Ile Lys Ser Ile Glu Asp Ala Ile Gln His Met Ile		
10010	10015	10020
Asp Glu Ile Lys Ala Arg Thr Asp Leu Thr Asp Lys Glu Lys Gln		
10025	10030	10035

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Glu Ala 10040	Ile Ala Lys Leu Asn 10045	Gln Leu Lys Glu Gln 10050	Ala Ile Gln
Ala Ile 10055	Gln Arg Ala Gln Ser 10060	Ile Asp Glu Ile Ser 10065	Glu Gln Leu
Glu Gln 10070	Phe Lys Ala Gln Met 10075	Lys Ala Ala Asn Pro 10080	Thr Ala Lys
Glu Leu 10085	Ala Lys Arg Lys Gln 10090	Glu Ala Ile Ser Arg 10095	Ile Lys Asp
Phe Ser 10100	Asn Glu Lys Ile Asn 10105	Ser Ile Arg Asn Ser 10110	Glu Ile Gly
Thr Ala 10115	Asp Glu Lys Gln Ala 10120	Ala Met Asn Gln Ile 10125	Asn Glu Ile
Val Leu 10130	Glu Thr Ile Arg Asp 10135	Ile Asn Asn Ala His 10140	Thr Leu Gln
Gln Val 10145	Glu Ala Ala Leu Asn 10150	Asn Gly Ile Ala Arg 10155	Ile Ser Ala
Val Gln 10160	Ile Val Thr Ser Asp 10165	Arg Ala Lys Gln Ser 10170	Ser Ser Thr
Gly Asn 10175	Glu Ser Asn Ser His 10180	Leu Thr Ile Gly Tyr 10185	Gly Thr Ala
Asn His 10190	Pro Phe Asn Ser Ser 10195	Thr Ile Gly His Lys 10200	Lys Lys Leu
Asp Glu 10205	Asp Asp Asp Ile Asp 10210	Pro Leu His Met Arg 10215	His Phe Ser
Asn Asn 10220	Phe Gly Asn Val Ile 10225	Lys Asn Ala Ile Gly 10230	Val Val Gly
Ile Ser 10235	Gly Leu Leu Ala Ser 10240	Phe Trp Phe Phe Ile 10245	Ala Lys Arg
Arg Arg 10250	Lys Glu Asp Glu Glu 10255	Glu Glu Leu Glu Ile 10260	Arg Asp Asn
Asn Lys 10265	Asp Ser Ile Lys Glu 10270	Thr Leu Asp Asp Thr 10275	Lys His Leu
Pro Leu 10280	Leu Phe Ala Lys Arg 10285	Arg Arg Lys Glu Asp 10290	Glu Glu Asp
Val Thr 10295	Val Glu Glu Lys Asp 10300	Ser Leu Asn Asn Gly 10305	Glu Ser Leu
Asp Lys 10310	Val Lys His Thr Pro 10315	Phe Phe Leu Pro Lys 10320	Arg Arg Arg
Lys Glu 10325	Asp Glu Glu Asp Val 10330	Glu Val Thr Asn Glu 10335	Asn Thr Asp
Glu Lys 10340	Val Leu Lys Asp Asn 10345	Glu His Ser Pro Leu 10350	Leu Phe Ala
Lys Arg 10355	Arg Lys Asp Lys Glu 10360	Glu Asp Val Glu Thr 10365	Thr Thr Ser
Ile Glu 10370	Ser Lys Asp Glu Asp 10375	Val Pro Leu Leu Leu 10380	Ala Lys Lys
Lys Asn 10385	Gln Lys Asp Asn Gln 10390	Ser Lys Asp Lys Lys 10395	Ser Ala Ser
Lys Asn 10400	Thr Ser Lys Lys Val 10405	Ala Ala Lys Lys Lys 10410	Lys Lys Lys
Ala Lys 10415	Lys Asn Lys Lys		

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<210> SEQ ID NO 30
 <211> LENGTH: 340
 <212> TYPE: PRT
 <213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 30

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Met Lys Lys Lys Leu Leu Val Leu Thr Met Ser Thr Leu Phe Ala Thr
 1           5           10          15
Gln Ile Met Asn Ser Asn His Ala Lys Ala Ser Val Thr Glu Ser Val
          20          25          30
Asp Lys Lys Phe Val Val Pro Glu Ser Gly Ile Asn Lys Ile Ile Pro
          35          40          45
Ala Tyr Asp Glu Phe Lys Asn Ser Pro Lys Val Asn Val Ser Asn Leu
          50          55          60
Thr Asp Asn Lys Asn Phe Val Ala Ser Glu Asp Lys Leu Asn Lys Ile
          65          70          75          80
Ala Asp Ser Ser Ala Ala Ser Lys Ile Val Asp Lys Asn Phe Val Val
          85          90          95
Pro Glu Ser Lys Leu Gly Asn Ile Val Pro Glu Tyr Lys Glu Ile Asn
          100         105         110
Asn Arg Val Asn Val Ala Thr Asn Asn Pro Ala Ser Gln Gln Val Asp
          115         120         125
Lys His Phe Val Ala Lys Gly Pro Glu Val Asn Arg Phe Ile Thr Gln
          130         135         140
Asn Lys Val Asn His His Phe Ile Thr Thr Gln Thr His Tyr Lys Lys
          145         150         155         160
Val Ile Thr Ser Tyr Lys Ser Thr His Val His Lys His Val Asn His
          165         170         175
Ala Lys Asp Ser Ile Asn Lys His Phe Ile Val Lys Pro Ser Glu Ser
          180         185         190
Pro Arg Tyr Thr His Pro Ser Gln Ser Leu Ile Ile Lys His His Phe
          195         200         205
Ala Val Pro Gly Tyr His Ala His Lys Phe Val Thr Pro Gly His Ala
          210         215         220
Ser Ile Lys Ile Asn His Phe Cys Val Val Pro Gln Ile Asn Ser Phe
          225         230         235         240
Lys Val Ile Pro Pro Tyr Gly His Asn Ser His Arg Met His Val Pro
          245         250         255
Ser Phe Gln Asn Asn Thr Thr Ala Thr His Gln Asn Ala Lys Val Asn
          260         265         270
Lys Ala Tyr Asp Tyr Lys Tyr Phe Tyr Ser Tyr Lys Val Val Lys Gly
          275         280         285
Val Lys Lys Tyr Phe Ser Phe Ser Gln Ser Asn Gly Tyr Lys Ile Gly
          290         295         300
Lys Pro Ser Leu Asn Ile Lys Asn Val Asn Tyr Gln Tyr Ala Val Pro
          305         310         315         320
Ser Tyr Ser Pro Thr His Tyr Val Pro Glu Phe Lys Gly Ser Leu Pro
          325         330         335
Ala Pro Arg Val
          340

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<210> SEQ ID NO 31
 <211> LENGTH: 636
 <212> TYPE: PRT
 <213> ORGANISM: Staphylococcus sp.

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<400> SEQUENCE: 31

Met Lys Lys Gln Ile Ile Ser Leu Gly Ala Leu Ala Val Ala Ser Ser
 1 5 10 15
 Leu Phe Thr Trp Asp Asn Lys Ala Asp Ala Ile Val Thr Lys Asp Tyr
 20 25 30
 Ser Gly Lys Ser Gln Val Asn Ala Gly Ser Lys Asn Gly Thr Leu Ile
 35 40 45
 Asp Ser Arg Tyr Leu Asn Ser Ala Leu Tyr Tyr Leu Glu Asp Tyr Ile
 50 55 60
 Ile Tyr Ala Ile Gly Leu Thr Asn Lys Tyr Glu Tyr Gly Asp Asn Ile
 65 70 75 80
 Tyr Lys Glu Ala Lys Asp Arg Leu Leu Glu Lys Val Leu Arg Glu Asp
 85 90 95
 Gln Tyr Leu Leu Glu Arg Lys Lys Ser Gln Tyr Glu Asp Tyr Lys Gln
 100 105 110
 Trp Tyr Ala Asn Tyr Lys Lys Glu Asn Pro Arg Thr Asp Leu Lys Met
 115 120 125
 Ala Asn Phe His Lys Tyr Asn Leu Glu Glu Leu Ser Met Lys Glu Tyr
 130 135 140
 Asn Glu Leu Gln Asp Ala Leu Lys Arg Ala Leu Asp Asp Phe His Arg
 145 150 155 160
 Glu Val Lys Asp Ile Lys Asp Lys Asn Ser Asp Leu Lys Thr Phe Asn
 165 170 175
 Ala Ala Glu Glu Asp Lys Ala Thr Lys Glu Val Tyr Asp Leu Val Ser
 180 185 190
 Glu Ile Asp Thr Leu Val Val Ser Tyr Tyr Gly Asp Lys Asp Tyr Gly
 195 200 205
 Glu His Ala Lys Glu Leu Arg Ala Lys Leu Asp Leu Ile Leu Gly Asp
 210 215 220
 Thr Asp Asn Pro His Lys Ile Thr Asn Glu Arg Ile Lys Lys Glu Met
 225 230 235 240
 Ile Asp Asp Leu Asn Ser Ile Ile Asp Asp Phe Phe Met Glu Thr Lys
 245 250 255
 Gln Asn Arg Pro Lys Ser Ile Thr Lys Tyr Asn Pro Thr Thr His Asn
 260 265 270
 Tyr Lys Thr Asn Ser Asp Asn Lys Pro Asn Phe Asp Lys Leu Val Glu
 275 280 285
 Glu Thr Lys Lys Ala Val Lys Glu Ala Asp Asp Ser Trp Lys Lys Lys
 290 295 300
 Thr Val Lys Lys Tyr Gly Glu Thr Glu Thr Lys Ser Pro Val Val Lys
 305 310 315 320
 Glu Glu Lys Lys Val Glu Glu Pro Gln Ala Pro Lys Val Asp Asn Gln
 325 330 335
 Gln Glu Val Lys Thr Thr Ala Gly Lys Ala Glu Glu Thr Thr Gln Pro
 340 345 350
 Val Ala Gln Pro Leu Val Lys Ile Pro Gln Gly Thr Ile Thr Gly Glu
 355 360 365
 Ile Val Lys Gly Pro Glu Tyr Pro Thr Met Glu Asn Lys Thr Val Gln
 370 375 380
 Gly Glu Ile Val Gln Gly Pro Asp Phe Leu Thr Met Glu Gln Ser Gly
 385 390 395 400
 Pro Ser Leu Ser Asn Asn Tyr Thr Asn Pro Pro Leu Thr Asn Pro Ile

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405	410	415
Leu Glu Gly Leu Glu Gly Ser Ser Ser Lys Leu Glu Ile Lys Pro Gln		
420	425	430
Gly Thr Glu Ser Thr Leu Lys Gly Thr Gln Gly Glu Ser Ser Asp Ile		
435	440	445
Glu Val Lys Pro Gln Ala Thr Glu Thr Thr Glu Ala Ser Gln Tyr Gly		
450	455	460
Pro Arg Pro Gln Phe Asn Lys Thr Pro Lys Tyr Val Lys Tyr Arg Asp		
465	470	475
Ala Gly Thr Gly Ile Arg Glu Tyr Asn Asp Gly Thr Phe Gly Tyr Glu		
485	490	495
Ala Arg Pro Arg Phe Asn Lys Pro Ser Glu Thr Asn Ala Tyr Asn Val		
500	505	510
Thr Thr His Ala Asn Gly Gln Val Ser Tyr Gly Ala Arg Pro Thr Tyr		
515	520	525
Lys Lys Pro Ser Glu Thr Asn Ala Tyr Asn Val Thr Thr His Ala Asn		
530	535	540
Gly Gln Val Ser Tyr Gly Ala Arg Pro Thr Gln Asn Lys Pro Ser Lys		
545	550	555
Thr Asn Ala Tyr Asn Val Thr Thr His Gly Asn Gly Gln Val Ser Tyr		
565	570	575
Gly Ala Arg Pro Thr Gln Asn Lys Pro Ser Lys Thr Asn Ala Tyr Asn		
580	585	590
Val Thr Thr His Ala Asn Gly Gln Val Ser Tyr Gly Ala Arg Pro Thr		
595	600	605
Tyr Lys Lys Pro Ser Lys Thr Asn Ala Tyr Asn Val Thr Thr His Ala		
610	615	620
Asp Gly Thr Ala Thr Tyr Gly Pro Arg Val Thr Lys		
625	630	635

<210> SEQ ID NO 32

<211> LENGTH: 745

<212> TYPE: PRT

<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 32

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

-continued

Ala	Lys	Leu	Lys	Thr	Val	Lys	Glu	Gln	Glu	Lys	Pro	Asp	Leu	Met	Leu	145	150	155	160
Asp	Ala	Gly	Asp	Ala	Phe	Gln	Gly	Leu	Pro	Leu	Ser	Asn	Gln	Ser	Lys	165	170	175	
Gly	Glu	Glu	Met	Ala	Lys	Ala	Met	Asn	Ala	Val	Gly	Tyr	Asp	Ala	Met	180	185	190	
Ala	Val	Gly	Asn	His	Glu	Phe	Asp	Phe	Gly	Tyr	Asp	Gln	Leu	Lys	Lys	195	200	205	
Leu	Glu	Gly	Met	Leu	Asp	Phe	Pro	Met	Leu	Ser	Thr	Asn	Val	Tyr	Lys	210	215	220	
Asp	Gly	Lys	Arg	Ala	Phe	Lys	Pro	Ser	Thr	Ile	Val	Thr	Lys	Asn	Gly	225	230	235	240
Ile	Arg	Tyr	Gly	Ile	Ile	Gly	Val	Thr	Thr	Pro	Glu	Thr	Lys	Thr	Lys	245	250	255	
Thr	Arg	Pro	Glu	Gly	Ile	Lys	Gly	Val	Glu	Phe	Arg	Asp	Pro	Leu	Gln	260	265	270	
Ser	Val	Thr	Ala	Glu	Met	Met	Arg	Ile	Tyr	Lys	Asp	Val	Asp	Thr	Phe	275	280	285	
Val	Val	Ile	Ser	His	Leu	Gly	Ile	Asp	Pro	Ser	Thr	Gln	Glu	Thr	Trp	290	295	300	
Arg	Gly	Asp	Tyr	Leu	Val	Lys	Gln	Leu	Ser	Gln	Asn	Pro	Gln	Leu	Lys	305	310	315	320
Lys	Arg	Ile	Thr	Val	Ile	Asp	Gly	His	Ser	His	Thr	Val	Leu	Gln	Asn	325	330	335	
Gly	Gln	Ile	Tyr	Asn	Asn	Asp	Ala	Leu	Ala	Gln	Thr	Gly	Thr	Ala	Leu	340	345	350	
Ala	Asn	Ile	Gly	Lys	Ile	Thr	Phe	Asn	Tyr	Arg	Asn	Gly	Glu	Val	Ser	355	360	365	
Asn	Ile	Lys	Pro	Ser	Leu	Ile	Asn	Val	Lys	Asp	Val	Glu	Asn	Val	Thr	370	375	380	
Pro	Asn	Lys	Ala	Leu	Ala	Glu	Gln	Ile	Asn	Gln	Ala	Asp	Gln	Thr	Phe	385	390	395	400
Arg	Ala	Gln	Thr	Ala	Glu	Val	Ile	Ile	Pro	Asn	Asn	Thr	Ile	Asp	Phe	405	410	415	
Lys	Gly	Glu	Arg	Asp	Asp	Val	Arg	Thr	Arg	Glu	Thr	Asn	Leu	Gly	Asn	420	425	430	
Ala	Ile	Ala	Asp	Ala	Met	Glu	Ala	Tyr	Gly	Val	Lys	Asn	Phe	Ser	Lys	435	440	445	
Lys	Thr	Asp	Phe	Ala	Val	Thr	Asn	Gly	Gly	Gly	Ile	Arg	Ala	Ser	Ile	450	455	460	
Ala	Lys	Gly	Lys	Val	Thr	Arg	Tyr	Asp	Leu	Ile	Ser	Val	Leu	Pro	Phe	465	470	475	480
Gly	Asn	Thr	Ile	Ala	Gln	Ile	Asp	Val	Lys	Gly	Ser	Asp	Val	Trp	Thr	485	490	495	
Ala	Phe	Glu	His	Ser	Leu	Gly	Ala	Pro	Thr	Thr	Gln	Lys	Asp	Gly	Lys	500	505	510	
Thr	Val	Leu	Thr	Ala	Asn	Gly	Gly	Leu	Leu	His	Ile	Ser	Asp	Ser	Ile	515	520	525	
Arg	Val	Tyr	Tyr	Asp	Ile	Asn	Lys	Pro	Ser	Gly	Lys	Arg	Ile	Asn	Ala	530	535	540	
Ile	Gln	Ile	Leu	Asn	Lys	Glu	Thr	Gly	Lys	Phe	Glu	Asn	Ile	Asp	Leu	545	550	555	560
Lys	Arg	Val	Tyr	His	Val	Thr	Met	Asn	Asp	Phe	Thr	Ala	Ser	Gly	Gly				

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565	570	575
Asp Gly Tyr Ser Met Phe Gly Gly Pro Arg Glu Glu Gly Ile Ser Leu		
580	585	590
Asp Gln Val Leu Ala Ser Tyr Leu Lys Thr Ala Asn Leu Ala Lys Tyr		
595	600	605
Asp Thr Thr Glu Pro Gln Arg Met Leu Leu Gly Lys Pro Ala Val Ser		
610	615	620
Glu Gln Pro Ala Lys Gly Gln Gln Gly Ser Lys Gly Ser Lys Ser Gly		
625	630	635
Lys Asp Thr Gln Pro Ile Gly Asp Asp Lys Val Met Asp Pro Ala Lys		
645	650	655
Lys Pro Ala Pro Gly Lys Val Val Leu Leu Leu Ala His Arg Gly Thr		
660	665	670
Val Ser Ser Gly Thr Glu Gly Ser Gly Arg Thr Ile Glu Gly Ala Thr		
675	680	685
Val Ser Ser Lys Ser Gly Lys Gln Leu Ala Arg Met Ser Val Pro Lys		
690	695	700
Gly Ser Ala His Glu Lys Gln Leu Pro Lys Thr Gly Thr Asn Gln Ser		
705	710	715
Ser Ser Pro Glu Ala Met Phe Val Leu Leu Ala Gly Ile Gly Leu Ile		
725	730	735
Ala Thr Val Arg Arg Arg Lys Ala Ser		
740	745	

<210> SEQ ID NO 33

<211> LENGTH: 628

<212> TYPE: PRT

<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 33

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

Pro	Asn	Phe	Phe	Gln	Asn	Gln	Asn	Ser	Glu	Asp	Asn	Met	Tyr	Leu	Ala
195						200				205					
Gln	Arg	Ile	Met	Tyr	Gln	Val	Asp	Asp	Ile	Leu	Lys	Glu	Asp	Met	Leu
210						215				220					
Asn	Glu	Tyr	Tyr	Tyr	Leu	Pro	Lys	Thr	Leu	Tyr	Asn	Thr	Leu	Ala	Ser
225				230						235		240			
Pro	Glu	Phe	Asp	Asp	Leu	Lys	Arg	Thr	Asp	Ala	Ser	Gln	Val	Asp	Gly
				245				250				255			
Gln	Asp	Asp	Thr	Ser	Glu	Asp	Asp	Asp	Asn	Glu	Ser	Glu	Lys	Ala	Asp
		260						265				270			
Ser	Lys	Ser	Ala	Asp	Ser	Glu	Ser	Lys	Gly	Gly	Ala	Tyr	Leu	Glu	Met
275						280						285			
Glu	Leu	His	Glu	Gly	Gln	Asn	Ser	Glu	Thr	Leu	Gly	Asn	Asp	Glu	Ala
290						295				300					
Arg	Glu	Gly	Asp	Ala	Thr	Asp	Asp	Met	Thr	Asp	Met	Met	Thr	Lys	Lys
305				310						315		320			
Gly	Lys	Gly	Ser	Asn	Asp	Thr	Leu	Asn	Arg	Glu	Glu	Gly	Asp	Ala	Val
				325				330				335			
Gly	Gln	Ser	Gln	Ala	Phe	Gln	Leu	Asp	Gly	Val	Asn	Lys	Asn	Val	Glu
		340						345				350			
Ile	Lys	Trp	Gln	Ile	Pro	Glu	Ile	Glu	Pro	Gln	Tyr	Val	Leu	Glu	Tyr
355						360						365			
Gln	Glu	Ser	Lys	Gln	Asp	Val	Gln	Tyr	Glu	Ile	Lys	Asp	Leu	Ile	Gln
370						375				380					
Ile	Ile	Lys	Lys	Thr	Ile	Glu	Arg	Glu	Gln	Arg	Asp	Ala	Arg	Phe	Asn
385				390						395		400			
Leu	Thr	Lys	Gly	Arg	Leu	Gln	Lys	Asp	Leu	Ile	Asn	Trp	Phe	Ile	Asp
				405				410				415			
Asp	Gln	Tyr	Lys	Leu	Phe	Tyr	Lys	Lys	Gln	Asp	Leu	Ser	Lys	Ser	Phe
		420						425				430			
Asp	Ala	Thr	Phe	Thr	Leu	Leu	Ile	Asp	Ala	Ser	Ala	Ser	Met	His	Asp
435						440						445			
Lys	Met	Ala	Glu	Thr	Lys	Lys	Gly	Val	Val	Leu	Phe	His	Glu	Thr	Leu
450						455				460					
Lys	Ala	Leu	Asn	Ile	Lys	His	Glu	Ile	Leu	Ser	Phe	Ser	Glu	Asp	Ala
465				470						475		480			
Phe	Asp	Ser	Asp	Glu	His	Ala	Gln	Pro	Asn	Ile	Ile	Asn	Glu	Ile	Ile
		485						490				495			
Asn	Tyr	Asp	Tyr	Ser	Thr	Phe	Glu	Lys	Asp	Gly	Pro	Arg	Ile	Met	Ala
500								505				510			
Leu	Glu	Pro	Gln	Asp	Asp	Asn	Arg	Asp	Gly	Val	Ala	Ile	Arg	Val	Ala
515						520						525			
Ser	Glu	Arg	Leu	Met	Arg	Arg	Asn	Gln	His	Gln	Arg	Phe	Leu	Ile	Val
530						535				540					
Phe	Ser	Asp	Gly	Glu	Pro	Ser	Ala	Phe	Asn	Tyr	Ser	Gln	Asp	Gly	Ile
545				550						555		560			
Ile	Asp	Thr	Tyr	Glu	Ala	Val	Glu	Met	Ser	Arg	Lys	Phe	Gly	Ile	Glu

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610	615	620
Leu Lys Ser Leu		
625		
 <210> SEQ ID NO 34		
<211> LENGTH: 508		
<212> TYPE: PRT		
<213> ORGANISM: Staphylococcus sp.		
 <400> SEQUENCE: 34		
Met Lys Asn Lys Leu Leu Val Leu Ser Leu Gly Ala Leu Cys Val Ser		
1 5 10 15		
Gln Ile Trp Glu Ser Asn Arg Ala Ser Ala Val Val Ser Gly Glu Lys		
20 25 30		
Asn Pro Tyr Val Ser Glu Ser Leu Lys Leu Thr Asn Asn Lys Asn Lys		
35 40 45		
Ser Arg Thr Val Glu Glu Tyr Lys Lys Ser Leu Asp Asp Leu Ile Trp		
50 55 60		
Ser Phe Pro Asn Leu Asp Asn Glu Arg Phe Asp Asn Pro Glu Tyr Lys		
65 70 75 80		
Glu Ala Met Lys Lys Tyr Gln Gln Arg Phe Met Ala Glu Asp Glu Ala		
85 90 95		
Leu Lys Lys Phe Phe Ser Glu Glu Lys Lys Ile Lys Asn Gly Asn Thr		
100 105 110		
Asp Asn Leu Asp Tyr Leu Gly Leu Ser His Glu Arg Tyr Glu Ser Val		
115 120 125		
Phe Asn Thr Leu Lys Lys Gln Ser Glu Glu Phe Leu Lys Glu Ile Glu		
130 135 140		
Asp Ile Lys Lys Asp Asn Pro Glu Leu Lys Asp Phe Asn Glu Glu Glu		
145 150 155 160		
Gln Leu Lys Cys Asp Leu Glu Leu Asn Lys Leu Glu Asn Gln Ile Leu		
165 170 175		
Met Leu Gly Lys Thr Phe Tyr Gln Asn Tyr Arg Asp Asp Val Glu Ser		
180 185 190		
Leu Tyr Ser Lys Leu Asp Leu Ile Met Gly Tyr Lys Asp Glu Glu Arg		
195 200 205		
Ala Asn Lys Lys Ala Val Asn Lys Arg Met Leu Glu Asn Lys Lys Glu		
210 215 220		
Asp Leu Glu Thr Ile Ile Asp Glu Phe Phe Ser Asp Ile Asp Lys Thr		
225 230 235 240		
Arg Pro Asn Asn Ile Pro Val Leu Glu Asp Glu Lys Gln Glu Glu Lys		
245 250 255		
Asn His Lys Asn Met Ala Gln Leu Lys Ser Asp Thr Glu Ala Ala Lys		
260 265 270		
Ser Asp Glu Ser Lys Arg Ser Lys Arg Ser Lys Arg Ser Leu Asn Thr		
275 280 285		
Gln Asn His Lys Pro Ala Ser Gln Glu Val Ser Glu Gln Gln Lys Ala		
290 295 300		
Glu Tyr Asp Lys Arg Ala Glu Glu Arg Lys Ala Arg Phe Leu Asp Asn		
305 310 315 320		
Gln Lys Ile Lys Lys Thr Pro Val Val Ser Leu Glu Tyr Asp Phe Glu		
325 330 335		
His Lys Gln Arg Ile Asp Asn Glu Asn Asp Lys Lys Leu Val Val Ser		
340 345 350		

-continued

Ala Pro Thr Lys Lys Pro Thr Ser Pro Thr Thr Tyr Thr Glu Thr Thr
355 360 365

Thr Gln Val Pro Met Pro Thr Val Glu Arg Gln Thr Gln Gln Gln Ile
370 375 380

Ile Tyr Asn Ala Pro Lys Gln Leu Ala Gly Leu Asn Gly Glu Ser His
385 390 395 400

Asp Phe Thr Thr Thr His Gln Ser Pro Thr Thr Ser Asn His Thr His
405 410 415

Asn Asn Val Val Glu Phe Glu Glu Thr Ser Ala Leu Pro Gly Arg Lys
420 425 430

Ser Gly Ser Leu Val Gly Ile Ser Gln Ile Asp Ser Ser His Leu Thr
435 440 445

Glu Arg Glu Lys Arg Val Ile Lys Arg Glu His Val Arg Glu Ala Gln
450 455 460

Lys Leu Val Asp Asn Tyr Lys Asp Thr His Ser Tyr Lys Asp Arg Ile
465 470 475 480

Asn Ala Gln Gln Lys Val Asn Thr Leu Ser Glu Gly His Gln Lys Arg
485 490 495

Phe Asn Lys Gln Ile Asn Lys Val Tyr Asn Gly Lys
500 505

<210> SEQ ID NO 35
 <211> LENGTH: 28
 <212> TYPE: DNA
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic primer

<400> SEQUENCE: 35

aactcgagat gaatcagcac gtaaaagt

28

<210> SEQ ID NO 36
 <211> LENGTH: 28
 <212> TYPE: DNA
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic primer

<400> SEQUENCE: 36

aaggatccct atagtaactt caaaatat

28

<210> SEQ ID NO 37
 <211> LENGTH: 25
 <212> TYPE: DNA
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic primer

<400> SEQUENCE: 37

aacatatgaa ttttaatgat attga

25

<210> SEQ ID NO 38
 <211> LENGTH: 31
 <212> TYPE: DNA
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic primer

<400> SEQUENCE: 38

aactcgagtt aattcattgc tttattaaaa t

31

-continued

<210> SEQ ID NO 39
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic primer

<400> SEQUENCE: 39

tcgatttttag taggtacgac

20

<210> SEQ ID NO 40
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic primer

<400> SEQUENCE: 40

tctacttttg aaggcgttgg

20

<210> SEQ ID NO 41
 <211> LENGTH: 322
 <212> TYPE: PRT
 <213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 41

Met Met Lys Met Lys Thr Arg Ile Val Ser Ser Val Thr Thr Thr Leu
 1 5 10 15

Leu Leu Gly Ser Ile Leu Met Asn Pro Val Ala Asn Ala Ala Asp Ser
 20 25 30

Asp Ile Asn Ile Lys Thr Gly Thr Thr Asp Ile Gly Ser Asn Thr Thr
 35 40 45

Val Lys Thr Gly Asp Leu Val Thr Tyr Asp Lys Glu Asn Gly Met His
 50 55 60

Lys Lys Val Phe Tyr Ser Phe Ile Asp Asp Lys Asn His Asn Lys Lys
 65 70 75 80

Ile Leu Val Ile Arg Thr Lys Gly Thr Ile Ala Gly Gln Tyr Arg Val
 85 90 95

Tyr Ser Glu Glu Gly Ala Asn Lys Ser Gly Leu Ala Trp Pro Ser Ala
 100 105 110

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

Asp Tyr Tyr Pro Arg Asn Ser Ile Asp Thr Lys Glu Tyr Met Ser Thr
 130 135 140

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

Ile Gly Gly Leu Ile Gly Ala Asn Val Ser Ile Gly His Thr Leu Lys
 165 170 175

Tyr Val Gln Pro Asp Phe Lys Thr Ile Leu Glu Ser Pro Thr Asp Lys
 180 185 190

Lys Val Gly Trp Lys Val Ile Phe Asn Asn Met Val Asn Gln Asn Trp
 195 200 205

Gly Pro Tyr Asp Arg Asp Ser Trp Asn Pro Val Tyr Gly Asn Gln Leu
 210 215 220

Phe Met Lys Thr Arg Asn Gly Ser Met Lys Ala Ala Glu Asn Phe Leu
 225 230 235 240

Asp Pro Asn Lys Ala Ser Ser Leu Leu Ser Ser Gly Phe Ser Pro Asp
 245 250 255

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Phe Ala Thr Val Ile Thr Met Asp Arg Lys Ala Thr Lys Gln Gln Thr
 260 265 270

Asn Ile Asp Val Ile Tyr Glu Arg Val Arg Asp Asp Tyr Gln Leu His
 275 280 285

Trp Thr Ser Thr Asn Trp Lys Gly Thr Asn Thr Lys Asp Lys Trp Thr
 290 295 300

Asp Arg Ser Ser Glu Arg Tyr Lys Ile Asp Trp Glu Lys Glu Glu Met
 305 310 315 320

Thr Asn

<210> SEQ ID NO 42
 <211> LENGTH: 80
 <212> TYPE: PRT
 <213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 42

Met Asn Gln His Val Lys Val Thr Phe Asp Phe Thr Asn Tyr Asn Tyr
 1 5 10 15

Gly Thr Tyr Asp Leu Ala Val Pro Ala Tyr Leu Pro Ile Lys Asn Leu
 20 25 30

Ile Ala Leu Val Leu Asp Ser Leu Asp Ile Ser Ile Phe Asp Val Asn
 35 40 45

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

Arg Leu Ile Asp Tyr Gln Ile Ala Asp Gly Asp Ile Leu Lys Leu Leu
 65 70 75 80

The invention claimed is:

1. A method of inducing an immune response in a subject with a staphylococcal infection comprising the step of administering to a subject an immunogenic composition comprising an isolated EsaC antigen that is 95% identical to SEQ ID NO:2.

2. The method of claim 1, further comprising at least one other staphylococcal antigen.

3. The method of claim 2, wherein the other staphylococcal antigen is one or more of EsaB, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, Hla, Emp, Eap, Ebh, SpA, IsdC, ClfA, ClfB, and/or SasF peptide.

4. The method of claim 1, wherein the composition further comprises an adjuvant.

5. The method of claim 4, wherein the EsaC antigen is coupled to an adjuvant.

6. The method of claim 1, wherein the EsaC antigen is at least 97% identical to SEQ ID NO:2.

7. The method of claim 1, wherein the EsaC antigen comprises the amino acid sequence of SEQ ID NO:2.

8. The method of claim 1, wherein the subject is human.

9. The method of claim 1, wherein the immune response is a protective immune response.

* * * * *