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(54) **COMPOSITIONS AND METHODS RELATED TO BACTERIAL EAP, EMP, AND/OR ADSA PROTEINS**

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Publication Classification

(51) **Int. Cl.**

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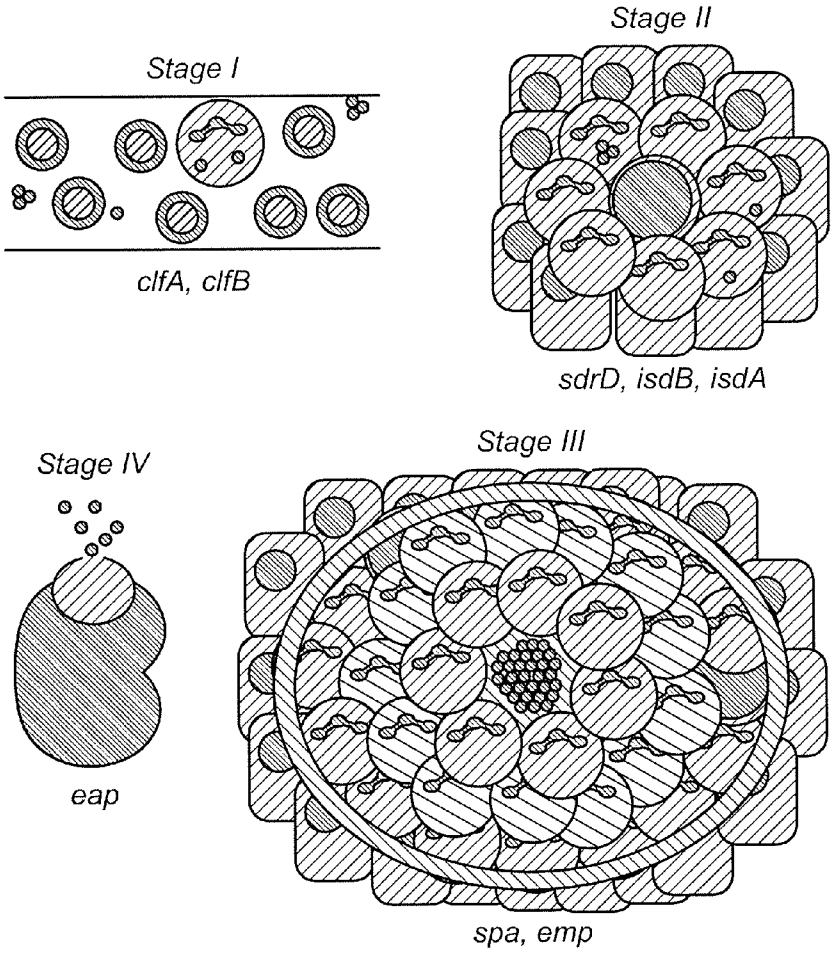
A61P 37/04	(2006.01)
C07K 19/00	(2006.01)

(52) **U.S. Cl.** **424/190.1**; 424/243.1; 424/197.11; 530/405; 424/200.1

(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 Eap, Emp and/or AdsA amino acid sequence, or an agent that binds and inhibits the same.



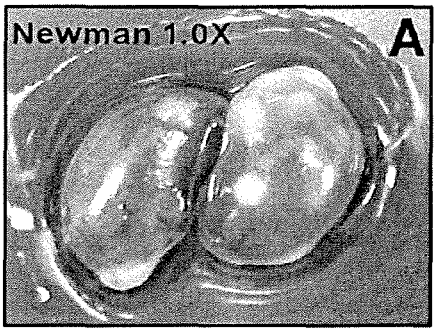


FIG. 1A

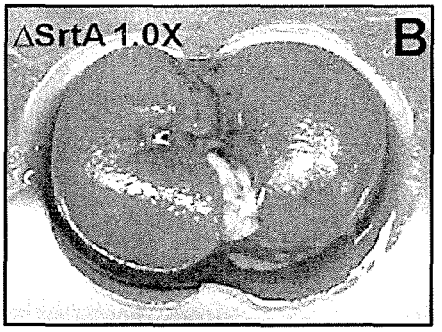


FIG. 1B

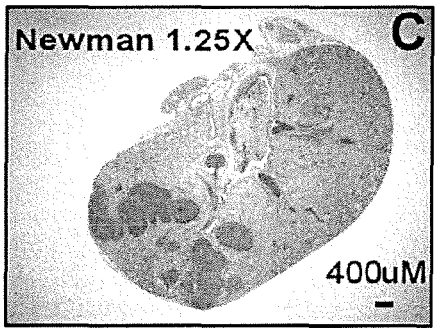


FIG. 1C

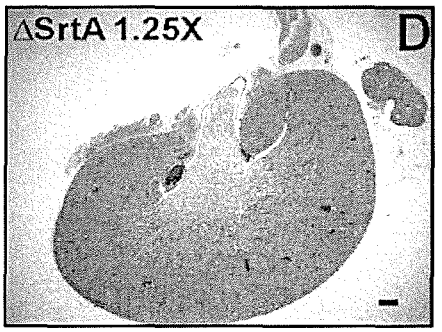


FIG. 1D

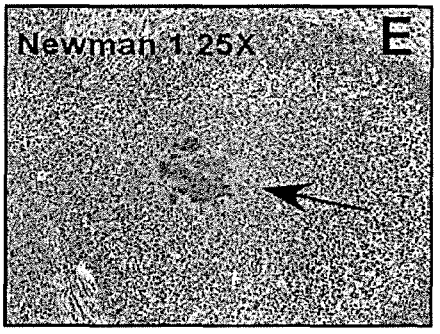


FIG. 1E

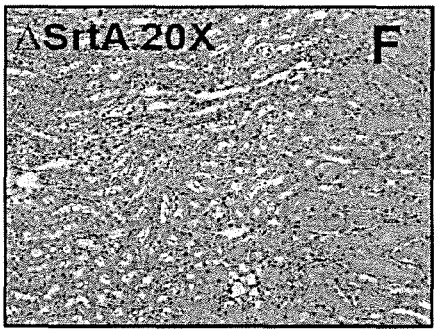


FIG. 1F

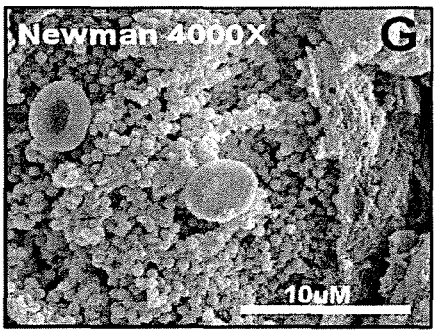


FIG. 1G

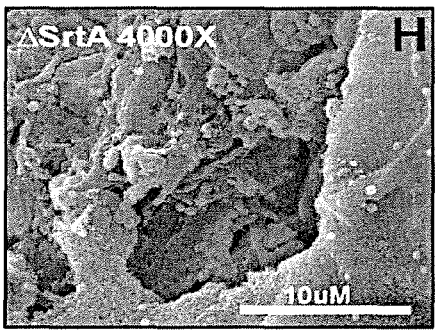


FIG. 1H

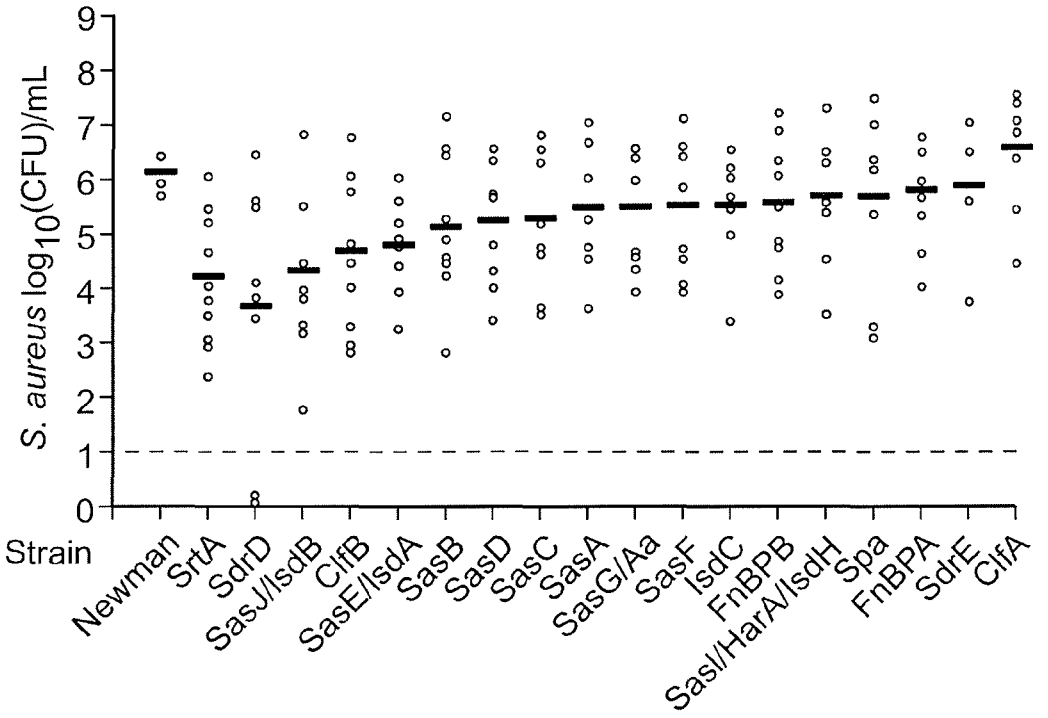

S. aureus log10(CFU)/mL
9
8
7
6
5
4
3
2
1
0
Strain
Newman
SrtA
SdrD
SasJ/IsdB
ClfB
SasE/IsdA
SasB
SasD
SasC
SasA
SasG/Aa
SasF
IsdC
FnBPB
SasI/HarA/IsdH
Spa
FnBPA
SdrE
ClfA

FIG. 2

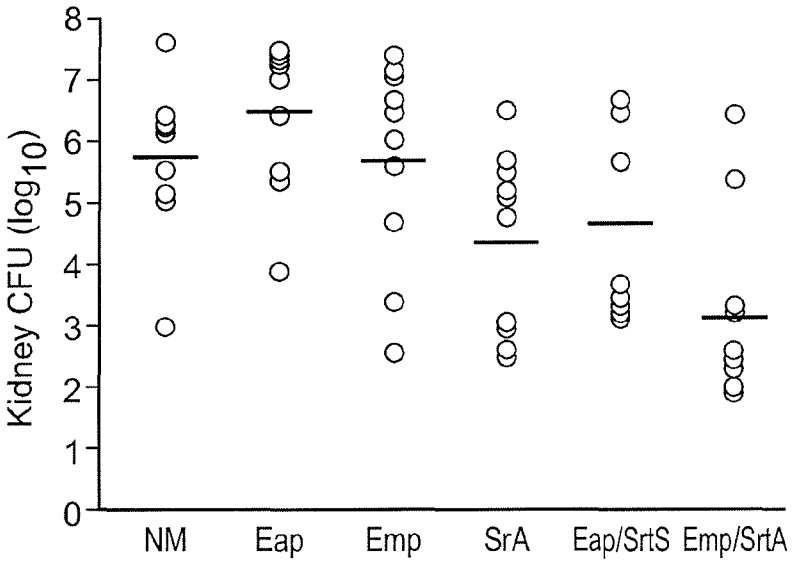

Kidney CFU (log10)
8
7
6
5
4
3
2
1
0
NM
Eap
Emp
SrA
Eap/SrtS
Emp/SrtA

FIG. 4A

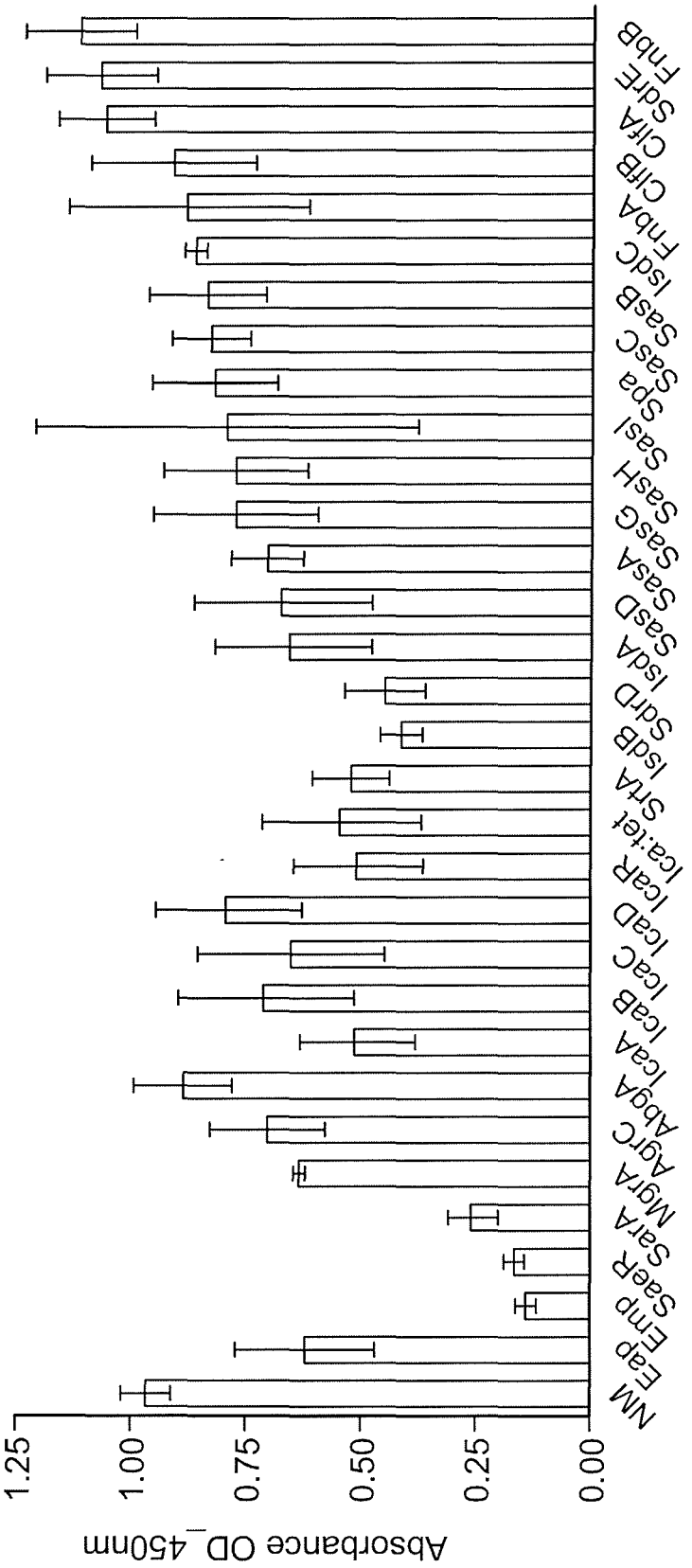

Absorbance OD_450nm
1.25
1.00
0.75
0.50
0.25
0.00
NM
Eap
Emp
SaeR
SarA
MgrA
AgrC
Abga
icaA
icaB
icaC
icaD
icaR
ica:tet
StrA
isdB
SdrD
isdA
SasD
SasA
SasG
SasH
SasI
Spa
SasC
SasB
isdC
FnbA
ClfB
ClfA
SdrE
FnbB

FIG. 3A

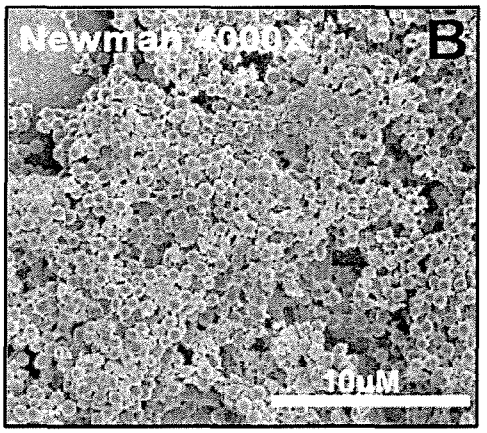


FIG. 3B

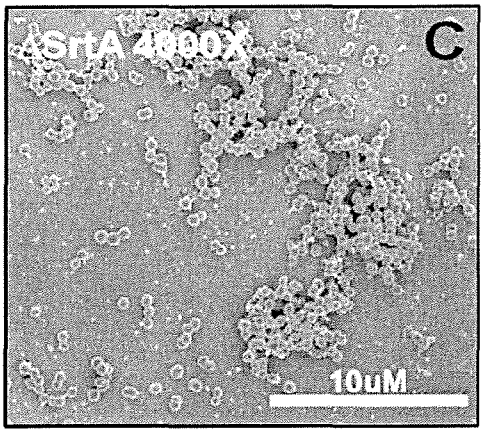


FIG. 3C

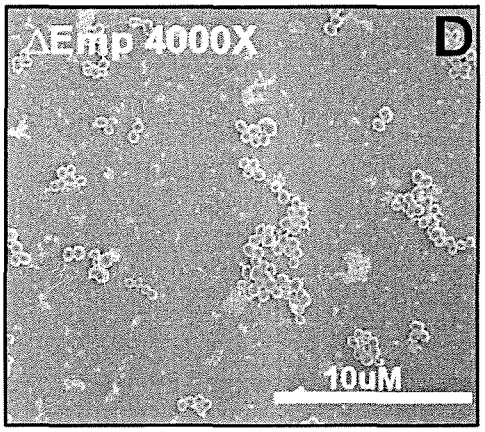


FIG. 3D

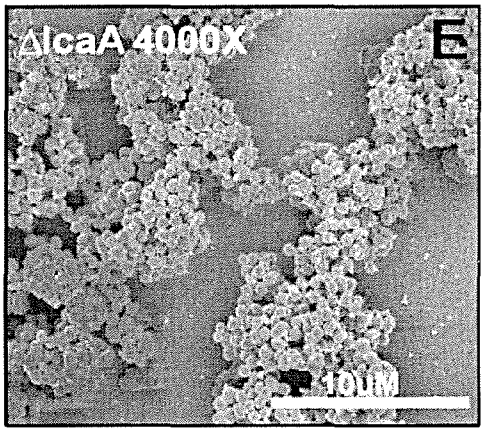


FIG. 3E

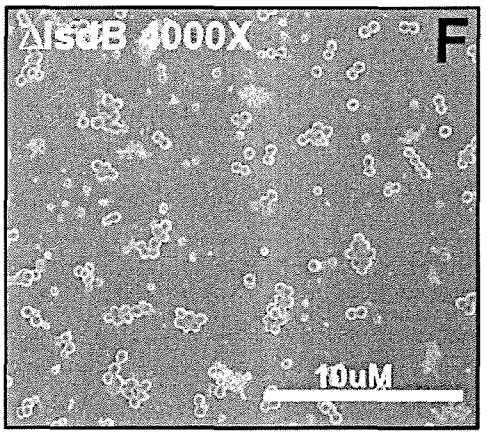


FIG. 3F

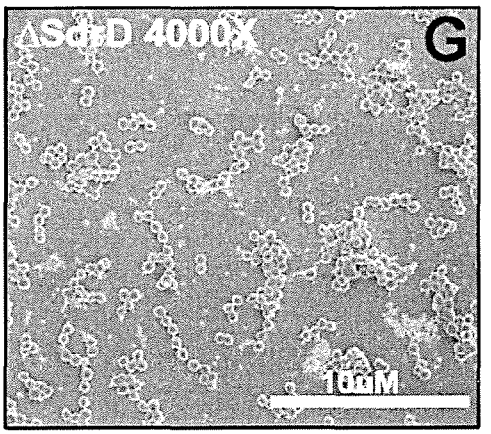


FIG. 3G

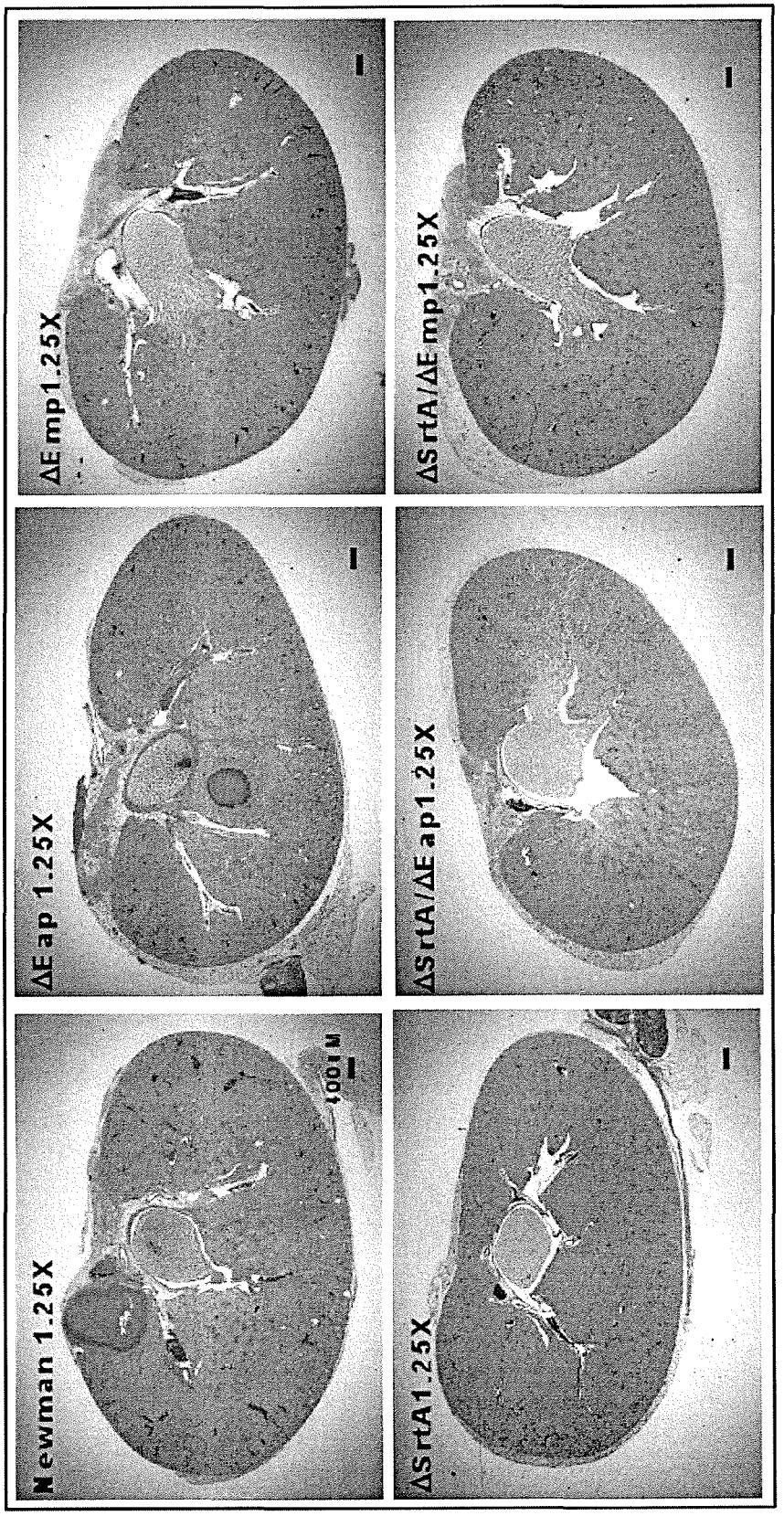

Newman 1.25X
ΔEap 1.25X
ΔEmp1.25X
ΔSrtA1.25X
ΔSrtA/ΔEap1.25X
ΔSrtA/ΔEmp1.25X
100 M

FIG. 4B

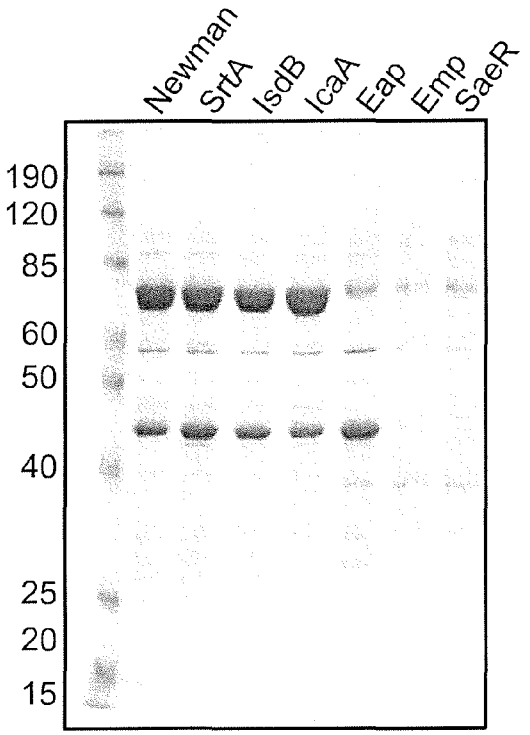


FIG. 5A

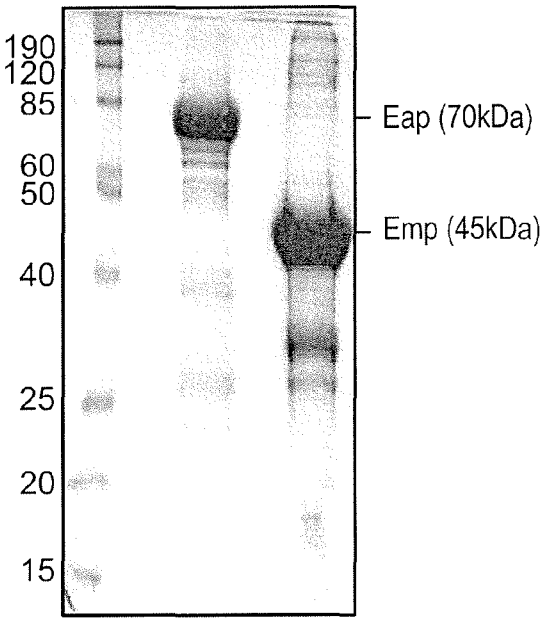


FIG. 5B

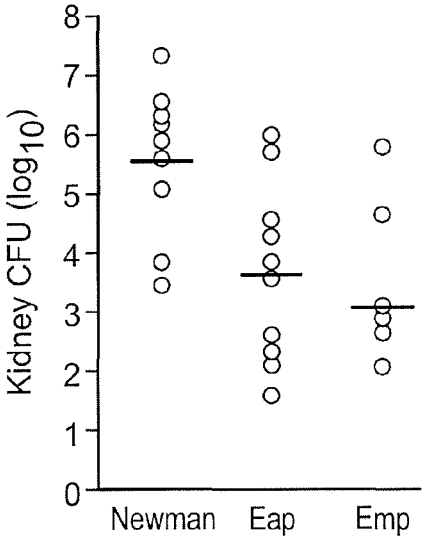


FIG. 5C

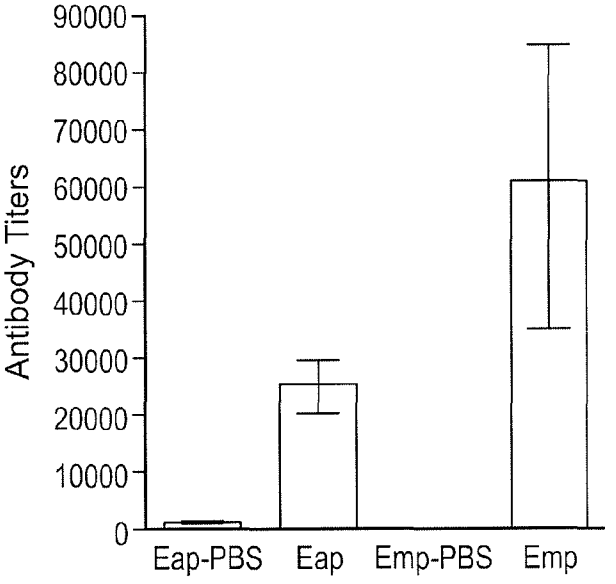


FIG. 5D

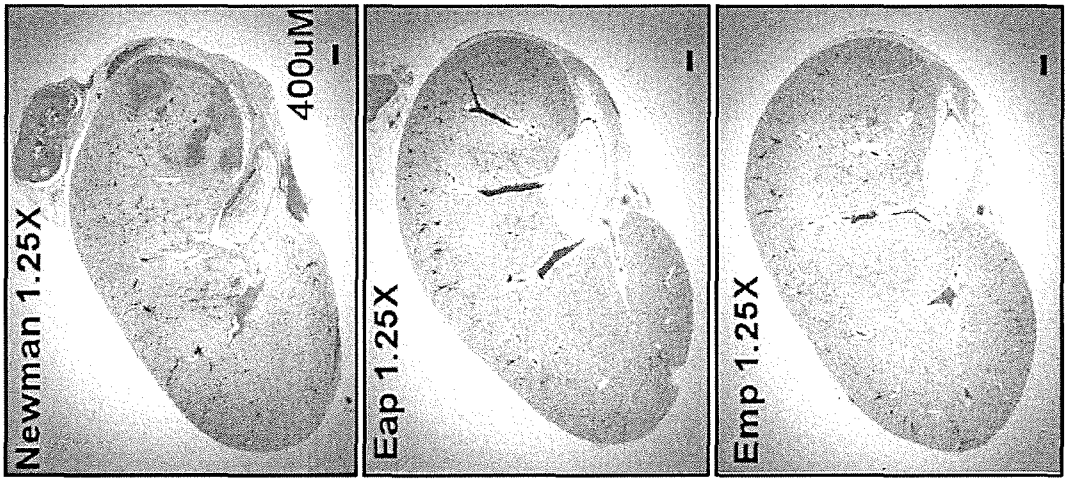

Newman 1.25X
400uM
Eap 1.25X
Emp 1.25X

FIG. 5E

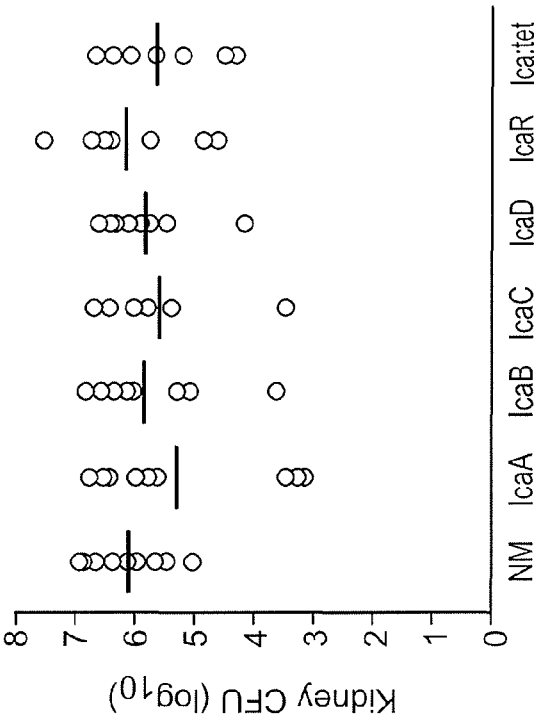

Kidney CFU (log10)
0
1
2
3
4
5
6
7
8
NM
IcaA
IcaB
IcaC
IcaD
IcaR
Ica:tet

FIG. 6A

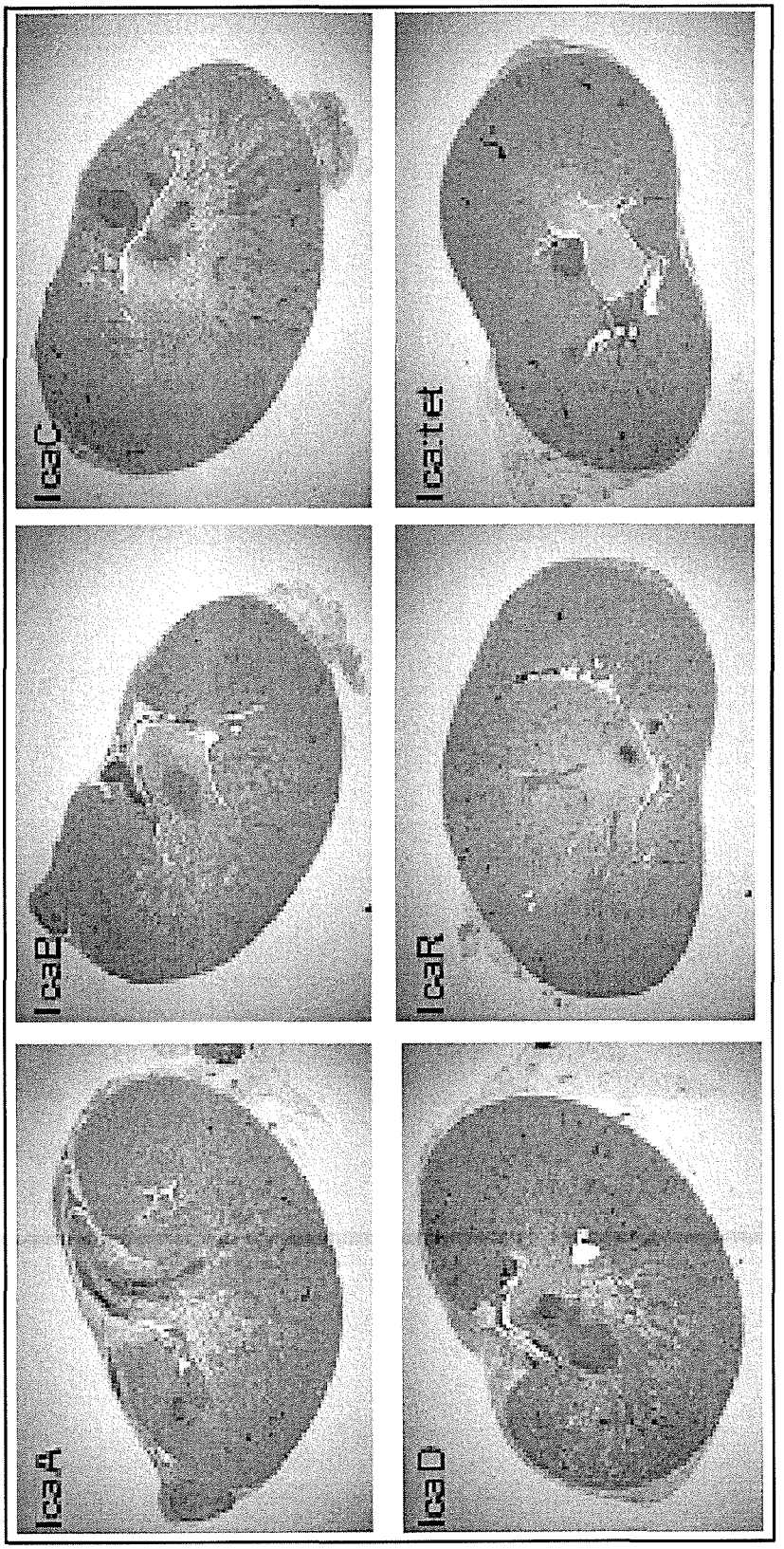


FIG. 6B

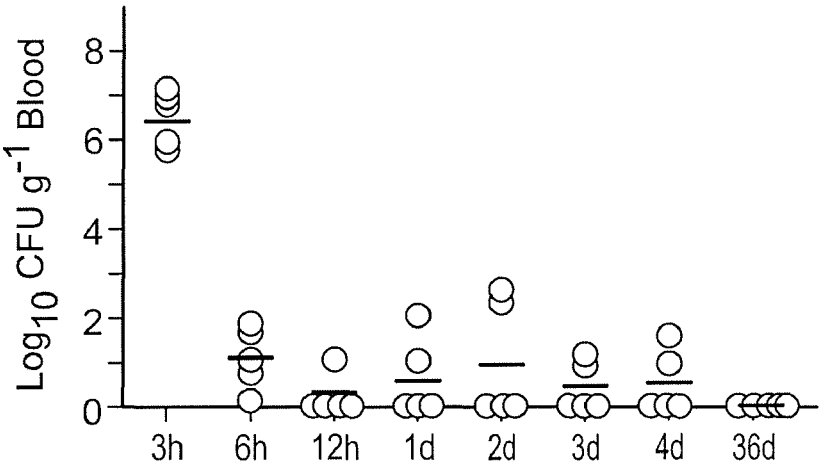


FIG. 7A

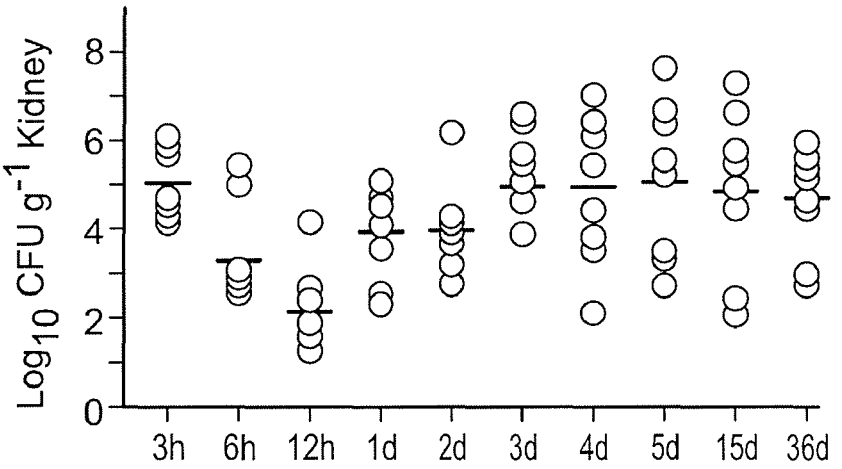


FIG. 7B

Abscess Diameter

Time	μm	SEM
d2	524	65
d3	611	50
d4	823	61
d5	934	42
d15	1667	90
d30	1511	129

FIG. 7C

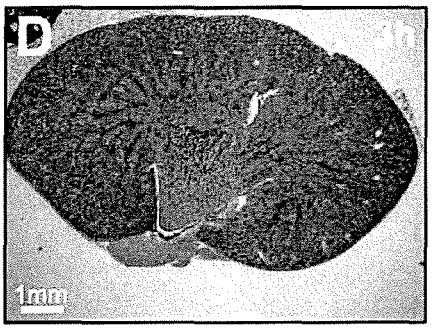


FIG. 7D

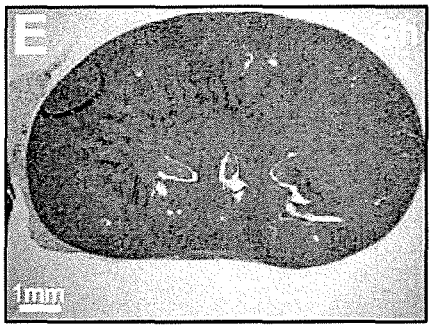


FIG. 7E

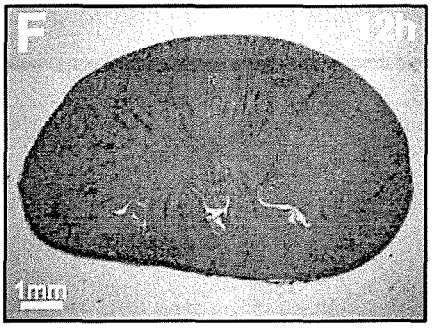


FIG. 7F

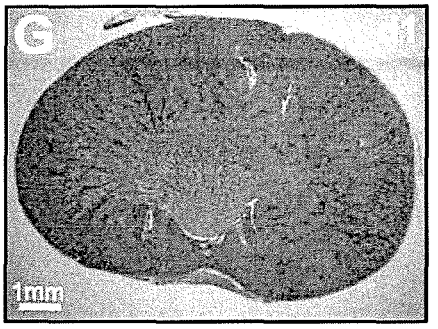


FIG. 7G

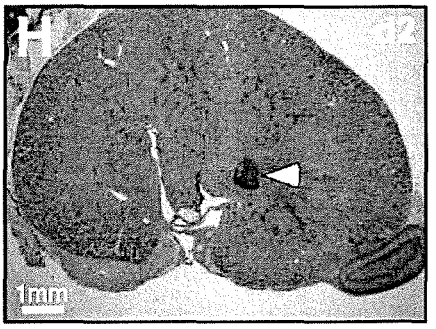


FIG. 7H

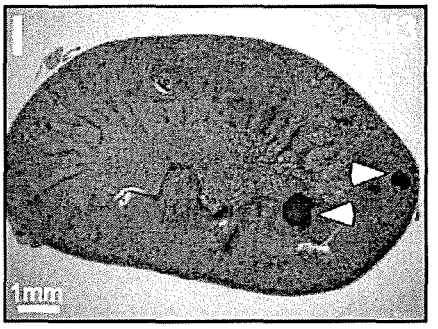


FIG. 7I

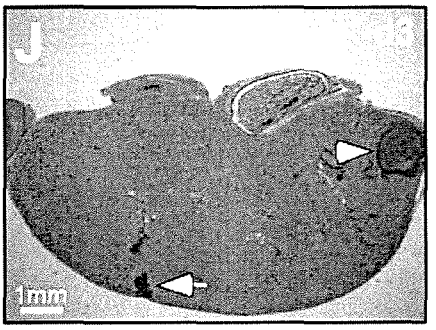


FIG. 7J

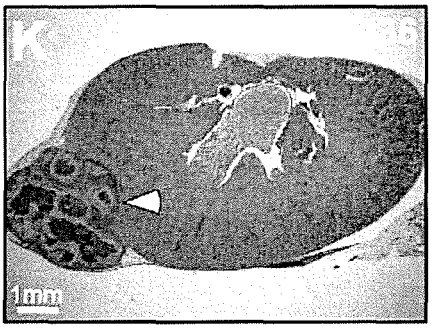


FIG. 7K

day 2

100x

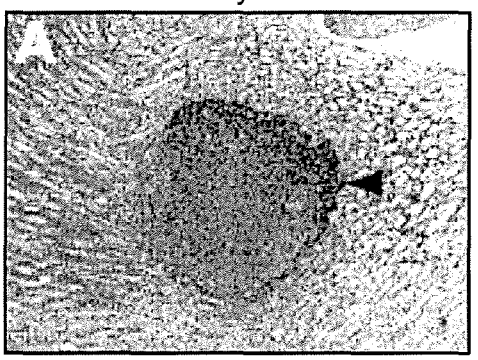


FIG. 8A

day 5

100x

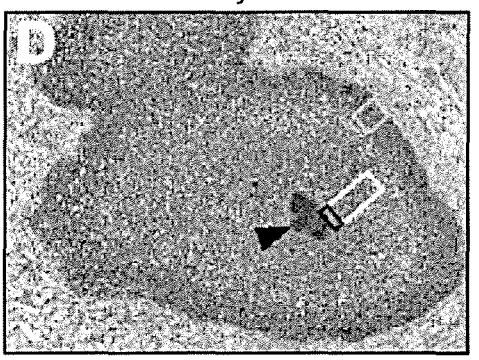


FIG. 8D

day 2

400X

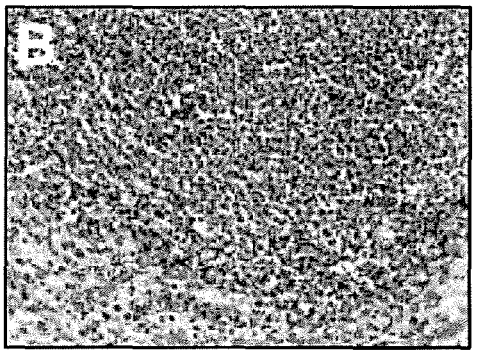


FIG. 8B

day 5

400X

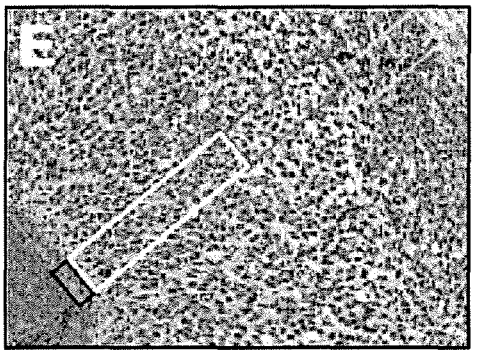


FIG. 8E

day 2

630X

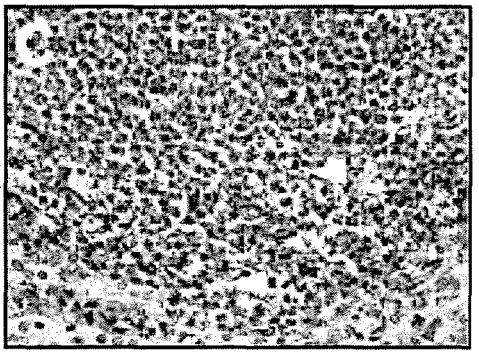


FIG. 8C

day 5

630X

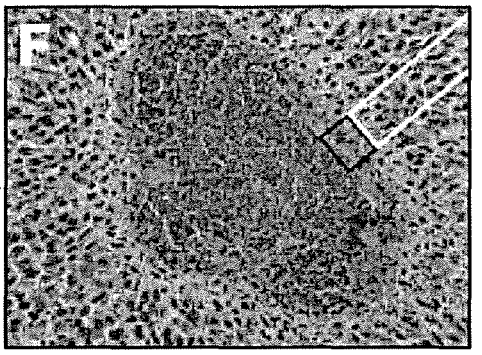


FIG. 8F

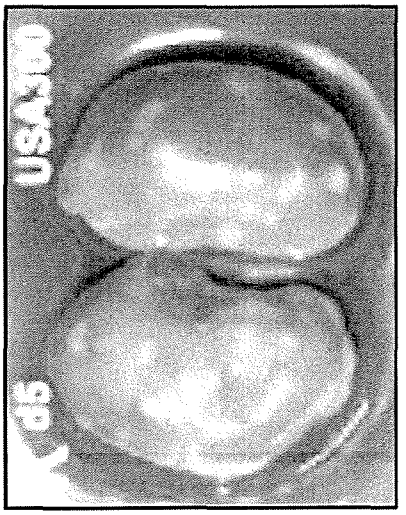


FIG. 9K

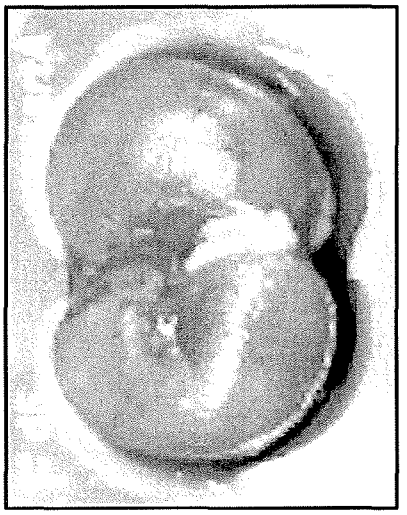


FIG. 9F

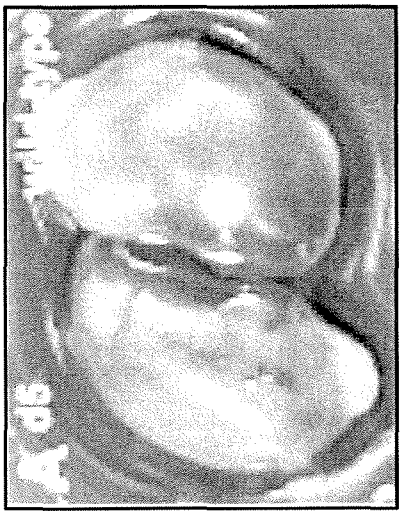


FIG. 9A

FIG. 9L

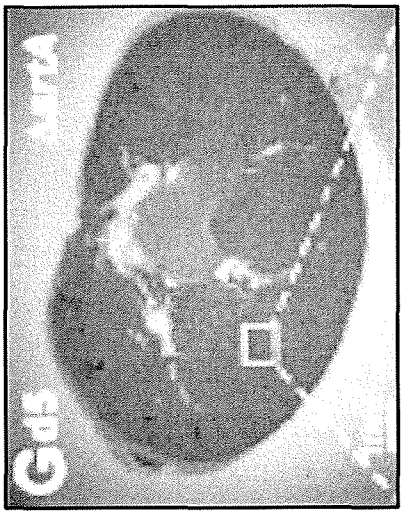


FIG. 9G

FIG. 9B

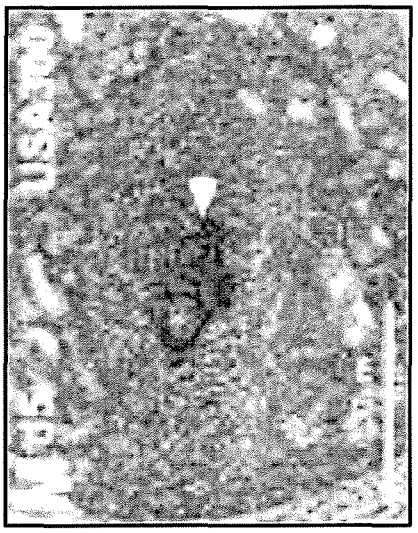


FIG. 9C

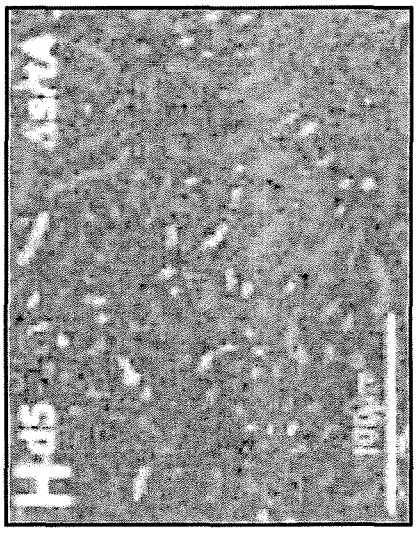


FIG. 9H

FIG. 9M

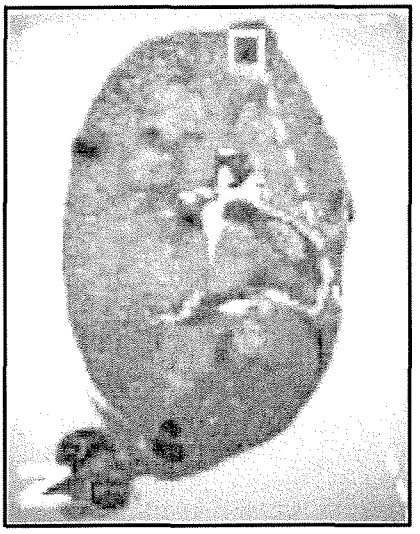


FIG. 9D

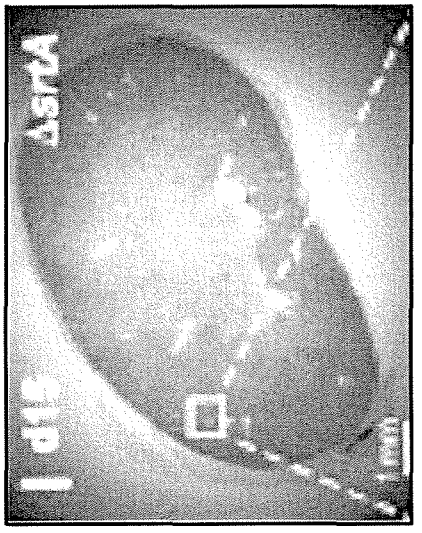


FIG. 9I

FIG. 9N

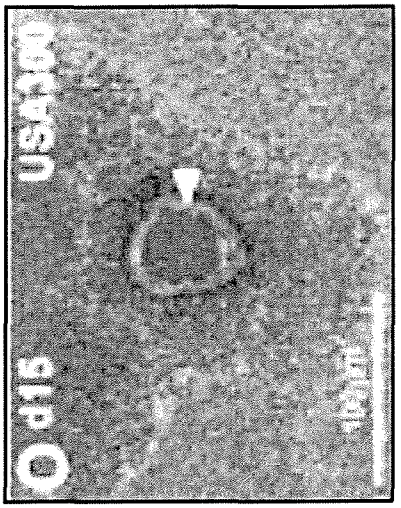


FIG. 9E

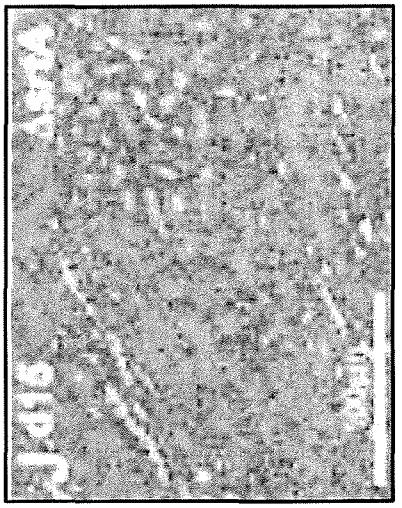


FIG. 9J

FIG. 9O

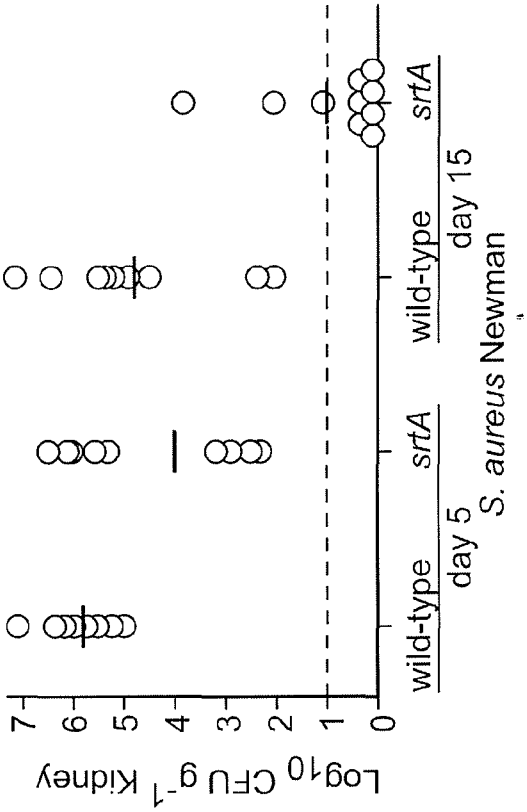


FIG. 9P

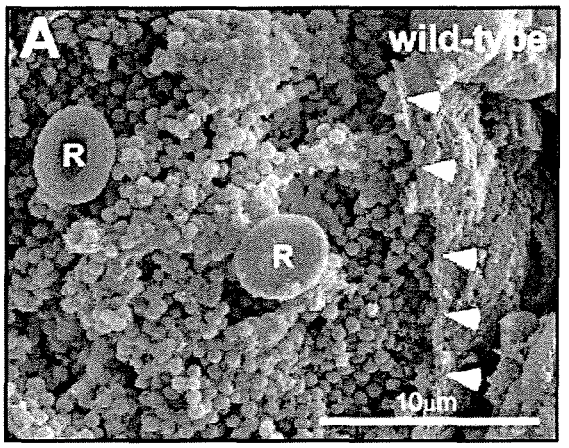


FIG. 10A

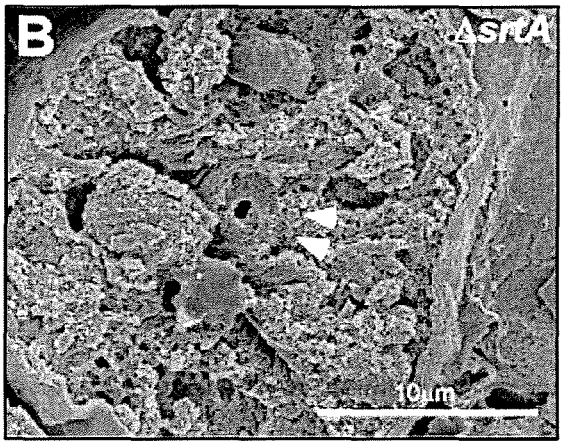


FIG. 10B

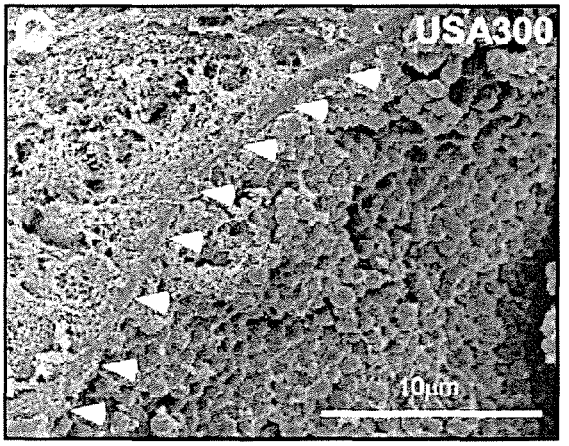


FIG. 10C

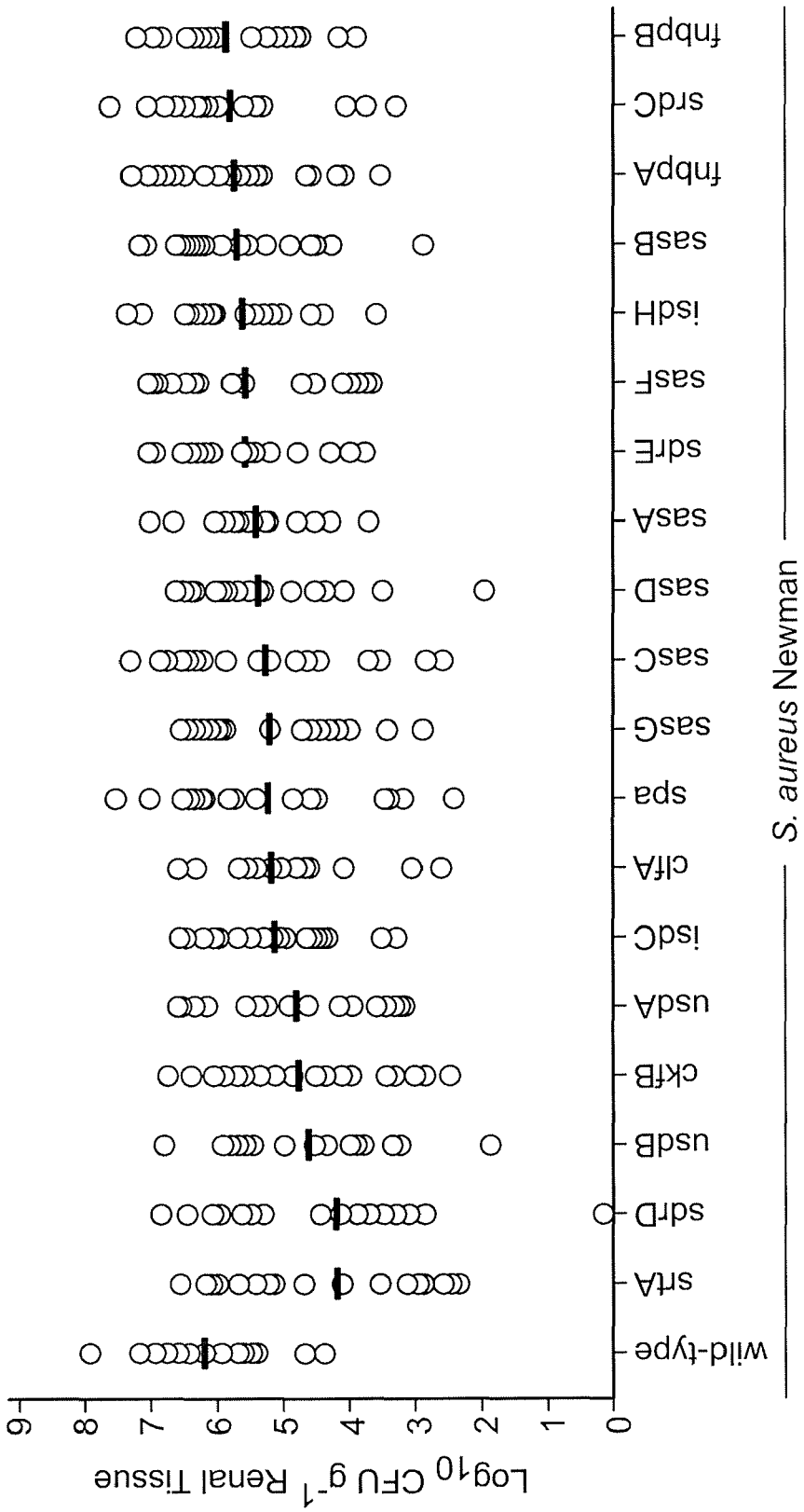

Log10 CFU g-1 Renal Tissue
0
1
2
3
4
5
6
7
8
9
wild-type
srtA
sdrD
usdB
ckfB
usdA
isdC
clfA
spa
sasG
sasC
sasD
sasA
sdrE
sasF
isdH
sasB
fnbpA
srdC
fnbpB
S. aureus Newman

FIG. 11A

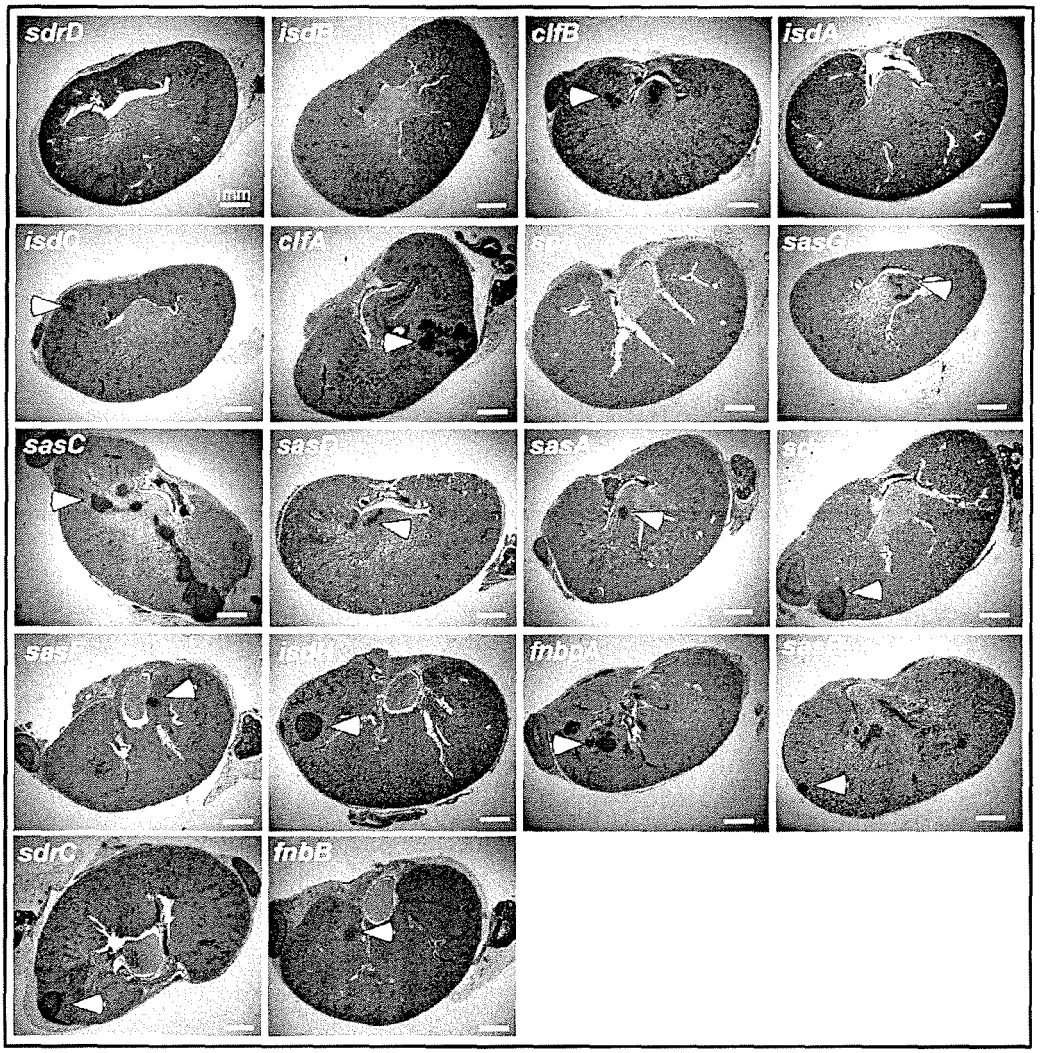

sdrD
isdB
clfB
isdA
isdC
clfA
sasG
sasC
sasB
sasA
sasF
isdA
fnbA
sdrC
fnbB

FIG. 11B

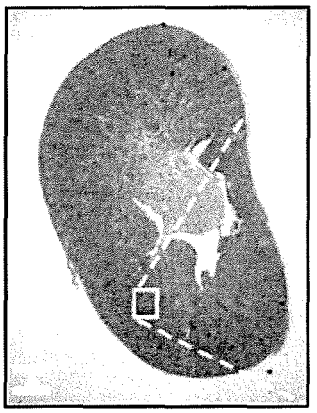


FIG. 12A

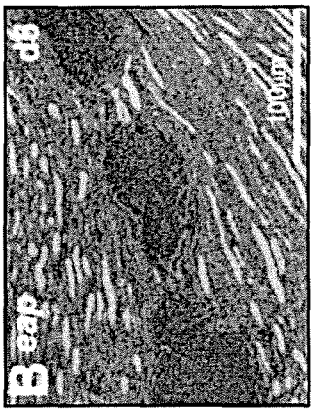


FIG. 12B

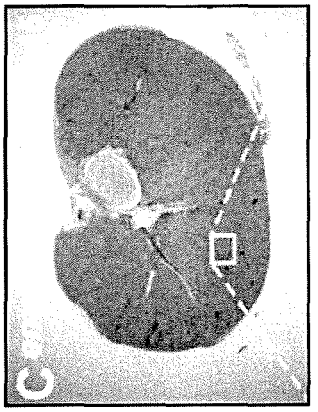


FIG. 12C

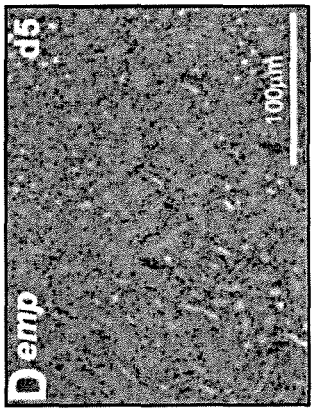


FIG. 12D

FIG. 12E

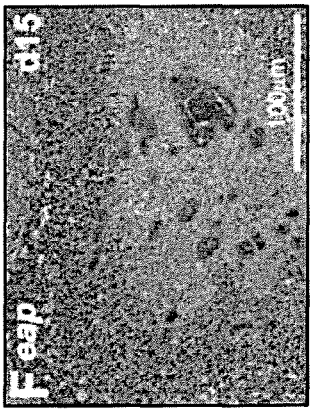


FIG. 12F

FIG. 12H

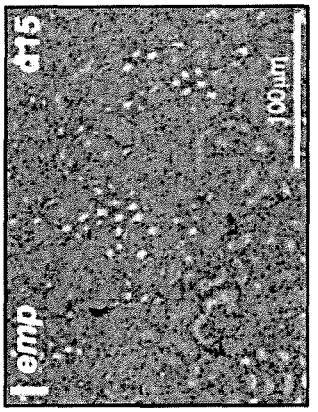


FIG. 12I

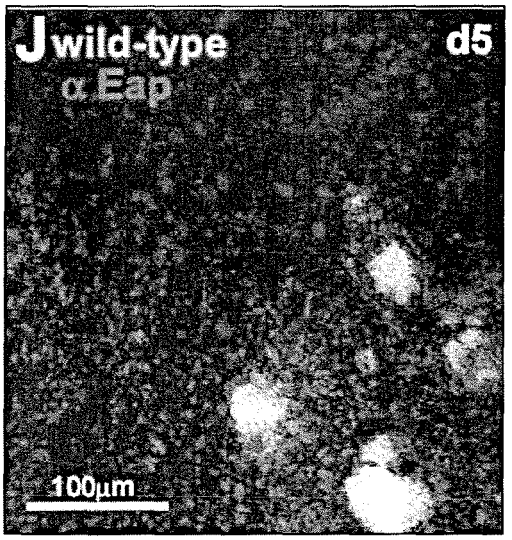


FIG. 12J

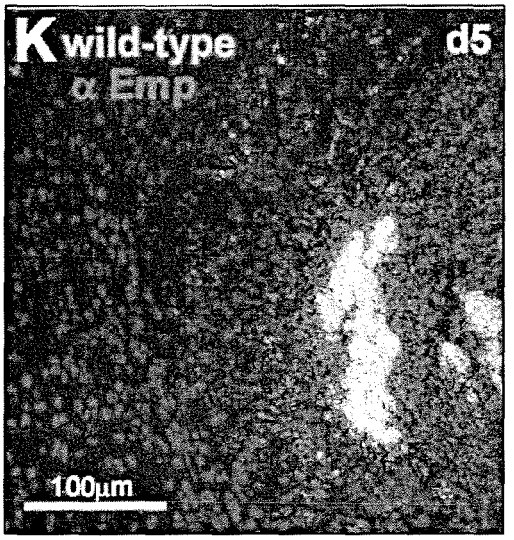


FIG. 12K

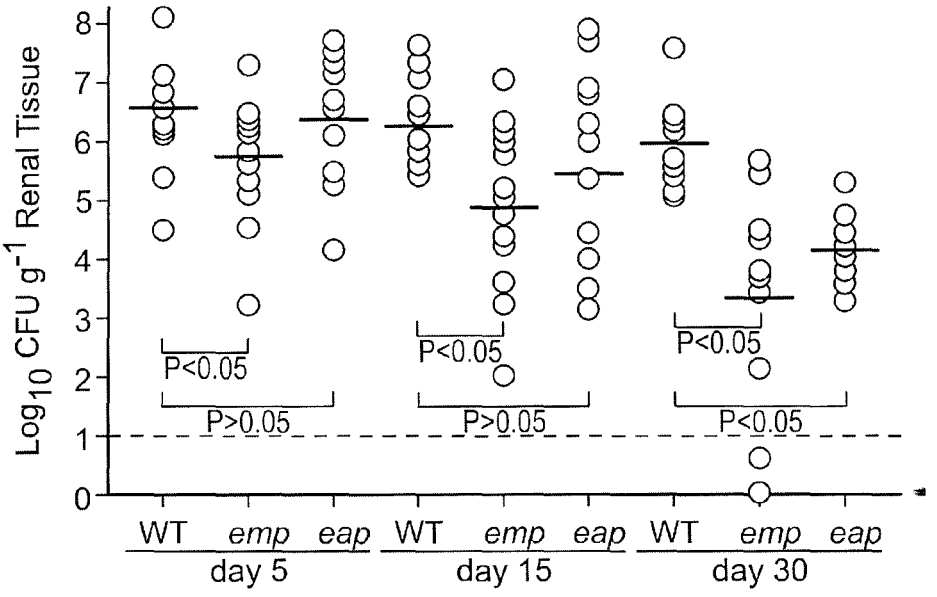


FIG. 12L

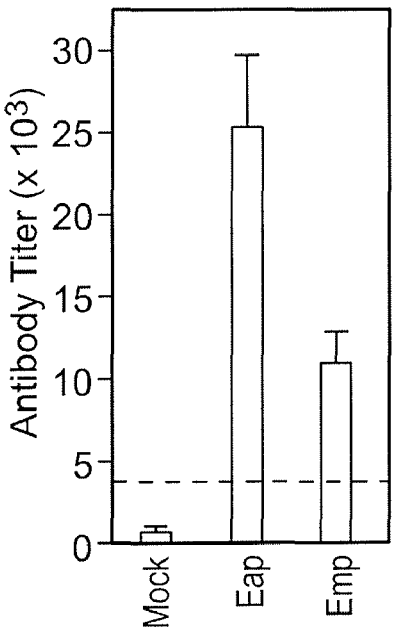


FIG. 13A

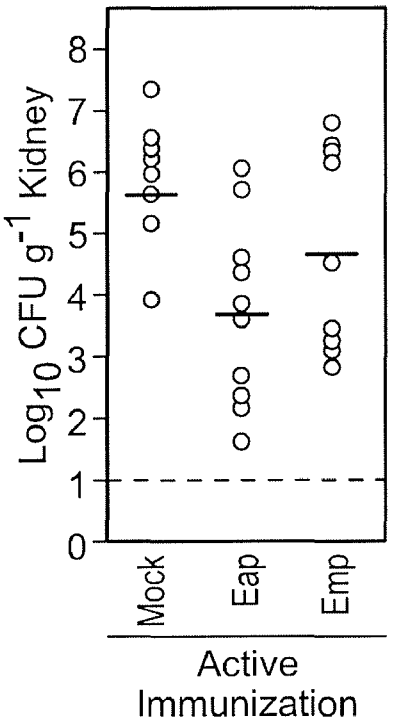


FIG. 13B

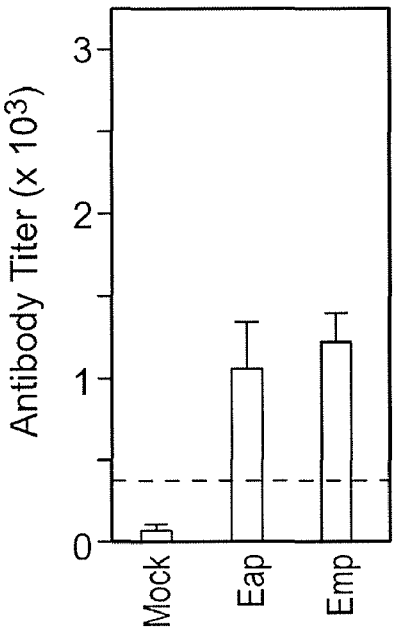


FIG. 13C

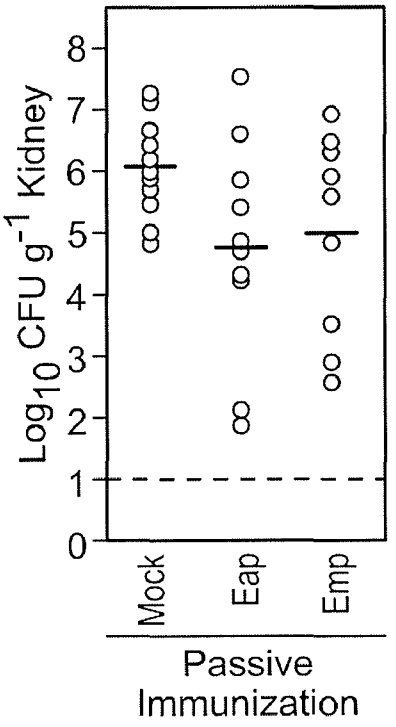


FIG. 13D

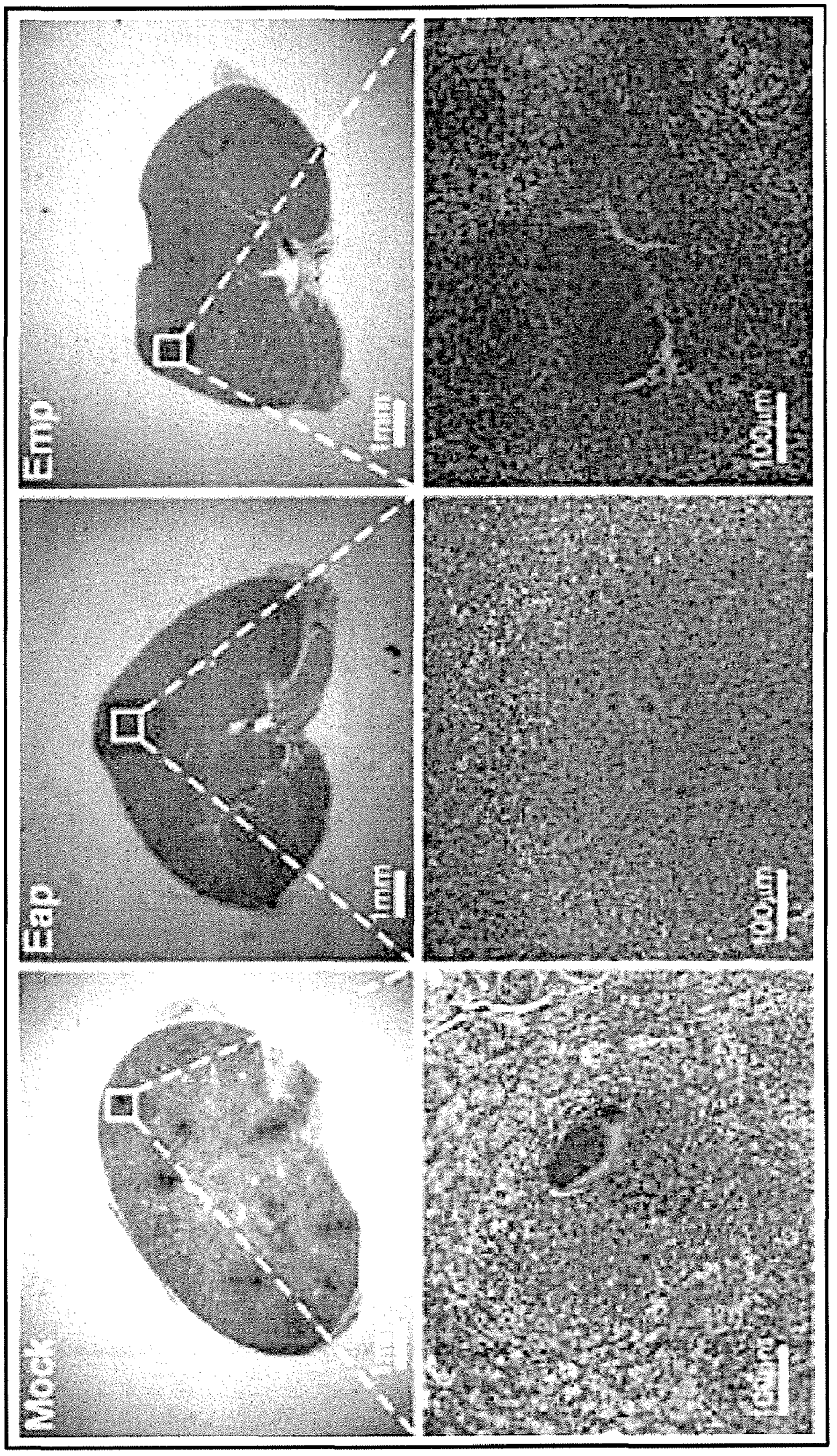


FIG. 13E

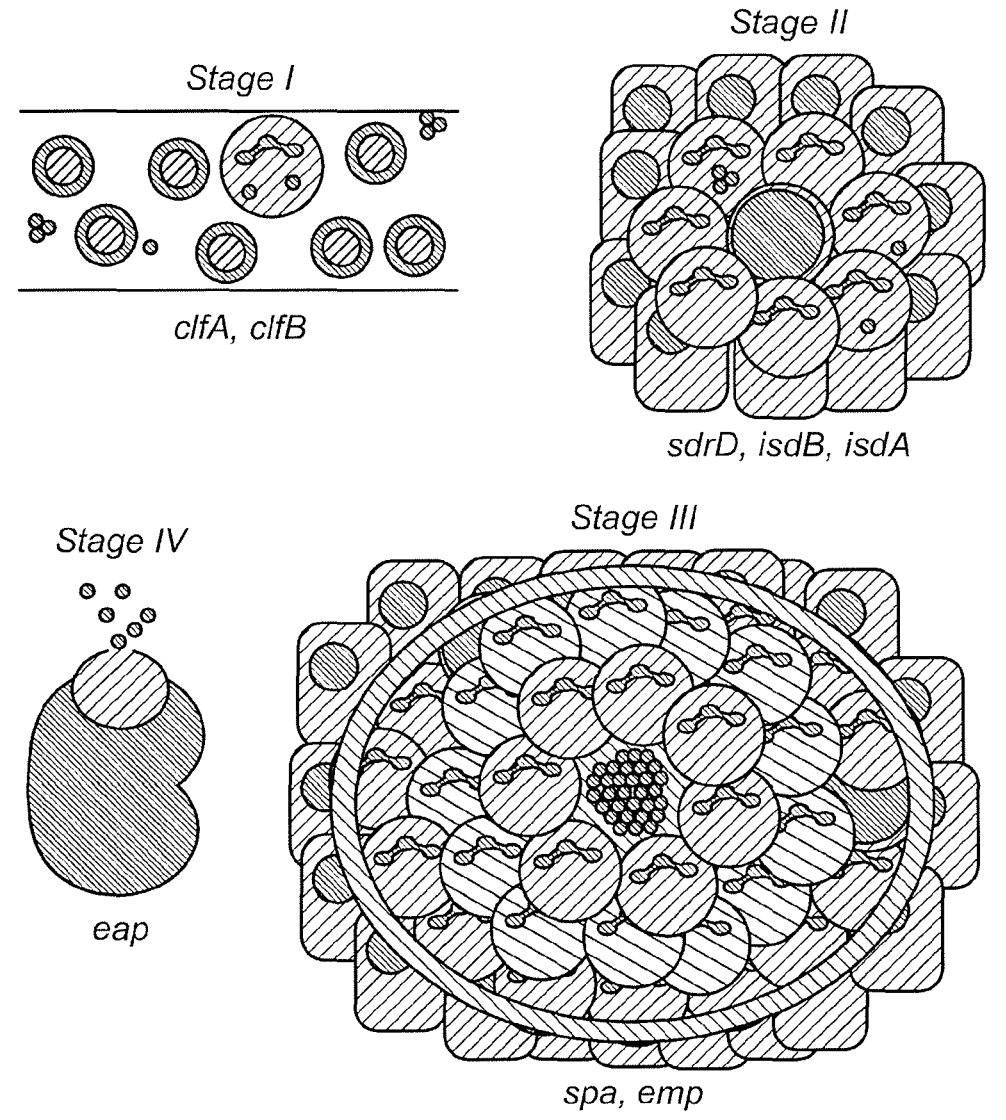

Stage I
clfA, clfB
Stage II
sdrD, isdB, isdA
Stage III
spa, emp
Stage IV
eap

FIG. 14

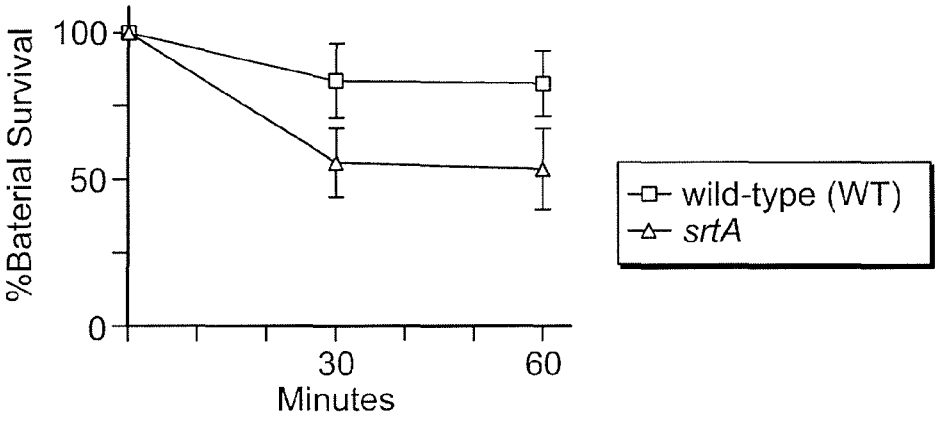


FIG. 15A

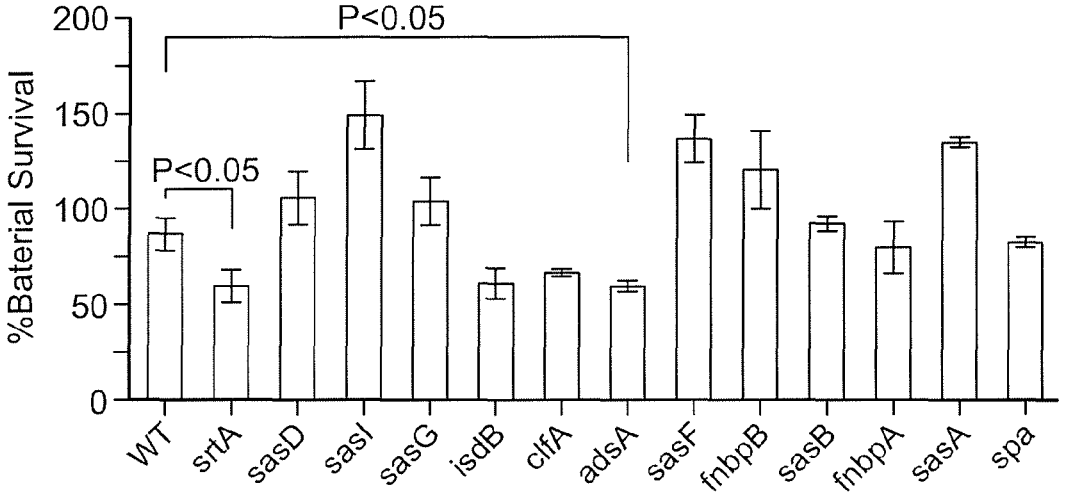


FIG. 15B

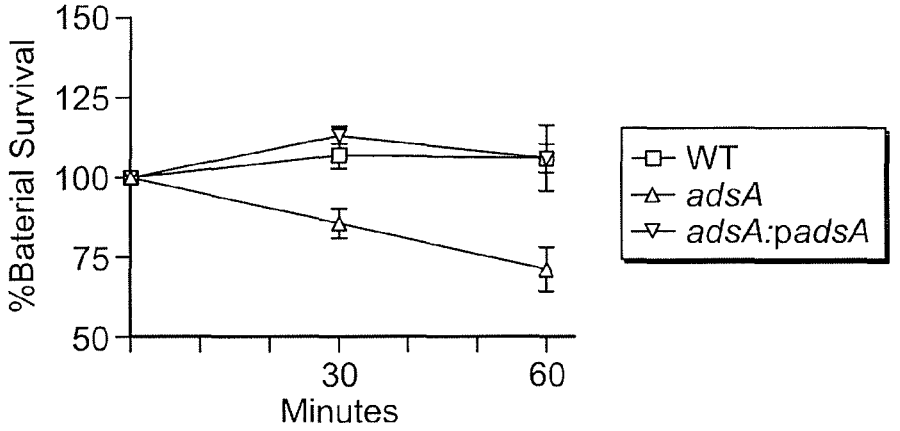


FIG. 15C

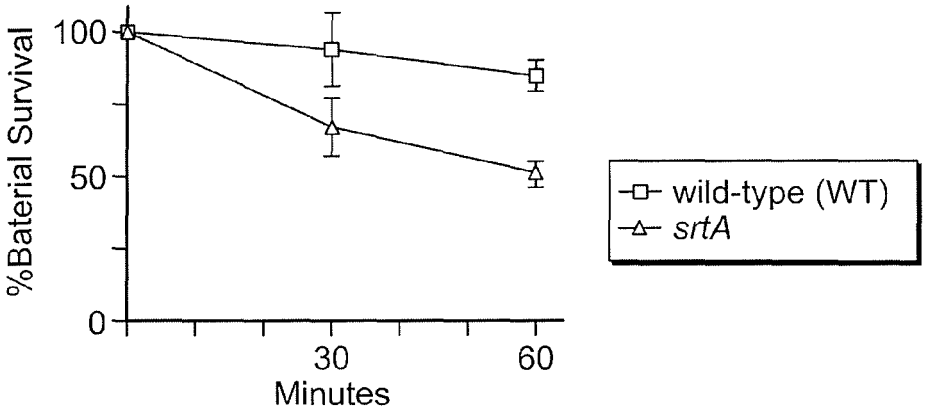


FIG. 15D

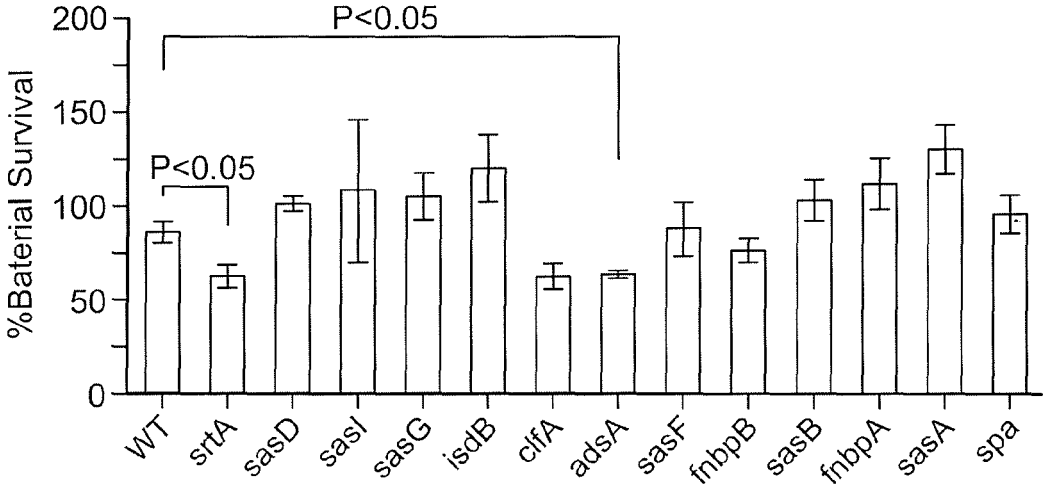


FIG. 15E

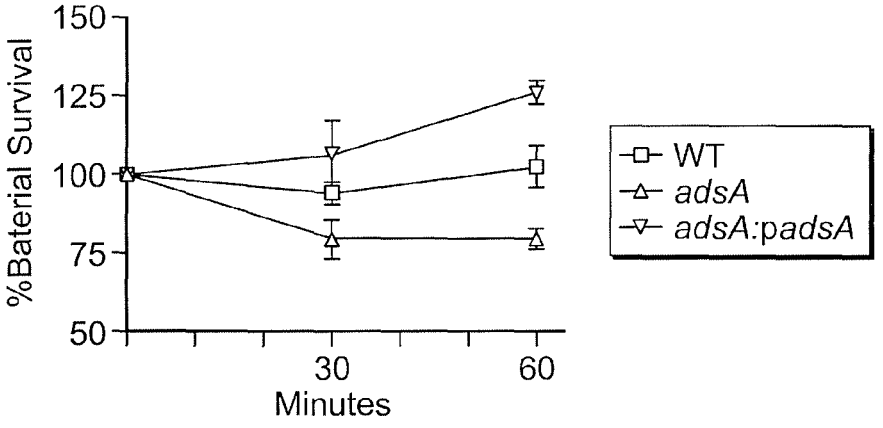


FIG. 15F

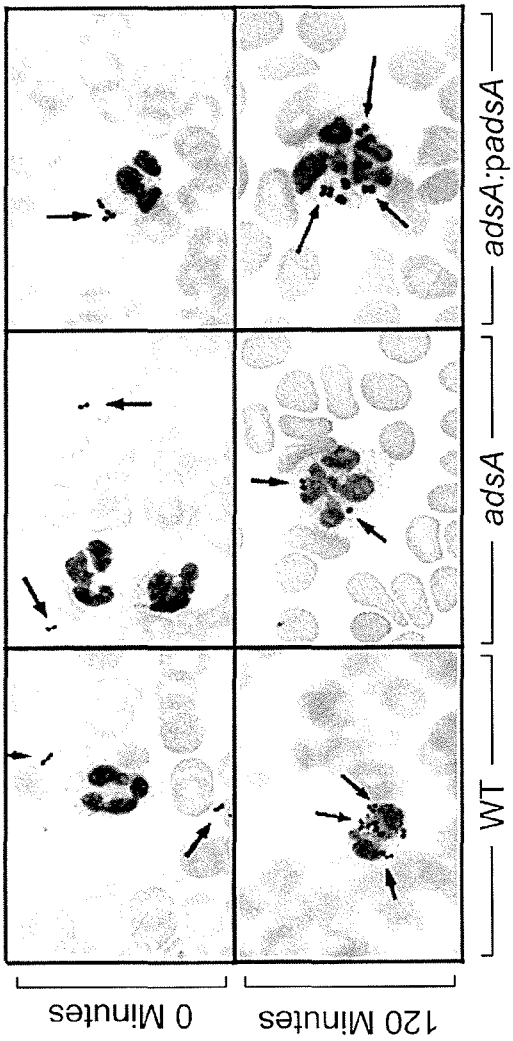


FIG. 15H

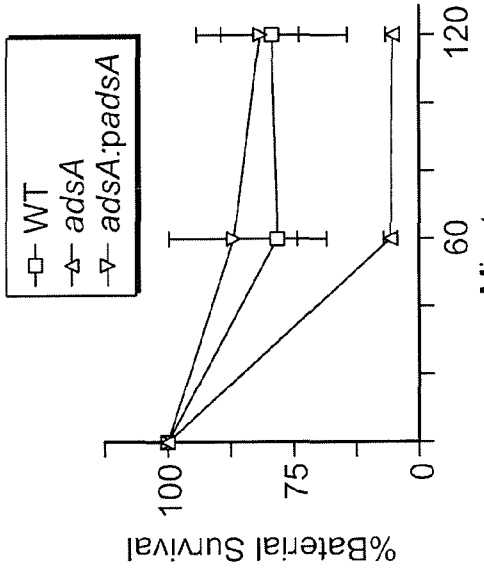


FIG. 15G

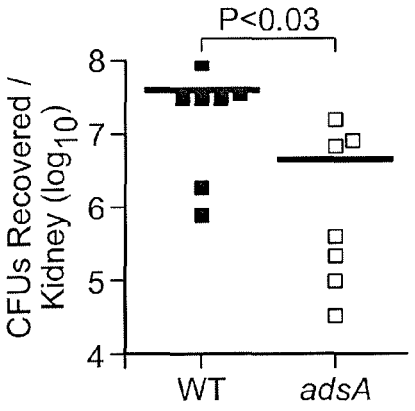


FIG. 16A

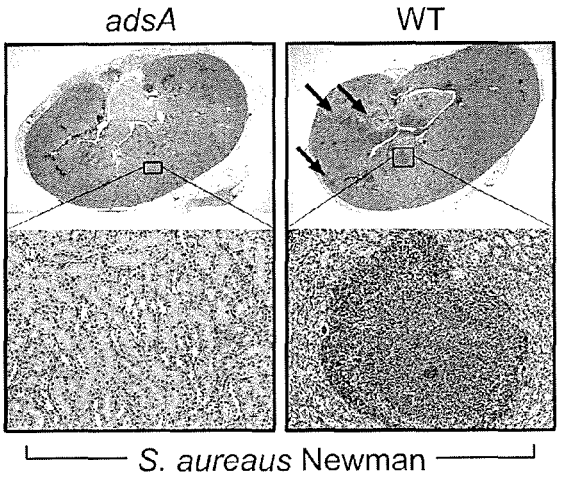


FIG. 16B

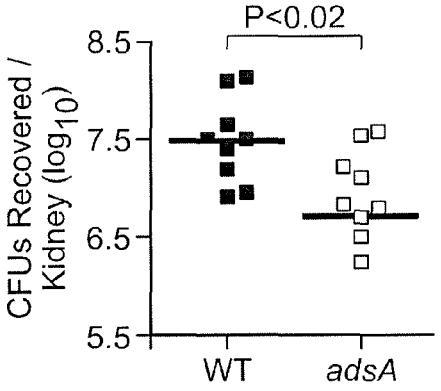


FIG. 16C

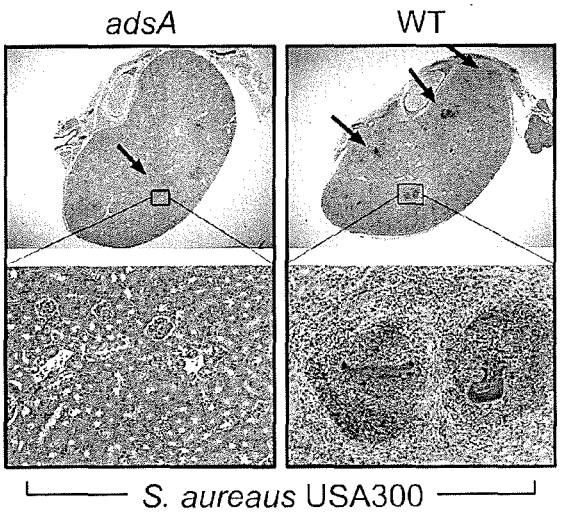


FIG. 16D

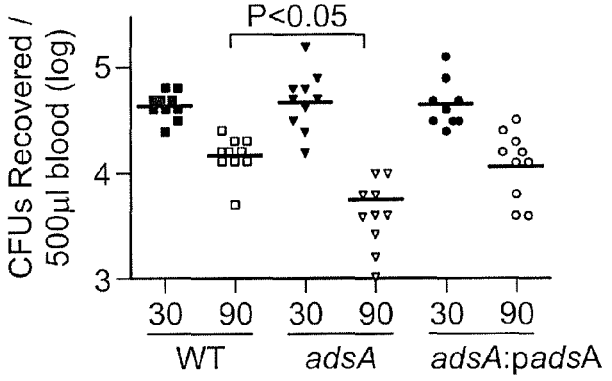


FIG. 16E

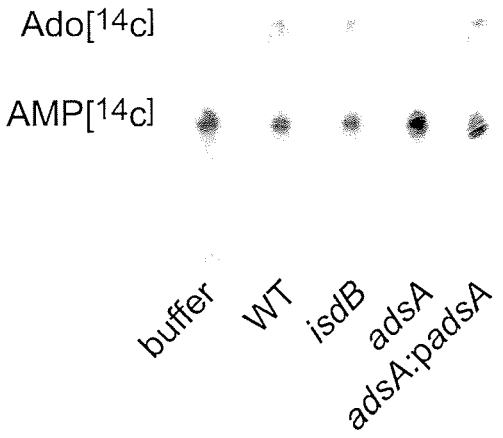


FIG. 17A

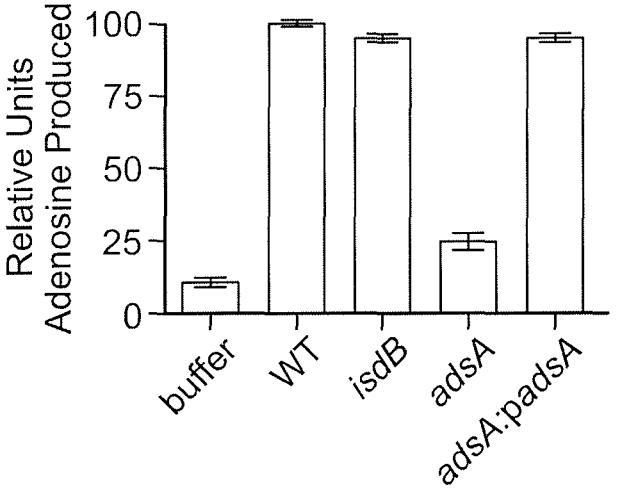


FIG. 17B

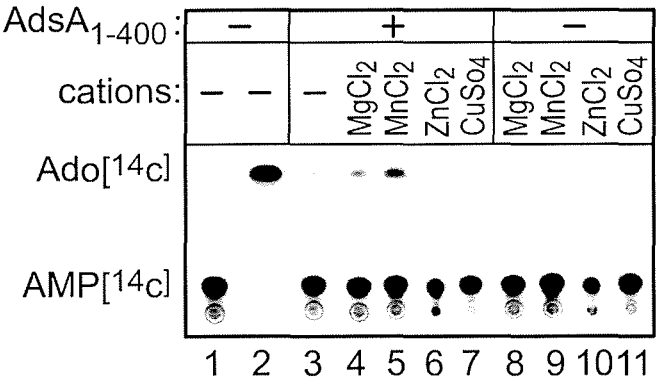


FIG. 17C

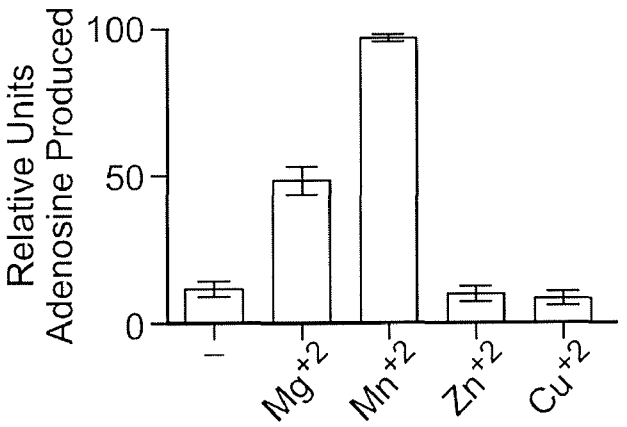


FIG. 17D

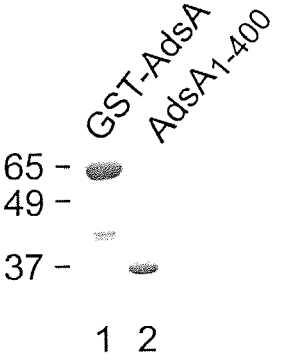


FIG. 17E

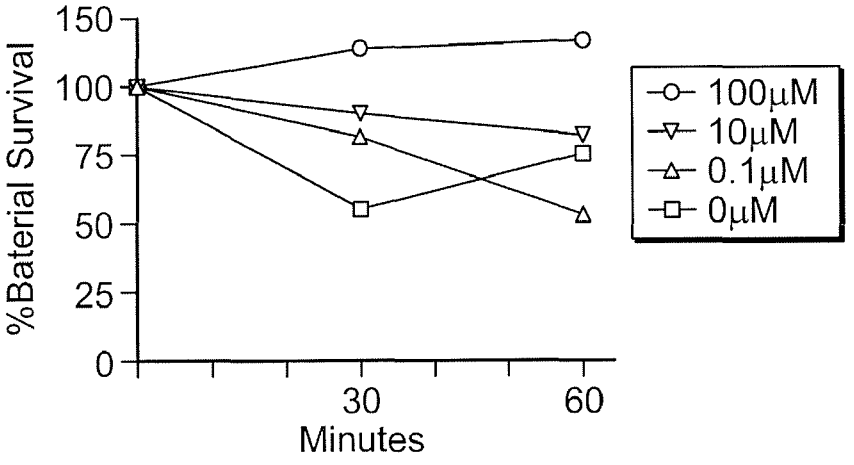


FIG. 17F

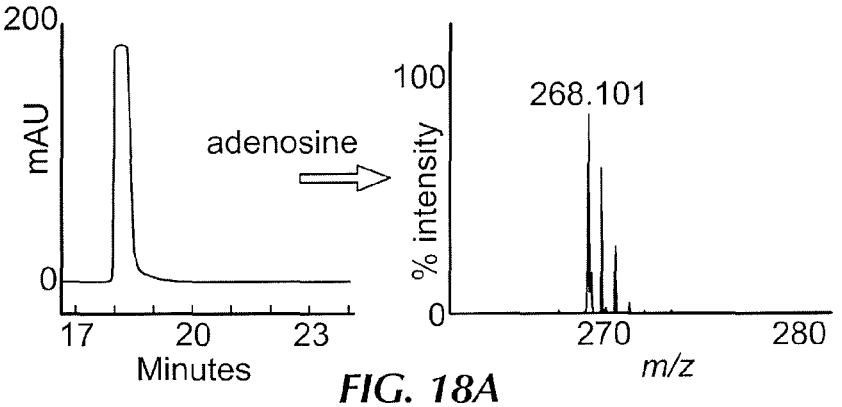


FIG. 18A

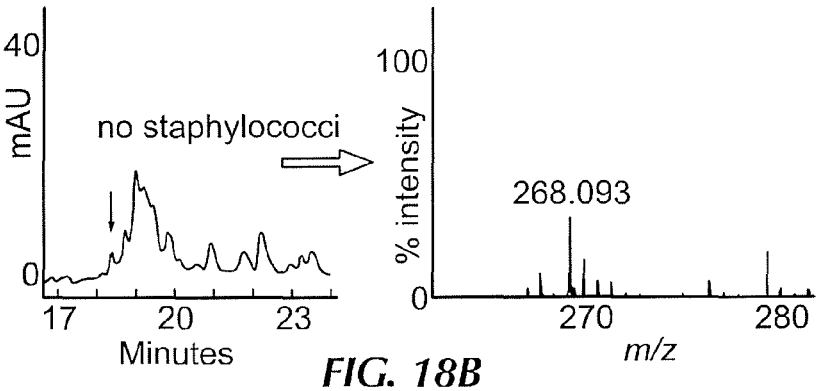


FIG. 18B

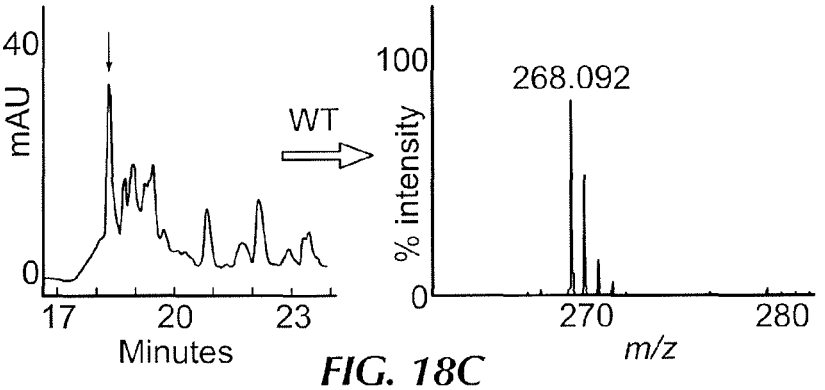


FIG. 18C

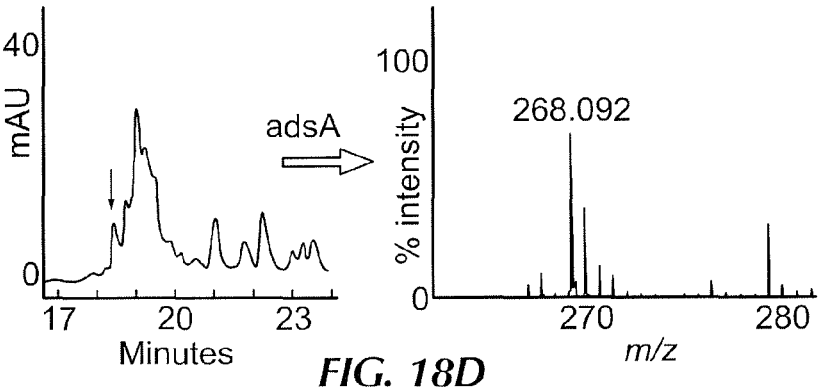


FIG. 18D

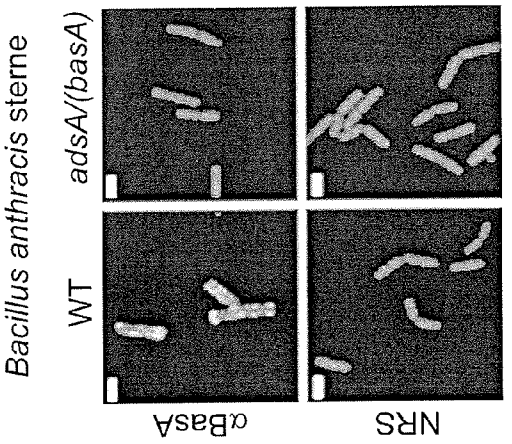


FIG. 19C

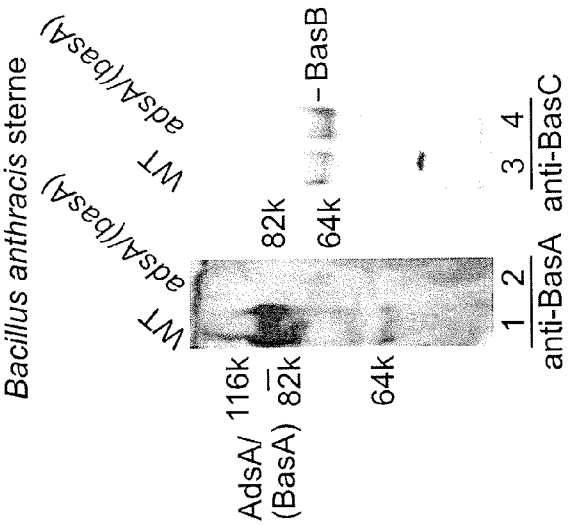


FIG. 19B

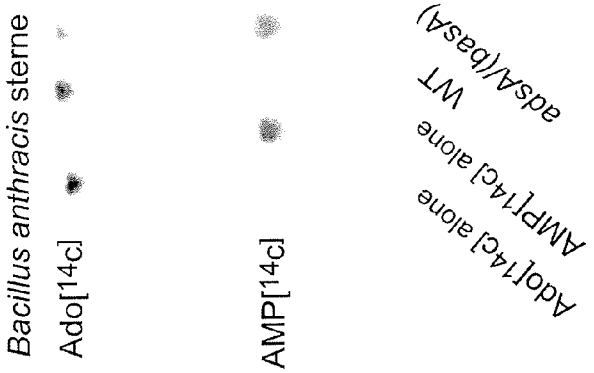


FIG. 19A

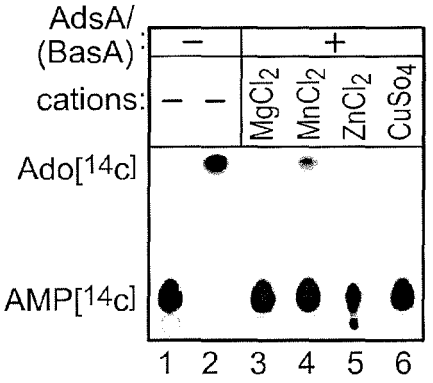


FIG. 19D

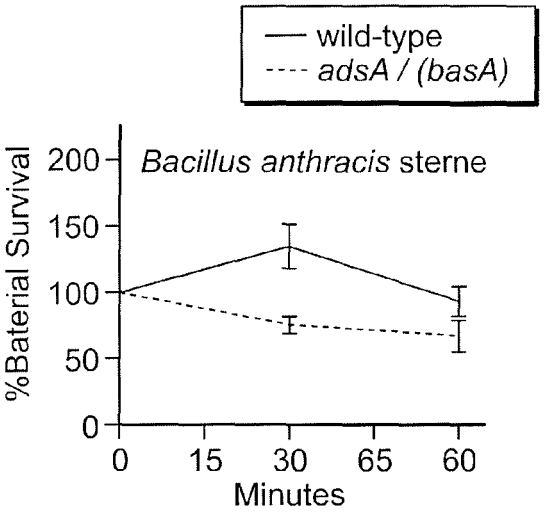


FIG. 19E

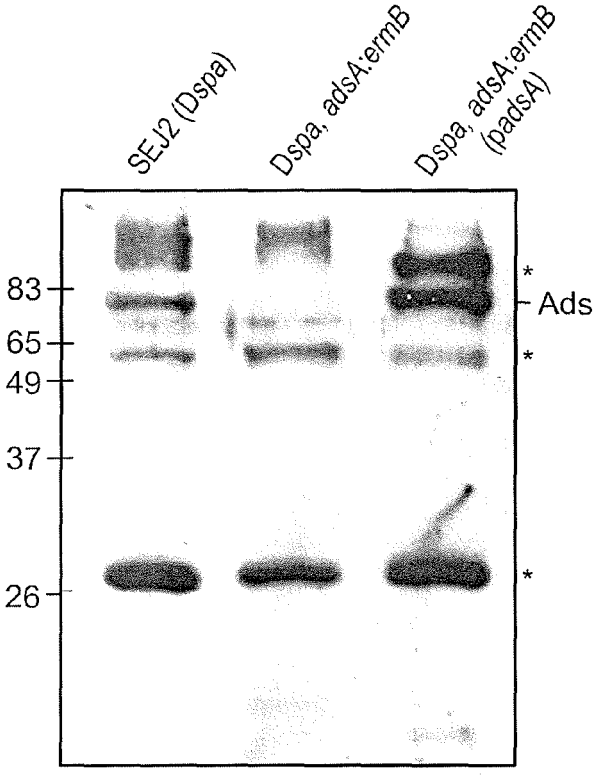


FIG. 20

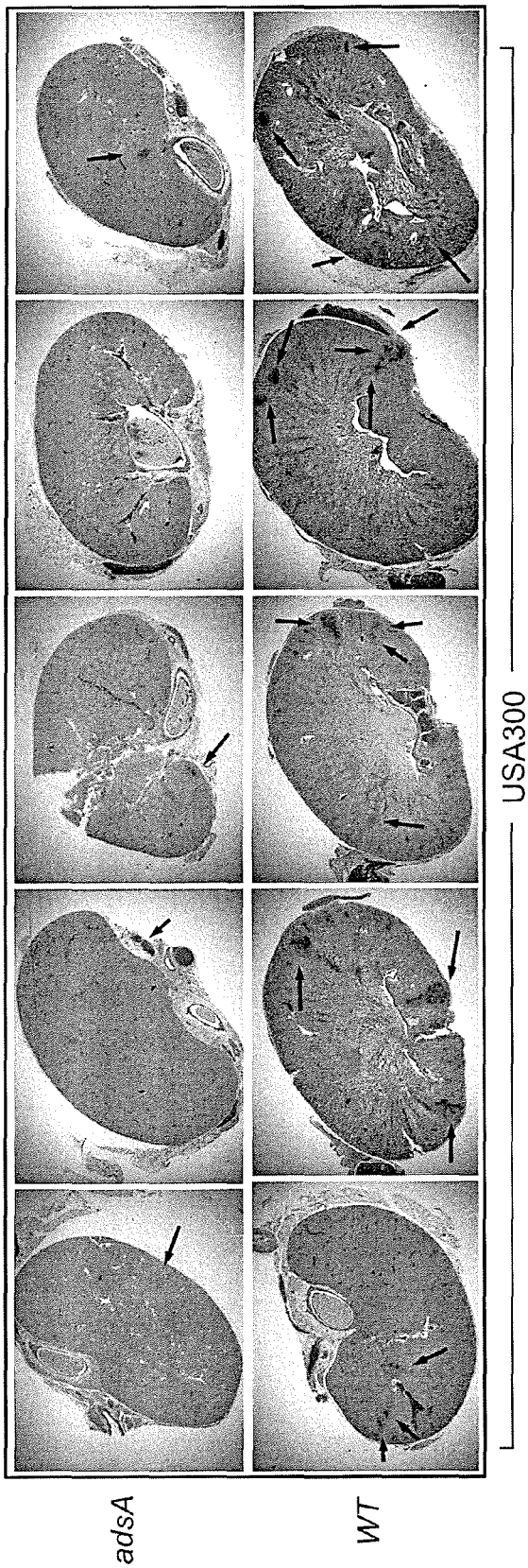


FIG. 21

COMPOSITIONS AND METHODS RELATED TO BACTERIAL EAP, EMP, AND/OR ADSA PROTEINS

[0001] This application claims benefit of priority to U.S. Provisional Application Ser. No. 61/103,196, filed Oct. 6, 2008, U.S. Provisional Application Ser. No. 61/103,190, filed Oct. 6, 2008, and U.S. Provisional Application Ser. No. 61/170,779, filed Apr. 20, 2009, the entire contents of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] I. Field of the Invention

[0003] 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 or provide passive immunotherapy. The proteins include Eap, Emp, bacterial adenosine synthase A (AdsA), and/or peptides or proteins comprising Eap, Emp, and/or AdsA amino acid sequences and antibodies that bind the same.

[0004] II. Background

[0005] The number of both community acquired and hospital acquired infections have increased over recent years. Hospital acquired (nosocomial) infections are a major cause of morbidity and mortality. In the United States, hospital acquired infections affect 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).

[0006] *Staphylococcus aureus*, Coagulase-negative Staphylococci (mostly *Staphylococcus epidermidis*), *enterococcus* spp., *Escherichia coli* and *Pseudomonas aeruginosa* are the major nosocomial pathogens. Although those pathogens cause approximately 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.

[0007] *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.

[0008] *Staphylococcus aureus* is the most common cause of nosocomial infections with significant morbidity and mortality. It can cause 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 that can be life-threatening. Problematically, methicillin-resistant *Staphylococcus aureus* (MRSA) has become a major cause of hospital-acquired infections.

[0009] *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 fears that MRSA strains are emerging and spreading for which no effective therapy is available.

[0010] 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 vaccines against staphylococcus infections. Additional compositions for treating staphylococcal infections are also needed.

SUMMARY OF THE INVENTION

[0011] *Staphylococcus aureus* is the single most frequent cause of bacteremia and soft tissue infection in hospitalized or healthy individuals, and dramatic increases in mortality are attributed to the spread of methicillin-resistant *S. aureus* (MRSA) strains that are often not susceptible to antibiotic therapy (Klevens et al., 2007; Klevens et al., 2006). Abscesses with characteristic fibrin deposits and massive immune cell infiltrates represent the pathological substrate of staphylococcal infection (Lowy, 1998). Scanning electron microscopy was used to observe biofilm-like structures at the center of staphylococcal abscesses. Genetic analyses revealed that in vitro biofilm formation was correlated with the ability of staphylococci to form abscesses, and the inventors identified envelope proteins that are essential for both processes. When purified and used for immunization of mice, Emp and Eap conferrs protective immunity to staphylococcal infection. Passive immunization using antibodies that bind Eap or antibodies that bind Emp also demonstrates therapeutic effects.

[0012] This application describes in one embodiment the use of Emp and/or Eap, or antibodies that bind all or part of Emp or Eap, in methods and compositions for the treatment of bacterial and/or staphylococcal infection. This application also provides an immunogenic composition comprising an Emp and/or Eap antigen or immunogenic fragment thereof. 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 Emp and/or Eap 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, and/or (iii) polysaccharides and the like.

[0013] In other aspects the subject can be administered an Emp and/or Eap modulator, such as an antibody (e.g., a polyclonal, monoclonal, or single chain antibody or fragment thereof) that binds Emp and/or Eap. An Emp and/or Eap modulator can bind Emp and/or Eap directly. The Emp and/or Eap modulator can be an antibody or cell that binds Emp and/or Eap. An antibody can be an antibody fragment, a humanized antibody, a human antibody, and/or a monoclonal antibody or the like. In certain aspects, the Emp and/or Eap modulator is elicited by providing an Emp and/or Eap peptide that results in the production of an antibody that binds Emp and/or Eap in the subject or a source subject (e.g., donor). The

Emp and/or Eap modulator is typically formulated in a pharmaceutically acceptable composition. The Emp and/or Eap modulator composition can further comprise at least one staphylococcal antigen or immunogenic fragment thereof, or antibody that binds such (e.g., EsxA, EsxB, EsaB, EsaC, SdrC, SdrD, Hla, SdrE, IsdA, IsdB, SpA, ClfA, ClfB, IsdC, SasB, SasH (AdsA, Ebh, Coa, vWa, or SasF). Additional staphylococcal antigens that can be used in combination with a Emp and/or Eap modulator include, but are not limited to 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. The staphylococcal antigen or antibody can be administered concurrently with the Emp and/or Eap modulator. The staphylococcal antigen or antibody and the Emp and/or Eap modulator can be administered in the same composition.

[0014] Certain embodiments are directed to a therapeutic composition comprising an isolated antibody, or fragment thereof, that binds an Emp and/or Eap antigen, or a fragment thereof, in a pharmaceutically acceptable composition wherein the composition is capable of attenuating a *staphylococcus* bacterial infection in a subject. The antibody can be a human or humanized antibody. In certain aspects the antibody is a polyclonal antibody, or monoclonal antibody, or single chain antibody, or fragment thereof. An antibody composition can further comprise at least one additional isolated antibody that binds an antigen selected from one or more of a group consisting of an isolated ClfA, ClfB, EsaB, EsaC, EsxA, EsxB, Hla, IsdA, IsdB, IsdC, SasB, SasF, SasH (AdsA), Ebh, Coa, vWa, SdrC, SdrD, SdrE, and SpA antigen, or a fragment thereof. Additional antibodies to a staphylococcal antigen that can be used in combination with a Emp and/or Eap modulator include, but are not limited to antibodies against 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.

[0015] The Emp and/or Eap modulator can also be a recombinant nucleic acid molecule encoding an Emp and/or Eap peptide. A recombinant nucleic acid molecule can encode the Emp and/or Eap peptide and at least one staphylococcal antigen or immunogenic fragment. A nucleic acid can encode or a polypeptide can comprise a number of antigens including 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of one or more of all or part of Eap, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, IsdC, ClfA, ClfB, SasB, SasF, SasH (AdsA), Ebh, Coa, vWa, SpA or variants thereof. Nucleic acids can encode additional staphylococcal antigens including, but not limited to 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.

[0016] In certain embodiments the methods and compositions use or include or encode all or part of the Emp and/or Eap polypeptide, peptide, or antigen, as well as antibodies that bind the same. In other aspects Emp and/or Eap may be used in combination with other staphylococcal or bacterial factors such as all or part of EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SasH (AdsA), Ebh, Coa, vWa, SpA, or immunogenic fragment thereof or combinations thereof. Additional staphylococcal antigens that can be used in combination with a Emp and/or Eap modulator include, but are not limited to 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 EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, IsdC, ClfA, ClfB, SasB, SasF, SasH (AdsA), Ebh, Coa, vWa, or SpA can be specifically excluded or included from a method, a composition, or a formulation of the invention. Additional staphylococcal antigens that can be explicitly excluded include, but are not limited to 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 (U56008341), 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.

[0017] 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 or other bacterium. In certain aspects, the composition comprises a bacterium that is not a Staphylococcal bacterium or does not contain Staphylococci bacteria. In certain embodiments a bacterial composition comprises an isolated or recombinantly expressed Emp and/or Eap polypeptide or a nucleotide encoding the same. In still further aspects, the isolated Emp and/or Eap polypeptide is multimerized, e.g., dimerized. 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 EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SasH (AdsA), Ebh, Coa, vWa, or SpA or immunogenic fragments thereof. Additional staphylococcal polypeptides that can be expressed or included in a bacterial composition include, but are not limited to 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. Alternatively, the composition may be or 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.

[0018] The term "Emp polypeptide" or "Eap polypeptide" refers to polypeptides that include isolated wild-type Emp or Eap proteins from *staphylococcus* bacteria, as well as variants and segments or fragments that stimulate an immune response against *staphylococcus* bacteria Emp or Eap proteins. Similarly, the term EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SasH (AdsA), Ebh, Coa, vWa, or SpA protein refers to a protein that includes isolated wild-type EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SasH (AdsA), or SpA polypeptides from *staphylococcus* bacteria, as well as variants, segments, or fragments that stimulate an immune response against *staphylococcus* bacteria EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SasH (AdsA), Ebh, Coa, vWa, or SpA proteins. Additionally, the terms 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 refers to a protein that includes isolated wild type 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 (U56008341), 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 from *staphylococcus* bacteria, as well as variants, segments, or fragments that stimulate an immune response against staphylococcal 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. 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

[0019] 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 antigens or segments/fragments thereof. Staphylococcal antigens include, but are not limited to an Eap, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SasH (AdsA), Ebh, Coa, vWa, or SpA, or a segment, fragment, or immunogenic fragment thereof. Additional Staphylococcal antigens include, but are not limited to 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.

[0020] In certain embodiments Emp and/or Eap polypeptides or immunogenic fragments thereof can be provided in combination with one or more antigens or immunogenic fragments of one or more of EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SasH (AdsA), Ebh, Coa, vWa, or SpA. Additional antigens or immunogenic fragments 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 can also be used.

[0021] Embodiments of the invention include compositions that may include a polypeptide, peptide, or protein that has or has at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity or similarity to Emp, Eap EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SasH (AdsA), Ebh, Coa, vWa, SpA, 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 (U56008341), 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 over 5, 10, 15, 20, 50, 100, 200, or more consecutive amino acids including all values and ranges there between. 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 Emp polypeptide (SEQ ID NO:2, 50-53) and/or Eap polypeptide (SEQ ID NO:4) or Emp nucleic acid (SEQ ID NO:1) and/or Eap nucleic acid (SEQ ID NO:3). In certain aspects the Emp polypeptide or Eap polypeptide will have an amino acid sequence of (SEQ ID NO:2) or (SEQ ID NO:4), respectively. 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.

[0022] The term "AdsA polypeptide" refers to polypeptides that include isolated wild-type bacterial AdsA proteins, e.g., staphylococcus (*S. aureus* SEQ ID NO:36) or bacillus (*B. anthracis* SEQ ID NO:41) bacteria, as well as variants and segments or fragments of AdsA proteins. In certain aspects, the AdsA polypeptide stimulates an immune response against bacterial AdsA proteins.

[0023] 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:6.

[0024] 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:8.

[0025] 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:10.

[0026] 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:12.

[0027] 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:14.

[0028] 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:16.

[0029] 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:18.

[0030] 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:20.

[0031] 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:22.

[0032] 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:24.

[0033] 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:26.

[0034] 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: 28.

[0035] 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 EsaB protein. In certain aspects the EsaB protein will have the amino acid sequence of SEQ ID NO: 30.

[0036] 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 EsaC protein. In certain aspects the EsaC protein will have the amino acid sequence of SEQ ID NO: 32.

[0037] 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 SasB protein. In certain aspects the SasB protein will have the amino acid sequence of SEQ ID NO: 34.

[0038] 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 SasH (AdsA) protein. In certain aspects the SasH (AdsA) protein will have the amino acid sequence of SEQ ID NO: 36 or SEQ ID NO:41.

[0039] 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 Hla protein. In certain aspects the Hla protein will have the amino acid sequence of SEQ ID NO: 37. In certain aspects, a variant Hla includes amino acid substitutions or D24C, H35C, H35K, H35L, R66c, E70C, or K110C, or any combination thereof (amino acids referred to using single letter code).

[0040] 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 the amino acid sequence of SEQ ID NO:38.

[0041] 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 Coa protein. In certain aspects the Coa protein will have the amino acid sequence of SEQ ID NO:39.

[0042] 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 vWa protein. In certain aspects the vWa protein will have the amino acid sequence of SEQ ID NO: 40.

[0043] In certain aspects, a polypeptide or segment/fragment can have a sequence that is at least 85%, at least 90%, at least 95%, at least 98% or at least 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.

[0044] The polypeptides or segments or fragments 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, 300, 350, 400, 450, 500, 550 or more 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:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, or SEQ ID NO:41.

[0045] In further embodiments a composition comprises a recombinant nucleic acid molecule encoding 1, 2, 3, 4, or more of Eap, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SasH (AdsA), SpA, Ebh, Coa, vWa, 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 (U56008341), 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.

[0046] 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 Emp and/or Eap polypeptide or peptide thereof; or, (ii) a nucleic acid molecule encoding an Emp and/or Eap polypeptide or peptide thereof, or (iii) administering an Emp and/or Eap polypeptide with any combination or permutation of bacterial proteins or polysaccharides described herein.

[0047] Yet still further embodiments include vaccines comprising a pharmaceutically acceptable composition having an isolated Emp and/or Eap polypeptides, or segment or fragment thereof, or any other combination or permutation of protein(s) or peptide(s) or polysaccharide(s) described, wherein the composition is capable of stimulating an immune response against a *staphylococcus* bacterium. The vaccine may comprise an isolated Emp and/or Eap polypeptide, and/or any other combination or permutation of protein(s) or peptide(s) or polysaccharide(s) described. In certain aspects of the invention the isolated Emp and/or Eap polypeptide, or any other combination or permutation of protein(s) or peptide (s) or polysaccharide(s) described are multimerized, e.g., dimerized.

[0048] 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-Emp and/or non-Eap 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.

[0049] In still yet further embodiments, a vaccine composition is a pharmaceutically acceptable composition having a recombinant nucleic acid encoding all or part of an Emp and/or Eap polypeptide, and/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 Emp and/or Eap polypeptide, and/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.

[0050] 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 Emp and/or Eap polypeptide or segment/fragment thereof comprising one or more of (i) a EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SasH (AdsA), SpA, Ebh, Coa, vWa, 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 polypeptide or segment or fragment thereof; or, (ii) a nucleic acid molecule encoding the same. Methods of the invention also include Emp and/or Eap compositions that contain 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SasH (AdsA), SpA, Ebh, Coa, vWa, 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 various combinations. In certain aspects a vaccine formulation includes an IsdA polypeptide or segment or fragment thereof.

[0051] In still a further aspect the invention includes a staphylococcal bacterium lacking an Emp and/or Eap polypeptide and/or EsaB polypeptide. Such a bacterium will be limited or attenuated with respect to prolonged or persistent abscess formation and/or biofilm formation. This characteristic can be used to provide bacterial strains 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, Emp and/or Eap can be overexpressed in an attenuated bacterium to further enhance or supplement an immune response or vaccine formulation.

[0052] Any embodiment discussed with respect to one aspect of the invention applies to other aspects of the invention as well. In particular, any embodiment discussed in the context of an Emp and/or Eap peptide or nucleic acid may be implemented with respect to EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SasH (AdsA), SpA, Ebh, Coa, vWa, 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 proteins or nucleic acids or antibodies that bind the same, and vice versa.

[0053] The inventors have examined the ability of *S. aureus* to escape phagocytic clearance in blood and identified adenosine synthase A (AdsA), a cell wall anchored enzyme that converts adenosine monophosphate to adenosine, as a critical virulence factor. Staphylococcal synthesis of adenosine in blood, escape from phagocytic clearance, and subsequent formation of organ abscesses were all dependent on adsA and could be rescued by an exogenous supply of adenosine. An AdsA homolog was identified in the anthrax pathogen and adenosine synthesis also enabled escape of *Bacillus anthracis* from phagocytic clearance. Taken together, these results suggest that staphylococci and other bacterial pathogens exploit the immunomodulatory attributes of adenosine to escape host immune responses. Certain embodiments of the invention are based on the discovery that the synthesis of the signaling molecule adenosine is immunosuppressive and modulation of its synthesis activity can be exploited for therapeutic purposes.

[0054] This application describes in one embodiment the use of AdsA, or antibodies that bind all or part of AdsA, or inhibitors of AdsA activity in methods and compositions for the treatment of bacterial and/or staphylococcal infection. This application also provides an immunogenic composition comprising an AdsA antigen or immunogenic fragment thereof. Furthermore, the present invention provides methods and compositions that can be used to treat (e.g., modulating phagocytic uptake of bacteria) 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 a bacterial AdsA polypeptide or antigen, and in certain aspects other bacterial proteins and bacterial polysaccharides. 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.

[0055] In other aspects the subject can be administered an AdsA modulator, such as an antibody (e.g., a polyclonal, monoclonal, or single chain antibody or fragment thereof) that binds AdsA or a small molecule that inhibits AdsA activity or stability. An AdsA modulator may bind AdsA directly. The AdsA modulator can be an antibody or cell that binds AdsA. An antibody can be an antibody fragment, a humanized antibody, a human antibody, and/or a monoclonal antibody or the like. In certain aspects, the AdsA modulator is elicited by providing an AdsA peptide or a bacteria expressing the same that results in the production of an antibody that binds AdsA in the subject. The AdsA modulator is typically formulated in a pharmaceutically acceptable composition. The AdsA modulator composition can further comprise at least one staphylococcal antigen or immunogenic fragment thereof, or antibody that bind such (e.g., Eap, Emp, EsaB, EsaC, EsxA, EsxB, SasB, SdrC, SdrD, SdrE, Hla, IsdA, IsdB, Spa, ClfA, ClfB, IsdC, Coa, Ebh, vWa or SasF). The staphylococcal antigen or antibody can be administered concurrently with the AdsA modulator. An antigen and/or antibody and/or antibiotic, and an AdsA modulator can be administered in the same composition.

[0056] Certain embodiments are directed to a therapeutic composition comprising an isolated antibody, or fragment thereof, that binds an AdsA protein or antigen, or a fragment thereof, in a pharmaceutically acceptable composition wherein the composition is capable of attenuating a *staphylococcus* bacterial infection in a subject, e.g., modulating phagocytic uptake of bacteria. The modulator can be a small molecule, such as an adenosine analog. The antibody can be a human or humanized antibody. In certain aspects the antibody is a polyclonal antibody, or monoclonal antibody, or single chain antibody, or fragment thereof.

[0057] An antibody composition can further comprise at least one additional isolated antibody that binds a antigen selected from a group consisting of an isolated ClfA, ClfB, Eap, Emp, EsaB, EsaC, EsxA, EsxB, Hla, IsdA, IsdB, IsdC, SasB, SasF, SdrC, SdrD, Coa, Ebh, vWa, SdrE, and SpA antigen, or a fragment thereof.

[0058] The AdsA modulator can also be a recombinant nucleic acid molecule encoding an AdsA peptide. A recombinant nucleic acid molecule can encode the AdsA peptide and/or at least one staphylococcal antigen or immunogenic fragment. A nucleic acid can encode or a polypeptide can comprise a number of antigens including 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of one or more of all or part of AdsA (SasH), Eap, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Coa, Ebh, vWa, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, or SpA.

[0059] The AdsA modulator can also be a recombinant nucleic acid molecule encoding an AdsA peptide. A recombinant nucleic acid molecule can encode the AdsA peptide and/or at least one staphylococcal antigen or immunogenic fragment. A nucleic acid can encode or a polypeptide can comprise a number of antigens including 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of one or more of all or part of AdsA (SasH), Eap,

Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Coa, Ebh, vWa, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, or SpA.

[0060] 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 or other 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 AdsA polypeptide or a nucleic acid encoding the same. In still further aspects, the isolated AdsA polypeptide is multimerized, e.g., dimerized. 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 AdsA, Eap, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, Coa, Ebh, vWa, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, or SpA or immunogenic fragments thereof. Alternatively, the composition may be or 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.

[0061] Similarly, the term Eap, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, Coa, Ebh, vWa, SasF, or SpA protein refers to a protein that includes the respective isolated wild-type polypeptides from *staphylococcus* bacteria, as well as variants, segments, or fragments that stimulate an immune response against the same. 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 Bacterial AdsA polypeptides include, but are not limited to all or part of the amino acid sequences of the following bacteria (accession number): *Staphlyococcus aureus* (ref|YP_001573948, ref|YP_184935, ref|YP_039500, ref|NP_373261, ref|NP_370547, ref|YP_042156, ref|NP_644838, ref|YP_415541, dbj|BAA82250); *Staphlyococcus hemolyticus* (ref|YP_254367); *Streptococcus sanguinis* (ref|YP_001035187); *Streptococcus gordonii* (ref|YP_001450531); *Enterococcus faecalis* (ref|NP_813870); *Streptococcus suis* (dbj|BAB83980, ref|YP_001200571, ref|YP_001198366); *Streptococcus mutans* (ref|NP_721592); *Streptococcus thermophilus* (ref|YP_141373, ref|YP_139455); *Alkaliphilus metalliredigens* (ref|YP_001321391); *Clostridium botulinum* (ref|YP_001887045, ref|YP_001921966); *Paenibacillus* (ref|ZP 02846642); *Alkaliphilus oremlandii* (ref|YP_001512463); *Bacillus* clausii (ref|YP_174466); *Bacillus halodurans* (ref|NP_240892); *Clostridium difficile* (ref|ZP_03126518, ref|ZP_02748384, ref|YP_001089051, ref|ZP_02726436, ref|ZP_01801990); *Clostridium cellulolyticum* (ref|ZP_01574143); and *Anaerotruncus colihominis* (ref|ZP_02441436), each of which is incorporated herein by reference. In certain aspects and AdsA polypeptide can have at least or more than 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, identity, including all values and ranges there between, to SEQ ID NO:36 or SEQ ID NO:41.

[0062] 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 AdsA polypeptide (SEQ ID NO:36) or AdsA nucleic acid (SEQ ID NO:35), in certain aspects the AdsA polypeptide will have an amino acid sequence of (SEQ ID NO:36). 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.

[0063] The compositions may be formulated in a pharmaceutically acceptable composition. In certain aspects of the invention the staphylococcus bacterium is an *S. aureus* or *S. epidermidis* bacterium. In another aspect, the bacteria is a *bacillus* or *B. anthracis*.

[0064] The activity of the compounds as inhibitors of AdsA can be assessed using methods known to those of skill in the art, as well as methods described herein. Screening assays may include controls for purposes of calibration and confirmation of proper manipulation of the components of the assay. Blank wells that contain all of the reactants but no member of the chemical library are usually included. As another example, a known inhibitor (or activator) of AdsA, can be incubated with one sample of the assay, and the resulting decrease (or increase) in the enzyme activity used as a comparator or control. It will be appreciated that modulators can also be combined with the enzyme activators or inhibitors to find modulators which inhibit the enzyme activation or repression that is otherwise caused by the presence of the known the enzyme modulator. The term "high throughput screening" or "HTS" as used herein refers to the testing of many thousands of molecules (or test compounds) for their effects on the function of a protein. In the case of group transfer reaction enzymes many molecules may be tested for effects on their catalytic activity. HTS methods are known in the art and they are generally performed in multiwell plates with automated liquid handling and detection equipment; however, it is envisioned that the methods of the invention may be practiced on a microarray or in a microfluidic system. The term "library" or "drug library" as used herein refers to a plurality of chemical molecules (test compounds) having potential as a modulator of AdsA, a plurality of nucleic acids, a plurality of peptides, or a plurality of proteins, and a combination thereof. Wherein the screening is performed by a high-throughput screening technique, wherein the technique utilizes a multiwell plate or a microfluidic system.

[0065] One example of an assay/kit for assessing AdsA activity includes, but is not limited to a Diazyme Enzyme reaction kit: This kit is a 5'-Nucleotidase (5'-NT) assay kit is typically used for the determination of 5'-NT activity in human serum samples. The 5'-NT assay is based on the enzymatic hydrolysis of 5'-monophosphate (5'-IMP) to form inosine which is converted to hypoxanthine by purine nucleoside phosphorylase (PNP). Hypoxanthine is then converted to uric acid and hydrogen peroxide (H_2O_2) by xanthine oxidase (XOD). H_2O_2 is further reacted with N-Ethyl-N-(2-hydroxy-3-sulfopropyl)-3-methylaniline (EHSPT) and 4-aminoantipyrine (4-AA) in the presence of peroxidase (POD) to generate quinone dye which is monitored kinetically. This method is fast, but is not as sensitive as the radioactivity assays.

[0066] Inhibitors and inhibitor candidates include, but are not limited to derivatives or analogs of: α,β-methylene adenosine 5'-diphosphate (AOPCP), an inhibitor of 5'-ecto nucleotidase (human homologue of bacterial AdsA), this inhibitor does not inhibit secreted 5'-nucleotidases from trophozoites of Trichomonas gallinae (Borges et al., 2007); nucleoticidin and melanocidins A and B, these compounds exhibited potent inhibitory activity against 5'-nucleotidases from rat liver membrane and snake venom (Uchino et al., 1986); polyphenolic compounds, these compounds poss-sess anti-tumor activity and inhibit 5'-nucleotidases from a variety of sources and have been isolated from the seeds of Areca catechu (betel nuts) as well as grapes (Iwamoto et al., 1988; Uchino et al., 1988; Toukairin et al., 1991).

[0067] In still further embodiments, a composition comprises a recombinant nucleic acid molecule encoding an AdsA polypeptide or segments/fragments thereof. Typically a recombinant nucleic acid molecule encoding an AdsA polypeptide contains a heterologous promoter.

[0068] 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 additional 1, 2, 3, 4, 5, 6, 7, 8, or more polypeptide or peptide.

[0069] In certain aspects a composition includes a recombinant, non-staphylococcus bacterium containing or expressing one or more polypeptide described herein in, e.g., an AdsA 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 capable of eliciting an immune response is contemplated. In further aspects the staphylococcus bacterium containing or expressing the AdsA polypeptide is a *Staphylococcus aureus*. In further embodiments the immune response is a protective and/or therapeutic immune response.

[0070] 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 AdsA polypeptide or peptide thereof; or, (ii) a nucleic acid molecule encoding an AdsA polypeptide or peptide thereof, or (iii) administering an AdsA polypeptide with any combination or permutation of bacterial proteins or polysaccharides described herein.

[0071] Yet still further embodiments include vaccines comprising a pharmaceutically acceptable composition having an isolated AdsA polypeptide, a segment or fragment thereof, 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 AdsA polypeptide and/or any other combination or permutation of protein(s), peptide(s) or polysaccharides described. In certain aspects of the invention the isolated AdsA polypeptide, or any other combination or permutation of protein(s) or peptide(s) described are multimerized, e.g., dimerized.

[0072] 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-AdsA 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.

[0073] In still yet further embodiments, a vaccine composition is a pharmaceutically acceptable composition having a recombinant nucleic acid encoding all or part of an AdsA polypeptide, and/or any other combination or permutation of protein(s) or peptide(s) described herein, wherein the composition is capable of stimulating an immune response against a staphylococcus or bacillus bacteria. The vaccine composition may comprise a recombinant nucleic acid encoding all or part of an AdsA polypeptide, and/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.

[0074] In further embodiments, a vaccine composition is a pharmaceutically acceptable composition comprising an isolated antibody, or fragment thereof, that binds an AdsA protein or antigen, or a fragment thereof, wherein the composition is capable of attenuating a staphylococcus bacterial infection in a subject, e.g., modulating phagocytic uptake of bacteria. The antibody can be a human or humanized antibody. In certain aspects the antibody is a polyclonal antibody, or monoclonal antibody, or single chain antibody, or fragment thereof.

[0075] The vaccine composition can further comprise at least one additional isolated antibody that binds a antigen selected from a group consisting of an isolated ClfA, ClfB, EsaB, EsaC, EsxA, EsxB, Hla, IsdA, IsdB, IsdC, Emp, Eap, SasB, SasF, SdrC, SdrD, Coa, Ebh, vWa, SdrE, and SpA antigen, or a fragment thereof.

[0076] 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 AdsA polypeptide or segment/fragment thereof comprising one or more of (i) a Eap, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, IsdC, Spa, ClfA, ClfB, Coa, Ebh, vWa, IsdC, SasB, SasF, or SpA polypeptide or segment or fragment thereof; or, (ii) a nucleic acid molecule encoding the same. Methods of the invention also include AdsA compositions that contain 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of Eap, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, Coa, Ebh, vWa, SdrE, Hla or a variant thereof, IsdA, IsdB, IsdC, SpA, ClfA, ClfB, IsdC, SasB, SasF,

or Spa in various combinations. In certain aspects a vaccine formulation includes an IsdA polypeptide or segment or fragment thereof.

[0077] In still a further aspect the invention includes a staphylococcal bacterium lacking an AdsA polypeptide. Such a bacterium will be limited or attenuated with respect to its ability to evade phagocyte uptake and/or recognition. This characteristic can be used to provide 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, AdsA can be overexpressed in an attenuated bacterium to further enhance or supplement an immune response or vaccine formulation.

[0078] Any embodiment discussed with respect to one aspect of the invention applies to other aspects of the invention as well. In particular, any embodiment discussed in the context of an AdsA peptide or nucleic acid may be implemented with respect to other secreted virulence factors, and/or cell surface proteins, such as Eap, Emp, EsaB, EsaC, Coa, Ebh, vWa, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, or SpA proteins or nucleic acids or antibodies that bind the same, and vice versa.

[0079] The term "providing" or "administering" 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 or administered by administering a nucleic acid that encodes the protein. In certain aspects the invention contemplates compositions comprising various combinations of antibodies, nucleic acid, antigens, peptides, epitopes, and/or polysaccharides and the like.

[0080] 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 (e.g., treating or preventing infection). 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.

[0081] 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.

[0082] The term "isolated" can refer to a nucleic acid or polypeptide or peptide that is substantially free of cellular material, bacterial material, viral material, or culture medium (when produced by recombinant DNA techniques or isolated from naturally occurring organism(s)) 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 does not naturally occur and/or function as a fragment and/or is not typically in the functional state.

[0083] Moieties of the invention, such as antibodies, 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. In still a further aspect the adjuvant is part of a recombinant protein and is comprised in a fusion protein comprising one or more antigens of interest.

[0084] The compositions may be formulated in a pharmaceutically acceptable composition. In certain aspects of the invention the staphylococcus bacterium is an *S. aureus* bacterium.

[0085] 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 nasal, pleural, oral, parenteral, subcutaneous, intramuscular, intravenous administration, or various combinations thereof, including inhalation or aspiration.

[0086] In still further embodiments, a composition comprises a recombinant nucleic acid molecule encoding an Emp, Eap and/or AdsA polypeptide or segments/fragments thereof. Typically a recombinant nucleic acid molecule encoding an Emp, Eap and/or AdsA polypeptide contains a heterologous promoter.

[0087] 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 additional 1, 2, 3, 4, 5, 6, 7, 8, or more polypeptides or peptides.

[0088] In certain aspects a composition includes a recombinant, non-staphylococcus bacterium containing or expressing one or more polypeptides described herein in, e.g., an Emp Eap and/or AdsA 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 capable of eliciting an immune response is contemplated. In further aspects the sta-

phylococcus bacterium containing or expressing the Emp, Eap and/or AdsA polypeptide is a *Staphylococcus aureus*. In further embodiments the immune response is a protective immune response.

[0089] 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 mice, dogs, cats, cattle, horses, goats, sheep and other domestic animals, i.e., mammals, including transgenic animals (e.g., animal manipulated to express human antibodies).

[0090] 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 prophylatically 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.

[0091] Any list provided herein may specifically exclude or include any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more members of the list.

[0092] The embodiments in the Example section are understood to be embodiments of the invention that are applicable to all aspects of the invention.

[0093] 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.

[0094] 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.

[0095] 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.

[0096] 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

[0097] 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.

[0098] FIGS. **1**A-**1**H Examination of abscess formation in staphylococcus aureus. (FIG. **1**A) Photograph of Newman infected kidneys. (FIG. **1**B) Photograph of srtA mutant infected kidneys. (FIG. **1**C) H&E histological section of Newman infected kidney. (FIG. **1**D) Histological section of ΔSrtA infected kidney. (FIG. **1**E) Closeup of Newman infected kidney. (FIG. **1**F) Closeup of ΔSrtA infected kidney. (FIG. **1**G) Scanning Electron Microscopy of Newman abscess. (FIG. **1**H) SEM of ΔSrtA infected kidney.

[0099] FIG. **2** Murine renal abscess screen. Recovered colony forming units (CFU) from kidneys infected with respective mutant strains.

[0100] FIGS. **3**A-**3**G Biofilm screen. (FIG. **3**A) 96 well plate assay for in vitro biofilm growth. (FIG. **3**B) SEM Newman in vitro biofilm (FIG. **3**C) ΔsrtA biofilm. (FIG. **3**D) ΔEmp biofilm. (FIG. **3**E) ΔIcaA biofilm. (FIG. **3**F) ΔIsdB biofilm. (FIG. **3**G) ΔSdrD biofilm.

[0101] FIGS. **4**A-**4**B Emp virulence. (FIG. **4**A) Recovered CFUs for Newman, ΔEap, ΔEmp, ΔSrtA, ΔEap/ΔSrtA, ΔEmp/ΔSrtA. (FIG. **4**B) Histopathology for respective strains.

[0102] FIGS. **5**A-**5**E Eap, Emp vaccination. (FIG. **5**A) SDS extraction of Newman, ΔSrtA, ΔIsdB, ΔIcaA, ΔEap, ΔEmp, ΔSaeR. (FIG. **5**B) Protein purification of Eap (70 kDa) and Emp (45 kDa). (FIG. **5**C) Recovered CFUs from mice vaccinated with PBS, Eap, or Emp and challenged with Newman. (FIG. **5**D) ELISA IgG titers from vaccinated mice. (FIG. **5**E) Histopathology from vaccinated mice.

[0103] FIGS. **6**A-**6**B Ica virulence. (FIG. **6**A) Recovered CFUs from mice infected with Newman, DIcaA, DIcaB, DIcaC, DIcaD, DIcaR, DIca:tet (entire operon deletion). (FIG. **6**B) Histopathology from infected mice.

[0104] FIGS. **7**A-**7**K Staphylococcal abscess formation following intravenous infection of mice. (A) BALB/c mice were infected with $1\times10_7$ colony forming units (CFU) of *S. aureus* Newman by retro-orbital injection. Cohorts of five mice were examined by cardiac puncture at timed intervals for bacterial load in blood; sample aliquots were plated on agar medium and CFU per ml of blood were enumerated. The means of these observations is indicated by a black bar. (B) Dissemination of *S. aureus* Newman into peripheral organ tissues and replication of the pathogen was measured at timed intervals in the kidneys of mice (cohorts of ten animals), which were homogenized and plated on agar medium for CFU. (C) Diameter of abscess lesions were measured in thin-sectioned hematoxylin-eosin stained tissues of infected kidneys at timed intervals. (D-K) Images of infected kidneys at timed intervals analyzed in thin-sectioned hematoxylin-eosin stained tissues. Arrowheads point to abscess lesions.

[0105] FIGS. **8**A-**8**F Histopathology of staphylococcal abscess communities. BALB/c mice were infected with *S. aureus* Newman via retro-orbital injection. Thin-sectioned, hematoxylineosin stained tissues of infected kidneys on day 2 (ABC) and day 5 following infection (DEF) were analyzed by light microscopy and images captured. On day 2, a massive infiltrate (blue arrow in A) of polymorphonuclear granulocytes (PMNs) with occasional intracellular staphylococci (yellow arrows in C) are characteristic of early infectious lesions. By day 5, staphylococcal abscess communities developed as a central nidus (D, black arrow). Staphylococci were enclosed by an amorphous, eosinophilic pseudocapsule (boxed in black) and surrounded by a zone of dead PMNs (boxed in white), a zone of apparently healthy PMNs (boxed in red) and a rim of necrotic PMNs (boxed in green), separated through an eosinophilic layer from healthy kidney tissue.

[0106] FIGS. **9**A-**9**P Sortase A is required for abscess formation and staphylococcal persistence in host tissues. Kidneys of BALB/c mice (cohorts of ten animals) infected with *S. aureus* Newman, its isogenic sortase A mutant (ΔsrtA) or methicillin-resistant *S. aureus* USA300 were removed during necropsy of animals 5 (d5) and 15 days (d15) following inoculation. Kidneys were inspected for surface abscesses (A, F, K) or fixed in formalin, embedded, thin sectioned and stained with hematoxylin-eosin. Histopathology images were acquired with light microscopy at 10×(B, G, L, D, I, N) and 100×fold magnification (C, H, M, E, J, O). (P) Staphylococcal replication and persistence in kidney tissue was measured 5 and 15 days following infection. Kidneys were removed from infected mice during necropsy, tissue was homogenized and plated on agar medium for colony formation and enumeration.

[0107] FIGS. **10**A-**10**C Staphylococcal communities at the center of abscess lesions. Kidney tissue from mice infected with *S. aureus* Newman (wild-type), its isogenic sortase A mutant (ΔsrtA), or MRSA strain USA300 was sectioned, fixed, dehydrated and sputter coated with 80% platinum/20% palladium for scanning electron microscopy. (A) The wild-type pathogen is organized as a tightly associated lawn, the *staphylococcal abscess* community (SAC), at the abscess center that is contained within an amorphous pseudocapsule (white arrow heads), separating SACs from the cuff of leukocytes. Red blood cells were located among staphylococci (R). (B) The sortase mutant (ΔsrtA, arrows) did not form SACs and isolated staphylococci were found in healthy kidney tissue. (C) Similar to *S. aureus* Newman, MRSA strain USA300 also formed SACs contained within a pseudocapsule (white arrow heads).

[0108] FIGS. **11**A-**11**B Formation of staphylococcal abscess communities requires specific surface proteins. (A) *S. aureus* Newman variants with *bursa aurealis* insertions in surface protein genes were examined five days following infection of BALB/c mice (cohorts of 20 animals) for bacterial load in homogenized kidney tissues. (B) Hematoxylin-eosin stained thin sections of infected kidneys were examined by light microscopy and 10× fold magnification for abscess lesions (white arrows).

[0109] FIGS. **12**A-**12**L Emp and Eap in staphylococcal abscess lesions. Kidneys of BALB/c mice infected with *S. aureus* Newman variants carrying *bursa aurealis* insertions in emp or eap were removed 5 (d5) and 15 days (d15) following inoculation. Kidneys were stained with hematoxylin-eosin and histopathology images acquired with light microscopy at 10×(A, C, E, H) and 100× fold magnification (B, D, F, I). Expression of Eap (J) and Emp (K) in abscess lesions of wild-type *S. aureus* Newman were detected with rabbit anti-Emp or anti-Eap and secondary Alexafluor-647 labeled antibodies (red) in renal tissue stained with Hoechst-dye (blue) to detect nuclei of polymorphonuclear leukocytes, and with BODIPY-vancomycin (green) to reveal staphylococcal abscess communities. (L) Staphylococcal replication and persistence in kidney tissue was measured 5, 15 and 30 days following intravenous inoculation. Kidneys were removed from infected mice (cohorts of 10 animals), tissue was homogenized and plated on agar medium for colony formation and enumeration.

[0110] FIGS. **13**A-**13**E Active and passive immunization with Eap generates protection from staphylococcal challenge. (A) BALB/c mice were immunized with purified Eap or Emp or mock treated with adjuvant alone and serum IgG titers analyzed by ELISA. (B) Three weeks following immunization, animals were challenged via intravenous inoculation of staphylococci. Five days following infection, kidneys were removed during necropsy and renal tissue analyzed for staphylococcal load or histopathology. (C) Rabbit antibodies directed against Eap or Emp were purified by affinity chromatography and passively transferred by intraperitoneal injection into mice. Twenty-four hours later, serum IgG titers of passively immunized animals were analyzed by ELISA. (D) Animals passively immunized with purified antibodies against Eap or Emp as well as mock immunized animals subsequently challenged with *S. aureus* Newman and bacterial load enumerated on day 4. (E) Abscess formation in kidneys was detected in thin-sectioned, hematoxylin-eosin stained tissues.

[0111] FIG. **14** A working model for staphylococcal abscess formation and persistence in host tissues. Stage I—following intravenous inoculation, *S. aureus* survives in the blood stream and disseminates via the vasculature to peripheral organ tissues. Stage II—in renal tissues, staphylococci attract a massive infiltrate of polymorphonuclear leukocytes and other immune cells. Stage III—abscesses mature with a central accumulation of the pathogen (staphylococcal abscess communities—SAC), enclosed by an eosinophilic pseudocapsule. The SAC is surrounded by a zone of dead PMNs, apparently healthy PMNs and finally an outer zone of dead PMNs with a rim of eosinophilic material. Stage 4—abscesses mature and rupture on the organ surface, thereby releasing staphylococci into circulation and initiating new rounds of abscess development. Genes for bacterial envelope components that are required for specific stages of staphylococcal abscess development are printed in red underneath the corresponding stage during which these genes function.

[0112] FIGS. **15**A-**15**H AdsA is a cell wall associated protein essential for survival in blood. Comparison of the survival of wild-type *S. aureus* Newman (WT) and isogenic srtA variants in blood from BALB/c mice (FIG. **15**A) or Sprague-Dawley rats (FIG. **15**D). Data are the means and standard error of the means from three independent analyses (±SEM). To assess the relative contribution of sortase A-anchored cell wall surface proteins for staphylococci survival in blood, isogenic mutants with transposon insertions in the indicated genes were incubated in blood from mice (FIG. **15**B) or rats (FIG. **15**E) for 60 minutes. Expression of padsA rescues staphylococcal survival of an adsA mutant in blood from mice (FIG. **15**C), rats (FIG. **15**F), or human volunteers (FIG. **15**G). Visualization of WT, adsA, and adsA (padsA) staphylococci with phagocytic cells in Giemsa-stained human blood samples (FIG. **15**H). Arrows indicate both extracellular and neutrophil associated *S. aureus*. Data are representative of two independent analyses with two different donors.

[0113] FIGS. **16**A-**16**E AdsA is a virulence factor that enables staphylococcal replication and abscess formation in vivo. Staphylococcal burden in kidneys after infection of cohorts of 10 BALB/c mice with *S. aureus* Newman wild-type and adsA mutant (FIG. **16**A) or USA300 wild-type and adsA mutant (FIG. **16**C) ($P<0.03$ for infections for both Newman and USA300, unpaired t-test). Microscopic images of hematoxylin-eosin stained kidney tissue at ×10 (top panels) and ×100 magnification (lower panels) obtained following necropsy of mice infected with *S. aureus* Newman wild-type and adsA mutant (FIG. **16**B) or *S. aureus* USA300 wild-type and adsA mutant (FIG. **16**D). Black arrows denote a central concentration of staphylococci and PMN infiltrates. Data are

representative samples of cohorts of 5 animals per bacterial strain and 2 independent analyses. (FIG. **16**E) Bacterial load was measured as CFUs per 500 μl blood obtained from BALB/c mice infected by retroorbital injection with either wild-type (WT), adsA or adsA:padsA *S. aureus* Newman for 30 or 90 minutes. Data are representative of two independent analyses using cohorts of 10 animals for each time point. Unpaired t-test was used for statistical analysis.

[0114] FIGS. **17**A-**17**F AdsA exhibits 5'-nucleotidase activity and hydrolyzes AMP. Lysostaphin cell wall extracts from the indicated bacterial strains were incubated with radiolabeled [^{14}C]AMP and generation of [^{14}C]Ado (adenosine) was measured by thin layer chromatography (TLC). (FIG. **17**A) Radioactive signals for [^{14}C]AMP and [^{14}C]Ado following TLC were captured by PhosphorImager. (FIG. **17**B) Radioactive [^{14}C]Ado signals from (a) were quantified, calibrated for adenosine synthase activity in *S. aureus* Newman (100%) and displayed as percent amount. Data are the means of three independent analyses, error bars represent SEM. ($P<0.05$ for WT vs. adsA). (FIG. **17**C) Radiolabeled [^{14}C]AMP was incubated in the presence or absence of purified $AdsA_{1-400}$ (2 μM) in the presence or absence of 5 mM of various metal ions. Radioactive signals for [^{14}C]AMP and [^{14}C]Ado following TLC were captured by PhosphorImager. (FIG. **17**D) Radioactive [^{14}C]Ado signals from (c) were quantified, calibrated for adenosine synthase activity in the presence of manganese chloride (Mn^{2+})(100%) and displayed as percent amount. Displayed data are the mean of 2 independent analyses and error bars represent SEM. ($P<0.05$ for Zn^{+2} vs Mn^{+2} and Cu^{+2} vs Mn^{+2}). (FIG. **17**E) GST-AdsA was purified from recombinant *Escherichia coli*, cleaved with thrombin to generate $AdsA_{1-400}$ and purified proteins were analyzed by Coomassie-stained SDS-PAGE. (FIG. **17**F) Survival of adsA staphylococci in rat blood in the presence or absence of variable concentrations of adenosine.

[0115] FIGS. **18**A-**18**D Staphylococcal AdsA synthesizes adenosine in blood. (FIG. **18**A) Reversed-phase high performance liquid chromatography (RP-HPLC) to quantify adenosine (left panel, 100 μM adenosine) and identify its monoisotopic ions by matrix assisted laser desorption ionization mass spectrometry (MALDI-MS, right panel). Mouse blood was incubated without (FIG. **18**B) or with *S. aureus* Newman wild-type (WT) (FIG. **18**C) or its isogenic adsA variants (FIG. **18**D) for one hour. Plasma was deproteinized, filtered and subjected to RP-HPLC to quantify adenosine (left panels) and identify its monoisotopic ions by MALDI-MS (right panels). Calculated abundance of adenosine in blood extrapolated from the purified adenosine control was 1.1 μM (18B, no staphylococci), 13.2 μM (18C, WT *S. aureus* Newman) and 2.1 μM (18D, adsA mutant staphylococci).

[0116] FIGS. **19**A-**19**E 5'-Nucleotidase activity enhances *B. anthracis* survival. (FIG. **19**A) Mutanolysin extracts from *B. anthracis* strain Sterne (WT, wild-type) or adsA (basA) mutant bacilli were incubated with radiolabed [^{14}C]AMP and generation of adenosine was measured by TLC. (FIG. **19**B) Proteins from mutanolysin extracts were analyzed with antisera raised against BasA (aBasA) or BasC (aBasC), a control protein not involved in adenosine production. (FIG. **19**C) Fluorescence microsocopy images of wild-type (WT) *B. anthracis* Sterne and its isogenic adsA mutant stained with antiserum against BasA (top panel) or non-reactive serum (NRS) and Cy3-labeled secondary antibodies (red) as well as Hoechst staining of nucleic acids (blue). (FIG. **19**D) Radiolabeled [^{14}C]AMP was incubated with purified BasA (2 μM) in the presence of 5 mM of variable metal cations and generation of [^{14}C]Ado (adenosine) was measured by thin layer chromatography (TLC) and PhosphorImager. Data are representative of 3 independent analyses. (FIG. **19**E) Survival of wild-type and adsA/basA mutant *B. anthracis* strain Sterne in rat blood over time (minutes) measured as colony forming units on agar plates. Data are the average of two independent analyses and error bars represent the SEM.

[0117] FIG. **20** Visualization of adsA disruption and padsA complementation. To allow visualization of AdsA, we used a Protein A deficient (Aspa) *S. aureus* strain SEJ2, as Protein A specifically binds to Fc domains of antibodies and interferes with immunoblotting analyses. Cell wall extracts from wild type Aspa SEJ2 (lane 1), Δspa, adsA:ermB (lane 2) or Δspa, adsA:ermB cells transformed with padsA were separated by SDS-PAGE and immunoblotting analyses conducted with anti-sera raised against GST-$AdsA_{1-400}$. * denotes non-specific reactive species

[0118] FIG. **21** Histological examination of kidneys isolated from mice infected with USA300. Microscopic images of hematoxylin-eosin stained kidney tissue at x10 obtained following necropsy of mice infected for 4 days with *S. aureus* USA300 wild-type (bottom panels) and adsA mutants (top panels). Black arrows denote a central concentration of staphylococci and PMN infiltrates. Data are representative samples of cohorts of 5 animals per bacterial strain and 2 independent analyses.

DETAILED DESCRIPTION OF THE INVENTION

[0119] Biofilms are microbial communities embedded in a secreted extracellular matrix (Hall-Stoodley et al., 2004; Kolter and Greenberg, 2006). Many bacterial species are capable of switching from planktonic growth to the formation of biofilms and thereby display increased antibiotic resistance (Drenkard and Ausubel, 2002), evasion from host immune defenses (Singh et al., 2002), and are more adept at establishing chronic infections in humans (Brady et al., 2008). Biofilms of staphylococcal species have been associated with a number of diseases including endocarditis (Xiong et al., 2005), osteomyelitis (Brady et al., 2006), and various implant-mediated infections including urinary catheters, prosthetic heart valves, and artificial joints (Cassat et al., 2007). This applies in particular to *Staphylococcus epidermidis*, an opportunistic pathogen that avidly forms biofilms in vitro and in vivo (Mack et al., 1996). While there is clear association between the ability to form biofilms and virulence in *S. epidermidis*, such correlation has not yet been demonstrated for *S. aureus* (Cassat et al., 2007).

[0120] *S. aureus* is a commensal of human skin and nares and the leading cause of bloodstream and skin/soft tissue infections (Klevens et al., 2007). The pathogenesis of staphylococcal infections is initiated as bacteria invade skin or blood stream via trauma, surgical wounds, or medical devices (Lowy, 1998). Some staphylococci are cleared from the blood stream by phagocytic killing, however staphylococci that escape immune defenses seed infections in organ tissues and induce a proinflammatory response mediated by the release of cytokines and chemokines from macrophages, neutrophils, and other phagocytes (Lowy, 1998). The resulting invasion of immune cells to the site of infection is accompanied by central liquefaction necrosis and formation of peripheral fibrin walls in an effort to prevent microbial spread and allow for removal of necrotic tissue debris (Lowy, 1998). Such lesions can be observed by microscopy as hypercellular areas con-

taining necrotic tissue, leukocytes, and a central nidus of bacteria. Organ abscesses occur within two days of infection (unpublished data) and represent a hallmark of staphylococcal disease.

I. Staphylococcal Antigens

[0121] 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.

[0122] 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.

[0123] Embodiments of the invention include, but are not limited to compositions and methods related to Emp and/or Eap. In certain embodiment Emp and/or Eap can be used in combination with other staphylococcal proteins such as EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SasH (AdsA), Ebh, Coa, vWa, and/or SpA proteins. Emp (SEQ ID NO:2) or Eap (SEQ ID NO:4) are staphylococcal polypeptides. Sequence of other Emp and/or Eap polypeptides can be found in the protein databases and include, but are not limited to accession numbers YP_185731, NP_371337, NP_645584, CAB75985, YP_416239, YP_040269, and NM0758 for Emp and YP_500650, CAB94853, YP_186825, CAB51807, NP_646697, YP_041404, NM1872 for Eap, each of which is incorporated herein by reference as of the priority date of this application. Additional Staphyloccal antigens include 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.

[0124] In mammals, adenosine assumes an essential role in regulating innate and acquired immune responses (Thiel et al., 2003). Strong or excessive host inflammatory responses, for example in response to bacterial infection, exacerbate the tissue damage inflicted by invading pathogens (Thiel et al., 2003). Successful immune clearance of microbes therefore involves the balancing of pro- and anti-inflammatory mediators. Cytokines IL-4, IL-10, IL-13 and TGF-β restrict excessive inflammation, however only adenosine is able to completely suppress immune responses (Nemeth et al., 2006). The immunoregulatory attributes of adenosine are mediated via four transmembrane adenosine receptors: A_1, A_{2A}, A_{2B}, and A_3 (Hasko and Pacher, 2008). T lymphocytes express the high affinity A_{2A} receptor as well as the low affinity A_{2B} receptor (Thiel et al., 2003). Depending on their activation state, macrophages and neutrophils express all four adenosine receptors, whereas B cells harbor only A_{2A} (Thiel et al., 2003). Engagement of A_{2A} inhibits IL-12 production, increases IL-10 in monocytes (Khoa et al., 2001) and dendritic cells (Panther et al., 2001), and decreases cytotoxic attributes and chemokine production in neutrophils (McColl et al., 2006; Cronstein et al., 1986). Generation of adenosine at sites of inflammation, hypoxia, organ injury, and traumatic shock is mediated by two sequential enzymes. Ecto-ATP diphosphohydrolase (CD39) converts circulating adenosine triphosphate (ATP) and adenosine diphosphate (ADP) to 5'-adenosine monophosphate (AMP) (Eltzshig et al., 2003). CD73, expressed on the surface of endothelial cells (Deussen et al., 1993) and subsets of T cells (Thompson et al., 1989; Thompson et al., 1987; Yang et al., 2005), then converts 5'-AMP to adenosine (Zimmermann, 1992).

[0125] Although extracellular adenosine is essential for the suppression of inflammation, build-up of excess adenosine is also detrimental. This is exemplified in patients with a deficiency in adenosine deaminase (ADA), an enzyme that converts adenosine into inosine (Giblett, et al., 1972). ADA deficiency causes the severe compromised immunodeficiency syndrome (SCID) with impaired cellular immunity and severely decreased production of immunoglobulins (Buckley et al., 1997). As the regulation of extracellular adenosine is critical in maintaining immune homeostasis, perturbation of adenosine levels is likely to impact host immune responses during infection. The inventors describe herein that bacteria, e.g., *S. aureus* and *Bacillus anthracis*, use adenosine synthesis to escape host immune responses and provide methods and composition for utilizing this information for the treatment and/or prevention of bacterial infection, e.g., bacteremia.

[0126] Certain embodiments of the invention are directed to inducing an immune response, providing an antibody to, or inhibiting AdsA. AdsA (SEQ ID NO:55) is a staphylococcal polypeptide. Sequence of other AdsA polypeptides can be found in the protein databases and include, but are not limited: *Staphlyococcus aureus* (ref|YP_001573948, ref|YP_184935, ref|YP_039500, ref|NP_373261, ref|NP_370547, ref|YP_042156, ref|NP_644838, ref|YP_415541, dbj|BAA82250); *Staphlyococcus hemolyticus* (ref|YP_254367); *Streptococcus sanguinis* (ref|YP_001035187); *Streptococcus gordonii* (ref|YP_001450531); *Enterococcus faecalis* (ref|NP_813870); *Streptococcus suis* (dbj|BAB83980, ref|YP_001200571, ref|YP_001198366); *Streptococcus mutans* (ref|NP_721592); *Streptococcus thermophilus* (ref|YP_141373, ref|YP_139455); *Alkaliphilus metalliredigens* (ref|YP_001321391); *Clostridium botulinum* (ref|YP_001887045, ref|YP_001921966); *Paenibacillus* (ref|ZP_02846642); Alkaliphilus oremlandii (ref|YP_001512463); *Bacillus clausii* (ref|YP_174466); *Bacillus halodurans* (ref|NP_240892); *Clostridium difficile* (ref|ZP_03126518, ref|ZP_02748384, ref|YP_001089051, ref|ZP 02726436, ref|ZP_01801990); *Clostridium cellulolyticum* (ref|ZP_01574143); *Anaerotruncus colihominis* (ref|ZP_02441436), each of which is incorporated herein by reference as of the priority date of this application. In certain aspects, AdsA polypeptide can have at least or more than 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, identity, including all values and ranges there between, to SEQ ID NO:36 or SEQ ID NO:41.

[0127] Certain aspects of the invention include methods and compositions concerning proteinaceous compositions including polypeptides, peptides, antibodies that bind such polypeptides and peptides, or nucleic acids encoding Emp and/or Eap and other staphylococcal antigens such as EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SasH (AdsA), Ebh, Coa, vWa, SpA, 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 combinations thereof. These proteins may be modified by deletion, insertion, and/or substitution.

[0128] Certain aspects of the invention include methods and compositions concerning proteinaceous compositions including polypeptides, peptides, and/or antibodies that bind such polypeptides and peptides, or nucleic acids encoding AdsA and other staphylococcal antigens such as Eap, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SasH (AdsA), Ebh, Coa, vWa, SpA, 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 combinations thereof. These proteins may be modified by deletion, insertion, and/or substitution.

[0129] These polypeptides include the amino acid sequence of proteins from bacteria in the Staphylococcus genus. The sequence may be from a particular *staphylococcus* species, such as *Staphylococcus aureus*, and may be from a particular strain, such as Newman.

[0130] 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 (gi|15926240), 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 (gi|15926241), 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 (gi|15924120), 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 (gi|15924119), 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.

[0131] 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.

[0132] 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.

[0133] 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.).

[0134] 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.

[0135] 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.

[0136] 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.

[0137] Amino acid sequence variants of Emp or Eap or AdsA and other polypeptides of the invention, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, Ebh, Coa, vWa, SpA, 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 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, 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, 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.

[0138] An antigen of the invention can comprise a segment or fragment of an antigen (AdsA, Emp, Eap, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, Ebh, Coa, vWa,

SpA, 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) described herein comprising amino acid 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, 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, 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and ranges there between) to amino acid 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, 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, 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between. Certain aspects of the invention are directed to an antibody that binds one or more of the above described fragments or segments.

[0139] 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.

[0140] 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 dissimilar, such as a polar or charged amino acid for a nonpolar or uncharged amino acid, and vice versa.

TABLE 1

Exemplary surface proteins of *S. aureus* strains.

SAV #	SA#	Surface	MW2	Mu50	N315	Newman	MRSA252*	MSSA476*
SAV0111	SA0107	SpA	492	450	450		516	492
SAV2503	SA2291	FnBPA	1015	1038	1038		—	1015
SAV2502	SA2290	FnBPB	943	961	961		965	957
SAV0811	SA0742	ClfA	946	935	989	933	1029	928
SAV2630	SA2423	ClfB	907	877	877	913	873	905
Np	np	Can	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		1351	2275
SAV2160	SA1964	SasB	686	2481	2481		2222	685
	SA1577	SasC	2186	213	2186		2189	2186
SAV0134	SA0129	SasD	241	241	241		221	241
SAV1130	SA0977	SasE/IsdA	350	350	350		354	350
SAV2646	SA2439	SasF	635	635	635		627	635
SAV2496		SasG	1371	525	927		—	1371
SAV0023	SA0022	SasH	772	—	772		786	786
SAV1731	SA1552	SasI	895	891	891		534	895
SAV1129	SA0976	SasJ/IsdB	645	645	645		652	645
	SA2381	SasK	198	211	211		—	197
	Np	SasL	—	232	—		—	—
SAV1131	SA0978	IsdC	227	227	227		227	227

[0141] 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.

[0142] 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

Codon Table

Amino Acids		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

TABLE 2-continued

Codon Table

Amino Acids		Codons
Lysine	Lys K	AAA AAG
Leucine	Leu L	UUA UUG CUA CUC CUG CUU
Methionine	Met M	AUG
Asparagine	Asn N	AAC AAU
Proline	Pro P	CCA CCC CCG CCU
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

TABLE 2-continued

Codon Table

Amino Acids		Codons
Valine	Val V	GUA GUC GUG GUU
Tryptophan	Trp W	UGG
Tyrosine	Tyr Y	UAC UAU

[0143] 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.

[0144] 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, e.g., immunogenicity.

[0145] 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.

[0146] 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.

[0147] 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.

[0148] 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 ng or 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 Emp, Eap, and/or AdsA and may be used in combination with other polypeptide sequences described herein.

[0149] 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.

[0150] A. Polypeptides and Polypeptide Production

[0151] 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.

[0152] 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.

[0153] 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.

[0154] 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-, hgprt- or aprt-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 hygro, which confers resistance to hygromycin.

[0155] 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).

[0156] 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.

[0157] 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.

[0158] 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.

[0159] 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: (3-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, and CRM197.

II. Therapeutic Methods

[0160] Active immunization with vaccines and passive immunization with immunoglobulins are promising alternatives to classical small molecule (e.g., antibiotic) therapy. A few bacterial diseases that once caused widespread illness, disability and death can now be prevented through the use of vaccines. The vaccines are based on weakened (attenuated) or dead bacteria, components of the bacterial surface or inactivated toxins. The immune response raised by a vaccine is mainly directed to immunogenic structures; a limited number of proteins or sugar structures on the bacteria that are actively processed by the immune system.

[0161] A method of the present invention includes treatment for a disease or condition caused by or related to a bacterial pathogen, e.g., staphylococcus or bacillus. An immunogenic polypeptide, and/or antibody that binds the same, can be given to induce or provide a therapeutic response in a person infected with a bacteria or suspected of having been exposed to a bacteria. Methods may be employed with respect to individuals who have tested positive for exposure to staphylococcus or *bacillus* or who are deemed to be at risk for infection based on possible exposure.

[0162] The invention encompasses methods of treatment of staphylococcal infection, particularly hospital acquired nosocomial infections. In particular, the invention encompasses methods of treatment for bacterial infection, particularly bacteremia. The therapeutic compositions and vaccines of the invention are particularly advantageous in cases of elective surgery. Such patients will know the date of surgery in advance and could be inoculated or treated in advance. The immunogenic compositions and vaccines of the invention are also advantageous in inoculating health care workers, first responders, and the like.

[0163] In some embodiments, the treatment is administered in the presence of adjuvants or carriers or other staphylococ-

cal antigens. Furthermore, in some examples, treatment comprises administration of other agents commonly used against bacterial infection, such as one or more antibiotics.

[0164] A. Vaccines

[0165] The present invention includes methods for preventing or ameliorating staphylococcal 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 from immunogenic Emp, Eap and/or AdsA polypeptide(s), such as the full-length Emp, Eap and/or AdsA antigen or immunogenic fragments thereof. In other embodiments Emp, Eap and/or AdsA can be used in combination with other secreted virulence proteins, surface proteins or immunogenic fragments thereof, including EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, Ebh, Coa, vWa, SpA, 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 other staphylococcal antigen, peptide, or protein known to one of skill in the art. 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.

[0166] 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 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, each of which is incorporated herein by reference in its entirety.

[0167] 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.

[0168] Vaccines may be conventionally administered by inhalation or parenterally by injection, e.g., 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, polyalkalene 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%.

[0169] The polypeptide, peptides and peptide-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.

[0170] 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.

[0171] The manner of application may vary 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.

[0172] In many instances, it will be desirable to have multiple administrations of the vaccine, usually at most, at least, or not exceeding six vaccinations, more usually four vacci-

nations, and typically one or more, usually at least about three vaccinations. The vaccinations will normally be at 1, 2, 3, 4, 5, 6, to 5, 6, 7, 8, 9, 10, 11, to 12 week intervals, including all values and ranges there between, more usually from three to five week intervals. Typically, periodic boosters at intervals of 1-5 years, usually three 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 supra, U.S. Pat. Nos. 3,791,932; 4,174, 384 and 3,949,064, are illustrative of these types of assays.

[0173] 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, or an adjuvant. Methods for performing this conjugation are well known in the art.

[0174] 1. Carriers

[0175] 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. Carriers include, but are not limited to 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, carbodiimyde, and bis-biazotized benzidine.

[0176] 2. Adjuvants

[0177] 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.

[0178] A number of adjuvants can be used to enhance an antibody response against an Emp, Eap and/or AdsA peptide or any other antigen described herein. In other embodiments Emp, Eap and/or AdsA can be used in combination with EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, Ebh, Coa, vWa, and/or SpA 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.

[0179] 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, GMCSP, 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 may also be used. 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.

[0180] 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.

[0181] A typical adjuvant is complete Freund's adjuvant (a non-specific stimulator of the immune response containing killed *Mycobacterium tuberculosis*), incomplete Freund's adjuvants, and aluminum hydroxide.

[0182] 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.

[0183] The distinction between 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+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.

[0184] In contrast, Th2-type responses are associated with the secretion of IL-4, IL-5, IL-6, IL-10.

[0185] 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 suppresser 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/m^2) (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.

[0186] B. Antibodies And Passive Immunization

[0187] Direct administration of therapeutic immunoglobulins, also referred to as passive immunization, does not require an immune response from the patient and, therefore, gives immediate protection. In addition, passive immunization can be directed to bacterial structures that are not immunogenic and that are less specific to the organism. Passive immunization against pathogenic organisms has been based on immunoglobulins derived from sera of human or non-human donors.

[0188] One aspect of the invention is a method of preparing an immunoglobulin for use in prevention or treatment of staphylococcal infection comprising the steps of immunizing a recipient with the vaccine of the invention and isolating immunoglobulin or antibodies from the recipient. An immunoglobulin prepared by this method is a further aspect of the invention. A pharmaceutical composition comprising the immunoglobulin 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.

[0189] 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, 1988).

[0190] 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.

[0191] An immunoglobulin produced in accordance with the present invention can include whole antibodies, antibody fragments or subfragments. Antibodies can be whole immunoglobulins, 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 immunoglobulin also includes natural, synthetic or genetically engineered proteins that act like an antibody by binding to specific antigens to form a complex. The term "immunoglobulin," as used herein, includes all immunoglobulin classes and subclasses known in the art including IgA, IgD, IgE, IgG, and IgM, and their subclasses (isotypes), e.g., IgA1, IgA2, IgG1, IgG2, IgG3 and IgG4. Preferably, the immunoglobulins of the invention are human immunoglobulins. Also, an antigen-binding and/or variable domain comprising fragment of an immunoglobulin is meant. Antigen-binding fragments include, inter alia, Fab, F(ab'), F(ab')2, Fv, dAb, Fd, complementarity-determining region (CDR) fragments, single-chain antibodies (scFv), bivalent single-chain antibodies, single-chain phage antibodies, diabodies, triabodies, tetrabodies, (poly)peptides that contain at least a fragment of an immunoglobulin that is sufficient to confer specific antigen binding to the (poly) peptide, etc.

[0192] An antigen composition or vaccine of the present invention can be administered to a recipient who then acts as a source of immunoglobulin, 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.

[0193] An additional aspect of the invention is a pharmaceutical composition comprising one or more monoclonal antibodies (or fragments thereof; preferably human or humanized) reactive against 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 antigens of the invention. They may also be fragments, e.g., F(ab')2, Fab', Fab, Fv and the like including hybrid fragments.

[0194] 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 human, humanized, or partly humanized by known methods.

[0195] C. Combination Therapy

[0196] The compositions and related methods of the present invention, particularly administration of a staphylococcal antigen, including a polypeptide or peptide of Emp, AdsA and/or Eap in combination with one or more of EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, Ebh, Coa, vWa, SpA, 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 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 a small molecule or non-peptide inhibitor of AdsA activity.

[0197] 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 treatment with the other agent 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.

[0198] Various combinations may be employed, for example antibiotic therapy is "A" and an immunogenic mol-

ecule or antibody given as part of an immune therapy regime, such as an antigen or an AdsA modulator, is "B":

[0199] 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

[0200] B/B/B/A B/B/A/B A/A/B/B A/B/A/B A/B/B/A B/B/A/A

[0201] B/A/B/A B/A/A/B A/A/A/B B/A/A/A A/B/A/A A/A/B/A

[0202] 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 Emp, Eap, and/or AdsA composition, or composition of any other antigen or antigen combination described herein. 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.

III. Pharmaceutical Compositions

[0203] 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, Emp, \ Eap and/or AdsA antigens in combination with members of the Ess pathway and including polypeptides or peptides of the Esa or Esx class, and/or members of sortase substrates, and/or secreted virulence factor and or polysaccharides may be administered to the patient to protect against or treat 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.

[0204] As used herein, the term "pharmaceutically acceptable" or "pharmacologically acceptable" refer 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. 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-bacterial agents, can also be incorporated into the compositions.

[0205] 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.

[0206] 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.

[0207] 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.

[0208] 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.

[0209] 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.

[0210] 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.

[0211] Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various 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.

[0212] 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 administration. 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.

[0213] 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 dosage 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.

[0214] 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.

[0215] 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.

[0216] 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.

[0217] A. In Vitro, Ex Vivo, or in Vivo Administration

[0218] 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.

[0219] 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 Emp, Eap and/or AdsA, and/or EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SpA, vWa, Coa, Ebh, 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 (U55,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein (or any combination thereof). The transduced cells can then be used for in vitro analysis, or alternatively for ex vivo administration.

[0220] 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.

[0221] B. Lipid Components and Moieties

[0222] 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.

[0223] 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.

[0224] 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-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) or Superfect (Qiagen) complex is also contemplated.

[0225] 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.

IV. Polysaccharides

[0226] 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.

[0227] A. PIA (PNAG)

[0228] 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.

[0229] PIA is a polysaccharide intercellular adhesin and is composed of a polymer of β-(1→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 a 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.

[0230] The polysaccharide previously known as poly-N-succinyl-β-(1→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→6)-linked glucosamine substituted with N-acetyl and O-succinyl constituents). Any size of PIA polysaccharide or oligosaccharide may be use in an immunogenic composition of the invention, however a size of over 40 kDa is preferred. 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). Preferred size ranges of PIA (PNAG) are 40-400 kDa, 40-300 kDa, 50-350 kDa, 60-300 kDa, 50-250 kDa and 60-200 kDa. PIA (PNAG) can have different degrees 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%, preferably less than 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*. Most preferably, 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.

[0231] In an embodiment, PNAG is a deaceylated 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.

[0232] The polysaccharide(s) included in the immunogenic composition of the invention are preferably conjugated to a carrier protein as described below or alternatively unconjugated.

[0233] B. Type 5 and Type 8 Polysaccharides from *Staphylococcus*

[0234] Most strains of *S. aureus* that cause infection in man 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 were reported as:

[0235] Type 5→4)-β-D-ManNAcA(3OAc)-(1→4)-α-L-FucNAc(1→3)-β-D-FucNAc-(1→

[0236] Type 8→3)-β-D-ManNAcA(4OAc)-(1→3)-α-L-FucNAc(1→3)-β-D-FucNAc-(1→

[0237] Recently (Jones, 2005) NMR spectroscopy revised the structures to:

[0238] Type 5→4)-β-D-ManNAcA-(1→4)-α-L-FucNAc(3OAc)-(1→3)-β-D-FucNAc-(1→

[0239] Type 8→3)-β-D-ManNAcA(4OAc)-(1→3)-α-L-FucNAc(1→3)-α-D-FucNAc(1→

[0240] Polysaccharides may be extracted from the appropriate strain of *S. aureus* using known methods, U.S. Pat. No. 6,294,177. ATCC 12902 is a Type 5 *S. aureus* strain and ATCC 12605 is a Type 8 *S. aureus* strain.

[0241] Polysaccharides are of native size or alternatively may be sized, for instance by microfluidisation, ultrasonic irradiation or by chemical treatment. 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 contains either type 5 or type 8 polysaccharide.

[0242] C. *S. Aureus* 336 Antigen

[0243] 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, where included in the immunogenic composition of the invention is preferably conjugated to a carrier protein as described below or are alternatively unconjugated.

[0244] D. Type I, II and III Polysaccharides from *S. Epidermidis*

[0245] Strains ATCC-31432, SE-360 and SE-10 of *S. epidermidis* are characteristic of three different capsular types, I, II and III respectively (Ichiman and Yoshida, 1981). Capsular polysaccharides extracted from each serotype of *S. epidermidis* constitute Type I, II, and III polysaccharides. Polysaccharides may be extracted by several methods including the method described in U.S. Pat. No. 4,197,290 or as described in Ichiman et al., 1991.

[0246] In one embodiment of the invention, the immunogenic composition comprises type I and/or II and/or III polysaccharides or oligosaccharides from *S. epidermidis*.

[0247] Polysaccharides are of native size or alternatively may be sized, for instance by microfluidisation, ultrasonic irradiation or chemical cleavage. The invention also covers oligosaccharides extracted from *S. epidermidis* strains. These polysaccharides are unconjugated or are preferably conjugated as described below.

[0248] E. Conjugation of Polysaccharides

[0249] 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 such a protein carrier 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. influenza* will preferably contain the N-terminal ⅓ 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/antigens may be used as carrier protein in the polysaccharide conjugates of the invention.

[0250] 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 a 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.

[0251] The polysaccharides may be linked to the carrier protein(s) by any known method (for example, U.S. Pat. Nos. 4,372,945, 4,474,757, and 4,356,170).

[0252] Preferably, CDAP conjugation chemistry is carried out (see WO95/08348). In CDAP, the cyanylating 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.

[0253] The polysaccharide is solubilized in water or a saline solution. CDAP is dissolved in acetonitrile and added immediately to the polysaccharide solution. The CDAP reacts with the hydroxyl groups of the polysaccharide to form a cyanate ester. After the activation step, the carrier protein is added. Amino groups of lysine react with the activated polysaccharide to form an isourea covalent link. After the coupling reaction, a large excess of glycine is then added to quench residual activated functional groups. The product is then passed through a gel permeation column to remove unreacted carrier protein and residual reagents.

[0254] 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.

V. Immune Response and Assays

[0255] As discussed above, the invention concerns evoking or inducing an immune response in a subject against an Emp, Eap and/or AdsA polypeptide. In other embodiments an immune response to other peptides or antigens can be evoked or induced, including EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SpA, Ebh, Coa, vWa, 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 any other Staphylococcal peptide or protein. 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 or treating a subject prior to hospital treatment.

[0256] A. Immunoassays

[0257] The present invention includes the implementation of serological assays to evaluate if an immune response is

induced or evoked by Emp, Eap and/or AdsA and any other polypeptide or peptide agent described herein. 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.

[0258] 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 example, 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 nonspecifically 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.

[0259] 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.

[0260] 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.

[0261] 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.

[0262] 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.

[0263] 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.

[0264] To provide a detecting means, the second or third antibody can have an associated label to allow detection. In certain aspects, this label 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.

[0265] 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 H_2O_2, 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).

[0266] B. Diagnosis of Bacterial Infection

[0267] 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 and diagnosing 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 binding to the polypeptides, proteins, and/or peptides, or polypeptides, proteins, and/or peptides binding to the antibodies in the sample.

[0268] 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, human, 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 Publication 20030153022, which is incorporated herein by reference in its entirety.

[0269] 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 ELISAs.

[0270] C. Protective Immunity

[0271] 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.

[0272] As used herein in the specification and in the claims section that follows, the term polypeptide and peptide 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 can be encoded by a polynucleotide according to any possible codon usage.

[0273] 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, carbohydrate 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.

[0274] A cellular immune response is elicited by the presentation of polypeptide antigens or 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, macrophages, NK cells, basophils, dendritic cells, astrocytes, microglia cells, eosinophils or other components of innate immunity.

[0275] As used herein "active immunity" refers to any immunity conferred upon a subject by administration of an antigen.

[0276] 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.

[0277] A monoclonal or polyclonal antibody composition may be used in passive immunization for the prevention or treatment of infection by organisms that carry or may be exposed to 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.

[0278] 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 with the antigenic 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 immune-compromised 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.

[0279] In certain aspects, methods include treating or preventing infection by administering the antibody compositions, such as antibodies that bind the above-described antigens, to a subject in need thereof. A target patient population for the treatment and prevention of infection includes mammals, such as humans, who are infected with or at risk of being infected by bacterial pathogens. In one embodiment, the infection to be treated or prevented is an *S. aureus* infection, including an infection of methicillin-resistant *S. aureus* or *S. aureus* producing alpha-toxin, or an *S. epidermidis* infection.

[0280] In accordance with one embodiment, the invention provides a method for treating or preventing an *S. aureus* infection using compositions comprising one or more *S.*

aureus AdsA, Emp, Eap, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SpA, Ebh, vWa, Coa, 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 antibodies and a pharmaceutically acceptable carrier. The *S. aureus* antibody can bind to any of those antigens described above. In one embodiment, the antibody composition is a antibody composition or a hyperimmune composition. In another embodiment, the antibodies are recombinant, human, or humanized antibodies. In yet another embodiment, the antibodies are monoclonal antibodies, or fragments thereof.

[0281] A therapeutically or prophylactically effective amount of the antibody compositions can be determined by methods that are routine in the art. Skilled artisans will recognize that the amount may vary according to the particular antibodies within the composition, the concentration of antibodies in the composition, the frequency of administration, the severity of infection to be treated or prevented, and subject details, such as age, weight and immune condition. In some embodiments, the dosage will be at least 1, 5, 10, 25, 50, or 100 μg or mg of antibody composition per kilogram of body weight (mg/kg), including at least 100 mg/kg, at least 150 mg/kg, at least 200 mg/kg, at least 250 mg/kg, at least 500 mg/kg, at least 750 mg/kg and at least 1000 mg/kg. Dosages for monoclonal antibody compositions typically may be lower, such as 1/10 of the dosage of an antibody composition, such as at least about 1, 5, 10, 25, or 50 μg or mg/kg, at least about 10 mg/kg, at least about 15 mg/kg, at least about 20 mg/kg, or at least about 25 mg/kg. The route of administration may be any of those appropriate for a passive vaccine. Thus, intravenous, subcutaneous, intramuscular, intraperitoneal, inhalation, and other routes of administration are envisioned. As noted above, a therapeutically or prophylactically effective amount of antibody is an amount sufficient to achieve a therapeutically or prophylactically beneficial effect.

[0282] A protective antibody composition may neutralize and/or prevent infection. A protective antibody composition may comprise amounts of AdsA, Emp, Eap, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, SpA, Ebh, Coa, vWa, 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 antibodies that are not protective on their own, but which, in combination, yield a protective antibody composition.

[0283] The antibody composition may be administered in conjunction with an anti-infective agent, an antibiotic agent, and/or an antimicrobial agent, in a combination therapy. Anti-infective agents include, but are not limited to vancomycin and lysostaphin. Antibiotic agents and antimicrobial agents include, but are not limited to penicillinase-resistant penicillins, cephalosporins and carbapenems, including vancomycin, lysostaphin, penicillin G, ampicillin, oxacillin, nafcillin, cloxacillin, dicloxacillin, cephalothin, cefazolin, cephalexin, cephradine, cefamandole, cefoxitin, imipenem, meropenem, gentamycin, teicoplanin, lincomycin and clindamycin. The dosages of these antibiotics are well known in the art. See for example, Merck Manual Of Diagnosis And Therapy, §13, Ch. 157, 100th Ed. (Beers & Berkow, eds., 2004). The anti-infective, antibiotic and/or antimicrobial agents may be combined prior to administration, or administered concurrently or sequentially with active or passive immunotherapies described herein.

[0284] In some embodiments, relatively few doses of antibody composition are administered, such as one or two doses, and conventional antibiotic therapy is employed, which generally involves multiple doses over a period of days or weeks. Thus, the antibiotics can be taken one, two or three or more times daily for a period of time, such as for at least 5 days, 10 days or even 14 or more days, while the antibody composition is usually administered only once or twice. However, the different dosages, timing of dosages and relative amounts of antibody composition and antibiotics can be selected and adjusted by one of ordinary skill in the art.

[0285] 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 recognize the epitope can be identified by in vitro assays that measure antigen-dependent proliferation, as determined by ^{3}H-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.

[0286] 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.

[0287] 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.

[0288] 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.

[0289] In order to produce polyclonal antibodies, a host, such as a rabbit, goat, sheep or human, 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.

[0290] 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 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.

[0291] 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.

[0292] 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).

[0293] 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.

[0294] 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.

[0295] 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.

VI. Nucleic Acids

[0296] In certain embodiments, the present invention concerns recombinant polynucleotides encoding the proteins, polypeptides and peptides of the invention. The nucleic acid sequences for Emp, Eap or AdsA, and other bacterial proteins including, but not limited to EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, Ebh, Coa, vWa, SpA, Coa, vWa, Ebh, 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 are included.

[0297] 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 cer-

tain 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.

[0298] 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 modification, or localization). As will be understood by those in the art, this term encompasses genomic sequences, expression cassettes, cDNA sequences, mRNA 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).

[0299] In particular embodiments, the invention concerns isolated nucleic acid segments and recombinant vectors incorporating nucleic acid sequences that encode Emp, Eap and/or AdsA, that may also be in combination with EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, Ebh, Coa, vWa, SpA, 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. Thus, an isolated nucleic acid segment or vector containing a nucleic acid segment may encode, for example, Emp Eap and/or AdsA, and/or EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, Ebh, Coa, vWa, SpA, 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 that is/are 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.

[0300] In other embodiments, the invention concerns isolated nucleic acid segments and recombinant vectors incorporating nucleic acid sequences that encode a peptide or polypeptide to generate an immune response in a subject. In various embodiments the nucleic acids of the invention may be used in genetic vaccines.

[0301] 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.

[0302] 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 (Emp), SEQ ID NO:3 (Eap), SEQ ID NO:5 (EsxA), SEQ ID NO:7 (EsxB), SEQ ID NO:9 (SdrD), SEQ ID NO:11 (SdrE), SEQ ID NO:13 (IsdA), SEQ ID NO:15 (IsdB), SEQ ID NO:17 (SpA), SEQ ID NO:19 (ClfB), SEQ ID NO:21 (IsdC), SEQ ID NO:23 (SasF), SEQ ID NO:25 (SdrC), SEQ ID NO:27 (ClfA), SEQ ID NO:29 (EsaB), SEQ ID NO:31 (EsaC), SEQ ID NO:33 (SasB), or SEQ ID NO:35 (Sas) or any other nucleic acid sequences encoding secreted virulence factors and/or surface proteins.

[0303] 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.

[0304] The invention also contemplates the use of polynucleotides which are complementary to all the above described polynucleotides.

[0305] 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.

[0306] The invention also provides for the use of a polynucleotide encoding an immunological fragment of a protein of the invention as hereinbefore defined.

[0307] A. Vectors

[0308] 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 Emp, Eap or AdsA polypeptide the vector can encode an EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, Ebh, Coa, vWa, SpA, 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 any other Staphylococcal peptides or proteins, 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.

[0309] Vectors of the invention may be used in a host cell to produce an Emp or Eap or AdsA polypeptide. In certain aspects the vectors may also produce EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, Ebh, Coa, vWa, SpA, 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 any other Staphylococcal peptides or proteins 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.

[0310] 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.

[0311] 1. Promoters and Enhancers

[0312] 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.

[0313] 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. No. 4,683,202, U.S. Pat. No. 5,928,906, each incorporated herein by reference).

[0314] 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.

[0315] 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 a 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-DRα (Sherman et al., 1989), 13-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), β-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), α1-Antitrypain (Latimer et al., 1990), H_2B (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; Sleigh 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; Celander et al., 1987; Thiesen et al., 1988; Celander 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).

[0316] 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—ElA (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 (Blanar et al., 1989); HSP70—ElA/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).

[0317] The particular promoter that is employed to control the expression of a 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.

[0318] In various embodiments, the human cytomegalovirus (CMV) immediate early gene promoter, the SV40 early promoter, or the Rous sarcoma virus long terminal repeat can be used to obtain high level expression of an Emp, AdsA and/or Eap polynucleotide. In other embodiments Emp, Eap and/or AdsA can be used expressed in combination with EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, Hla or a variant thereof, IsdA, IsdB, ClfA, ClfB, IsdC, SasB, SasF, Spa, vWa, Coa, Ebh, 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 any other bacterial polypeptide. 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.

[0319] 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 Emp, Eap and/or AdsA polypeptide for eliciting 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.

[0320] 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.

[0321] 2. Initiation Signals and Internal Ribosome Binding Sites (IRES)

[0322] 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.

[0323] 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 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).

[0324] 3. Multiple Cloning Sites

[0325] 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.

[0326] 4. Splicing Sites

[0327] 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.)

[0328] 5. Termination Signals

[0329] 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.

[0330] 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.

[0331] 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.

[0332] 6. Polyadenylation Signals

[0333] 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.

[0334] 7. Origins of Replication

[0335] 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.

[0336] 8. Selectable and Screenable Markers

[0337] 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.

[0338] 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 phenotype 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.

[0339] B. Host Cells

[0340] 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.

[0341] 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 (www.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, DH5α, JM109, and KC8, as well as a number of commercially available bacterial hosts such as SURE® Competent Cells and SOLOPACK™ Gold Cells (STRATAGENE®, 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.*

[0342] 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.

[0343] 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.

[0344] C. Expression Systems

[0345] 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.

[0346] 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®.

[0347] 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.

[0348] D. Amplification of Nucleic Acids

[0349] 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 samples without substantial purification of the template nucleic acid. The nucleic acid may be genomic DNA. Where RNA is used, it may be desired to first convert the RNA to a complementary DNA.

[0350] 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.

[0351] 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.

[0352] 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.

[0353] 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.

[0354] E. Methods of Gene Transfer

[0355] 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); or 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). Through the application of techniques such as these, organelle(s), cell(s), tissue(s) or organism(s) may be stably or transiently transformed.

VII. EXAMPLES

[0356] 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

Envelope Proteins Associated with Abscess Formation and Vaccine Protection

A. Results

[0357] The inventors sought to study the pathogenesis of staphylococcal abscess formation and identify the bacterial factors that enable staphylococcal survival and proliferation within this lesion. The studies used the murine renal abscess model, wherein mice are infected with a sub-lethal dose of *S. aureus* to develop a sustained infection (Burts et al., 2005). Mice were killed on the fifth day post-infection, their kidneys excised and subjected to histopathology of thin-sectioned hemotoxylin-eosin stained tissue or to enumeration of staphylococcal load by plating tissue homogenate for colony forming units (CFU). In comparison to the wild-type clinical isolated *S. aureus* Newman (Baba et al., 2008), an isogenic variant with a transposon insertion in the structural gene for sortase A failed to form abscesses (FIGS. **1**B, **1**D, and **1**F). Sortase A, which anchors a large spectrum of surface proteins with LPXTG motif sorting signals to the cell wall envelope, is responsible for the surface display of many different virulence factors (Mazmanian et al., 2000; Mazmanian et al., 1999). To quantify abscess formation, kidneys were visually inspected, and each individual organ was given a score of one (surface abscesses present) or zero (absent). The final sum was divided by the total number of kidneys to obtain a fractional value. In addition, three randomly chosen right-sided kidneys were placed in 10% formalin overnight, embedded, sectioned, and stained with hematoxylin and eosin. For each kidney, four sagittal sections at 200 μM intervals were viewed by microscopy. If a lesion was observed in any plane of inspection, the organ was judged positive for abscess formation. Mice infected with 3×10^7 CFU/ml *S. aureus* Newman displayed visible lesions on 16/20 kidneys (80% surface abscess) and were positive for abscess formation in 3/3 kidneys examined for histopathology (Table 3). In contrast, mice infected with the AsrtA mutant presented with 0% surface abscesses and 0/3 histological lesions (Table 3).

TABLE 3

Recovered Recovered CFUs with standard error, log reduction with respect to Newman, P-value (student's t-test), % surface abscesses observed, # histological abscesses observed.

	Staphylococcal load in kidney tissue			Kidney abscess formation	
Strain	$\log_{10}$ CFU g^{-1}	P-value	Reduction	Surface %	Histo-pathology
wild-type	6.040 ± 0.095	—	—	80	3
ΔsrtA	3.911 ± 0.389	0.0002	1.830	0	0
Surface protein genes					
sdrD	3.629 ± 0.758	0.0040	2.411	22	1
isdB	4.253 ± 0.510	0.0027	1.790	5	1
clfB	4.624 ± 0.446	0.0067	1.398	30	2
isdA	4.723 ± 0.280	0.0002	1.320	15	1
sasB	5.089 ± 0.448	0.0433	0.951	38	2
sasD	5.206 ± 0.375	0.0371	0.833	45	1
sasC	5.222 ± 0.400	0.0594	0.824	50	2
sasF	5.421 ± 0.360	0.1051	0.619	30	2
sasA	5.431 ± 0.403	0.1217	0.609	40	2
sasG	5.433 ± 0.360	0.1051	0.607	40	2
isdC	5.498 ± 0.292	0.0945	0.541	33	2
fnbpB	5.530 ± 0.359	0.1856	0.511	30	1
sasI	5.599 ± 0.416	0.2681	0.441	38	2
spa	5.681 ± 0.455	0.4487	0.359	10	1
fnbpA	5.751 ± 0.322	0.3800	0.289	40	2
sdrE	5.848 ± 0.334	0.5686	0.192	61	3
clfA	5.898 ± 0.296	0.1470	(+) 0.472	40	2
PNAG (PIA) genes					
icaA	5.326 ± 0.452	0.1122	0.822	40	3
icaB	5.894 ± 0.306	0.4917	0.254	35	2
icaC	5.651 ± 0.441	0.3004	0.497	35	2
icaD	5.886 ± 0.278	0.4394	0.262	45	2
icaR	6.201 ± 0.309	0.8837	−0.053	60	2
ica:tet	5.692 ± 0.280	0.1909	0.456	55	2
Envelope protein genes					
eap	6.530 ± 0.385	0.1217	(+)0.49	50	2
emp	5.716 ± 0.080	0.1051	0.324	10	1
eap/ΔsrtA	4.708 ± 0.545	0.0129	1.332	0	0
emp/ΔsrtA	3.165 ± 0.496	5.53×10^{-4}	2.875	0	0
Capsular polysaccharide genes					
capO	—	—	—	—	—

[a]Means of *staphylococcal* load in colony forming units (CFU) calculated as $\log_{10}$ CFU g^{-1} in homogenized renal tissues 5 days following infection in cohorts of fifteen BALB/c mice per challenge strain. Standard error of the means (±SEM) is indicated.

[b]Statistical significance was calculated with the students t-test and P-values recorded.

[c]Reduction in bacterial load calculated as $\log_{10}$ CFU g^{-1}.

[e]Abscess formation in kidney tissues five days following infection. was measured by macroscopic inspection (% positive) and histopathology of hematoxylene-eosine stained, thin sectioned tissues from three animals, whereby positive tissues were recorded as fractional values (⅔).

Recovered CFUs with standard error, log reduction with respect to Newman, P-value (student's t-test), % surface abscesses observed, # histological abscesses observed.

[0358] Scanning electron microscopy was used to examine infected tissues. Kidneys were sectioned, fixed, dehydrated in hexamethyldisilazane (HMDS), and sputter coated with 80% Pt/20% Pd prior to viewing. Kidney tissue infected with *S. aureus* Newman harbored bacteria within a central region of the abscess. Wild-type staphylococci were found in tightly associated lawns (FIG. **1**G), contained by a fibrous structure that is internal to the larger fibrin capsule. These staphylococcal nests are devoid of leukocytes and appear to be embedded by an adhesive extracellular matrix. Kidneys tissue infected with the srtA mutant also harbored staphylococci, however the bacteria were dispersed throughout healthy renal tissue and significantly reduced in number compared to the wild-type (FIG. **1**H).

[0359] To identify the specific sortase A substrates responsible for abscess formation, the inventors transduced *bursa aurealis* insertions in 17 sortase substrate genes (Bae et al., 2004) into *S. aureus* Newman and screened the variants for virulence defects. Mutations in sdrD, isdB, clfB, isdA, sasB, and sasD caused significantly reduced bacterial load ($P<0.05$) (FIG. **2**). Further, mutations in sdrD, isdB, and isdA presented with fewer abscesses when analyzed by macroscopic and microscopic techniques (Table 3). The inventors considered mutants with <30% surface abscesses and <⅓ histological scores to display a significant defect in abscess formation. Mutants with mismatched surface histological scores were not counted as defective; rather, it is attributed to screening errors. Interestingly, mutations in clfB and sasB exhibited defects in staphylococcal load but not in abscess formation, whereas mutations in protein A displayed increased load but

also displayed a defect in abscess formation. The inventors wondered whether defects in abscess formation and survival in renal tissue were due to the inability of these mutants to form functional biofilms. In other words, is the defect in abscess formation attributable to defects for in vitro biofilm growth? To study this the inventors cultured staphylococci in 96 well assay plates or on coverslips and measured safranin-stained biofilm by absorbance at 405 nm. *S. aureus* Newman does not form biofilm in laboratory broth, however Morrissey and colleagues reported biofilm growth in iron-depleted RPMI and 5% atmospheric CO_2 (Johnson et al., 2008). Using these conditions, all mutant strains tested here grew equally well (data not shown), however mutations in srtA, isdB, sdrD or isdA exhibited significant ($P<0.05$) defects in biofilm formation. These results were corroborated by scanning electron microscopy experiments (FIG. **3**B, **3**C, **3**D, **3**E, **3**F, **3**G, and Table 4), where *S. aureus* Newman grows as multicellular complexes embedded in a granular extracellular matrix (FIG. **3**B). Multicellular complexes are reduced and the extracellular matrix is diminished in staphylococci with mutations in srtA, isdB, or sdrD, the same mutations that also abolished abscess formation in mice. Thus, in vitro biofilm formation may indeed be correlated with the ability of staphylococci to form abscesses. The inventors also tested mutations in genes that abrogate the synthesis of other envelope factors in staphylococci, including poly-N-acetylglucosamine (PNAG/PIA which is synthesized by products of ica genes) (Heilmann et al., 1996; Gotz, 2002) as well as the cell wall associated proteins Eap (Scriba et al., 2008; Xie et al., 2006) and Emp (Hussain et al., 2001). Regulatory factors for staphylococcal virulence were also tested: saeR (Novick and Jiang, 2003), sarA (Cheung et al., 1992), mgrA (Chen et al., 2006), agrC, and agrA (Novick, 2003). Mutation in emp displayed the largest defect in biofilm formation with an 86% reduction in safranin absorbance and the absence of multicellular complexes by scanning EM, results that are in agreement with a similar study of Johnson et al (2008). In contrast, the Eap mutant displayed a slight, but significant defect in biofilm formation (FIG. **3**A, Table 4). Emp and Eap are envelope adhesins that mediate interaction between staphylococci and host extracellular matrix proteins fibronectin, vibronectin, and collagen (Scriba et al., 2008; Xie et al., 2006; Hussain et al., 2001). All sequenced strains of *S. aureus* harbor genes for both proteins, which are positively regulated by the two-component system SaeRS and the global transcription factor SarA, mutations in which also impact biofilm formation (Harraghy et al., 2005) (FIG. **3**A, Table 4).

TABLE 4

96 well plate in vitro biofilm assay. Mean absorbance at 450 nm with standard error, fraction reduction from Newman absorbance, P-value (student's t-test)

Strain	Mean absorbance @ 450 nm ± SEM	% Reduction (0.967-Abs)/0.967	P-value
Newman	0.967 ± 0.054	—	—
Eap	0.621 ± 0.152	0.357	0.011
Emp	0.131 ± 0.026	0.861	2.30 × 10−10
SaeR	0.161 ± 0.025		6.80 × 10−12
SarA	0.252 ± 0.051	0.83	1.37 × 10−5
MgrA	0.630 ± 0.012	0.793	0.064
AgrC	0.701 ± 0.121	0.319	0.388
AgrA	0.889 ± 0.106	0.272	0.204
IcaA	0.516 ± 0.121	0.081	4.34 × 10−4
IcaC	0.653 ± 0.204	0.466	0.041

TABLE 4-continued

96 well plate in vitro biofilm assay. Mean absorbance at 450 nm with standard error, fraction reduction from Newman absorbance, P-value (student's t-test)

Strain	Mean absorbance @ 450 nm ± SEM	% Reduction (0.967-Abs)/0.967	P-value
IcaD	0.791 ± 0.158	0.325	0.194
IcaB	0.713 ± 0.184	0.182	0.08
IcaR	0.511 ± 0.169	0.472	1.19 × 10−3
Ica:tet	0.546 ± 0.169	0.2	4.28 × 10−3
SrtA	0.524 ± 0.081	0.458	6.51 × 10−5
IsdB	0.415 ± 0.042	0.57	8.79 × 10−8
SdrD	0.447 ± 0.090	0.537	0.002
IsdA	0.658 ± 0.913	0.32	0.029
SasD	0.679 ± 0.187	0.298	0.064
SasA	0.707 ± 0.077	0.268	0.388
SasG	0.774 ± 0.184	0.2	0.204
SasH	0.777 ± 0.156	0.197	0.196
SpA	0.824 ± 0.136	0.176	0.136
SasC	0.833 ± 0.087	0.147	0.39
SasI	0.797 ± 0.142	0.138	0.419
SasB	0.841 ± 0.127	0.13	0.374
IsdC	0.863 ± 0.024	0.107	0.433
FnbA	0.886 ± 0.368	0.084	0.677
ClfB	0.913 ± 0.181	0.056	0.705
ClfA	1.061 ± 0.107	−0.097	0.705
SdrE	1.070 ± 0.124	−0.107	0.465
FnbB	1.120 ± 0.118	−0.158	0.419

[0360] To study if Emp is required for abscess formation, mice were challenged with emp mutant staphylococci and kidneys analyzed five days following infection. The emp mutant staphylococci were isolated from kidney tissue with similar abundance as the wild-type parent (FIG. **4**A), however these mutants failed to form abscesses and instead remained dispersed throughout kidney tissue (FIG. **4**B). These results identify Emp as an envelope factor that is uniquely required for abscess and biofilm formation in vitro and in vivo. It is noted that mutations in ica genes (icaABCDR), which mediate PNAG synthesis (Heilmann et al., 1997), exhibited only a slight decrease in biofilm formation. Although unable to produce exopolysaccharide, ica mutants were able to generate the extracellular matrix that can be detected by electron microscopy. Further, ica mutants failed to display in vivo defects in abscess formation or bacterial load (FIGS. **6**A, **6**B, Table 5). These data suggest therefore that the extracellular matrix of *S. aureus* Newman biofilms is not comprised of PNAG. Emp and Eap are cell wall associated surface proteins, whose production can be detected by SDS extraction of staphylococci and separation on Coomassie-stained PAGE (FIG. **5**A). With this assay it was observed that *S. aureus* Newman produces large quantities of Eap and Emp. Mutations in srtA or isdB do not affect production or cell wall association of Emp and Eap, in agreement with the conjecture that the observed defects of srtA and isdB mutants in abscess and biofilm formation are not due to secondary effects on Eap and Emp. Of note, mutations in emp affect the abundance of Eap and it is surmised that envelope deposition of Emp may affect the surface display of Eap.

TABLE 5

Ica virulence. Mean recovered CFUs, log reduction from Newman, P-value (student's t-test), % surface abscesses observed, # histological abscesses.

Strain	Mean *S. aureus* per kidneys ± SEM (log10(CFU)/mL)	Reduction (log10(CFU)/mL)	P-value	% surface abscess	# histology abscess
Newman	6.148 ± 0.194	—	—	0.7	3
IcaA	5.326 ± 0.452	0.822	0.1122	0.4	2
IcaB	5.894 ± 0.306	0.254	0.4917	0.35	2
IcaC	5.651 ± 0.441	0.497	0.3004	0.35	2
IcaD	5.886 ± 0.278	0.262	0.4394	0.45	2
IcaR	6.201 ± 0.309	−0.053	0.8837	0.6	2
Ica:tet	5.692 ± 0.280	0.456	0.1909	0.55	2
SrtA	3.319 ± 0.604	2.849	2.26 × 10−4	0	0
IcaA/SrtA	2.247 ± 0.559	3.901	3.45 × 10−6 (N) 1.84 × 10−5 (I) 0.2097 (S)	0	0

[0361] As both proteins displayed prominently on the staphylococcal surface, the inventors contemplated that Emp and Eap represent suitable vaccine antigens to prevent staphylococcal disease. The structural genes for each protein were cloned into pET15b and recombinant products purified by affinity chromatography via N-terminal His-6 tag under denaturing conditions. Following purification, Eap could be folded and soluble product purified by a second round of Ni-NTA chromatography in renaturing buffer. Purified Emp could not be refolded and was thenceforth kept in 8 M urea (FIG. **5**B). Mice were immunized with PBS, Eap or Emp emulsified in complete Freund adjuvant (CFA) and challenged mice with 3×10^7 CFU *S. aureus* Newman. FIG. **5**C shows that immunization with Emp or Eap conferred significant protection ($P<0.05$) against staphylococcal infection. Mice vaccinated with Eap displayed a two log reduction in staphylococcal load, whereas Emp immunized mice exhibited a 2.5 log reduction. Mice immunized with Eap (1:24,000) or Emp (>64,000) developed high titers of reactive IgG (FIG. **5**D). As expected, animal mock immunized with PBS developed 70% surface and 4/5 histological abscesses. In contrast, mice immunized with Eap and Emp presented with <20% surface abscesses and 1/5 histological lesions (FIG. **5**E). Thus, immunization with Eap or Emp generates specific humoral immune responses and protective immunity against staphylococcal infection.

[0362] Studies reveal an association between staphylococcal biofilm growth and the ability to form abscesses in infected host tissues. Previous work established that biofilms are required for colonization and persistent infection of implanted medical devices and allow for protection from antibiotics, antibodies, and phagocytic cells. Evidence presented here suggests that biofilms are required for effective seeding and persistent proliferation of staphylococci within organ tissues. Three sortase substrate genes were identified, sdrD, isdB, and isdA that displayed combinatorial defects in abscess formation, staphylococcal load in infected tissues and in vitro biofilm growth. Remarkably, the products of these surface protein genes were also identified as premier vaccine candidates in a comparative evaluation of staphylococcal sortase anchored surface proteins (Stranger-Jones et al., 2006). Such attribute can now also be expanded for two cell wall associated factors Emp and Eap. At least emp is required for abscess formation and biofilm growth and immunization with Emp product affords protective immunity against staphylococcal disease. Thus, these studies expand the list of suitable vaccine candidates to prevent human infections with *S. aureus* to select cell wall anchored and cell wall associated proteins, whose combined formulation should provide strong protective immunity against all staphylococcal strains.

[0363] Animal model for staphylococcal abscess formation and persistent infection. To characterize the pathogenesis of *S. aureus* abscess formation, the renal abscess model was modified (Albus et al., 1991), wherein BALB/c mice were infected by intravenous injection with 1×10^7 CFU of the human clinical isolate *S. aureus* Newman (Baba et al., 2007). Within 6 hours following infection, 99.999% of staphylococci disappeared from the blood stream and were distributed via the vasculature (FIG. **7**A). Staphylococcal dissemination to peripheral tissues occurred rapidly, as the bacterial load in kidney and other peripheral organ tissues reached 1×10^5 CFU g^{-1} within the first three hours (FIG. **7**B). The staphylococcal load in kidney tissues increased by 1.5 log CFU within twenty-four hours (FIG. **7**B). Forty-eight hours following infection, mice developed disseminated abscesses in multiple organs, detectable by light microscopy of hematoxylin-eosin stained, thin-sectioned kidney tissue (FIG. **7**D-K). The initial abscess diameter was 524 μM (±65 μM); lesions were initially marked by an influx of polymorphonuclear leukocytes (PMNs) and harbored no discernable organization of staphylococci, most of which appeared to reside within PMNs (FIG. **8**A-C). On day 5 of infection, abscesses had increased in size and enclosed a central population of staphylococci, surrounded by a layer of eosinophilic, amorphous material and a large cuff of PMNs (FIG. **8**D-F). Histopathology revealed massive necrosis of PMNs in proximity to the staphylococcal nidus at the center of abscess lesions as well as a mantle of healthy phagocytes (FIG. **8**D-F). A rim of necrotic PMNs at the periphery of abscess lesions, bordering eosinophilic, amorphous material that separated healthy renal tissue from the infected lesion were also observed (FIG. **8**D-F). Abscesses eventually reached a diameter of ≧1,524 μM on day 15 or 36 (FIG. **7**K). At later time intervals, staphylococcal load was increased to 10^4-10^6 CFU g^{-1} and growing abscess lesions migrated towards the organ's capsule (FIG. **7**J-K). Peripheral lesions were prone to rupture, thereby releasing necrotic material and staphylococci into the peritoneal cavity or the retroperitoneal space. These events resulted in bacteremia as well as a secondary wave of abscesses, eventually precipitating a lethal outcome of these infections (data not shown).

[0364] Staphylococcal abscess communities are enclosed by a pseudocapsule. To enumerate staphylococcal load in renal tissue, animals were killed, their kidneys excised and tissue homogenate spread on agar media for colony formation. On day 5 of infection, a mean of 1×10^6 CFU g^{-1} renal tissue for *S. aureus* Newman was observed (FIG. **9**P). To quantify abscess formation, kidneys were visually inspected, and each individual organ was given a score of one (FIG. **9**A) or zero (FIG. **9**F). The final sum was divided by the total number of kidneys to calculate percent surface abscesses (Table 6). In addition, randomly chosen kidneys were fixed in formalin, embedded, thin sectioned, and stained with hematoxylin and eosin. For each kidney, four sagittal sections at 200 μM intervals were viewed by microscopy (FIG. **9**). The numbers of lesions were counted for each section and averaged to quantify the number of abscesses within kidneys. *S. aureus* Newman caused 4.364±0.889 abscesses per kidney, and surface abscesses were observed on 14 out of 20 kidneys (70%) (Table 6).

[0365] Kidneys were sectioned, fixed, dehydrated and sputter coated with platinum/palladium for scanning electron microscopy. FIG. **10**A shows *S. aureus* Newman in tightly associated lawns at the center of abscesses. Staphylococci were contained by an amorphous pseudocapsule (white arrow heads, FIG. **10**A) that separated bacteria from the cuff of abscesses leukocytes. No immune cells were observed in these central nests of staphylococci, however occasional red blood cells were located among the bacteria (R, FIG. **10**A). Bacterial populations at the abscess center, designated staphylococcal abscess communities (SAC), appeared homogenous and were coated by an electron-dense, granular material. The kinetics of the appearance of infectious lesions and the morphological attributes of abscesses formed by *S. aureus* Newman were similar to those observed following mouse infection with *S. aureus* USA300 (LAC), the current epidemic community acquired methicillin-resistant *S. aureus* (CA-MRSA) clone in the United States (Diep et al., 2006) (FIG. **9**K-O and **10**C).

TABLE 6

Genetic requirements for *S. aureus* Newman abscess formation in mice.

	Staphylococcal load in kidney tissue			Abscess formation in kidney tissue		
Genotype	[a] $\log_{10}$ CFU g^{-1} tissue	[b] Significance (P-value)	[c] Reduction ($\log_{10}$ CFU g^{-1})	[d] Surface abscesses (%)	[e] Number of abscesses per kidney	[f] Significance (P-value)
wild-type	6.141 ± 0.192	—	—	70	4.364 ± 0.889	—
ΔsrtA	4.095 ± 0.347	6.7×10^{-6}	2.046	0	0.000 ± 0.000	0.0216
			Surface protein genes			
sdrD	4.092 ± 0.454	0.0001	2.049	15	0.600 ± 0.267	0.0265
isdB	4.535 ± 0.298	5.7×10^{-5}	1.606	5	0.500 ± 0.167	0.0227
clfB	4.672 ± 0.302	0.0001	1.469	30	1.852 ± 0.654	0.1298
isdA	4.723 ± 0.299	0.0002	1.418	15	0.375 ± 0.182	0.0350
isdC	5.050 ± 0.208	0.0004	1.091	27	1.000 ± 0.327	0.0737
clfA	5.103 ± 0.260	0.0025	1.038	40	1.125 ± 0.350	0.0848
spa	5.137 ± 0.374	0.0144	1.004	13	0.375 ± 0.374	0.0356
sasG	5.139 ± 0.287	0.0054	1.002	45	1.222 ± 0.425	0.0770
sasC	5.193 ± 0.337	0.0167	0.948	56	1.375 ± 0.595	0.1335
sasD	5.312 ± 0.291	0.0212	0.829	48	1.500 ± 0.462	0.1272
sasA	5.355 ± 0.217	0.0102	0.786	39	2.250 ± 0.453	0.2568
sdrE	5.498 ± 0.255	0.0475	0.643	65	2.333 ± 0.667	0.5023
sasF	5.518 ± 0.318	0.0884	0.623	47	1.333 ± 0.408	0.3187
isdH	5.555 ± 0.251	0.0676	0.586	44	1.125 ± 0.479	0.0859
sasB	5.650 ± 0.255	0.1641	0.491	59	1.720 ± 0.620	0.1651
fnbA	5.678 ± 0.270	0.1294	0.463	51	2.125 ± 0.666	0.2338
sdrC	5.693 ± 0.287	0.1908	0.448	33	1.000 ± 0.378	0.0741
fnbB	5.823 ± 0.246	0.3124	0.318	54	2.000 ± 0.567	0.2074
			PNAG (PIA) genes			
icaA	5.326 ± 0.452	0.3122	0.815	40	2.667 ± 1.453	0.5768
icaB	5.894 ± 0.306	0.4917	0.247	35	1.000 ± 0.270	0.2690
icaC	5.651 ± 0.441	0.3004	0.491	35	2.000 ± 1.527	0.4384
icaD	5.886 ± 0.278	0.4394	0.255	45	1.667 ± 0.667	0.3741
icaR	6.201 ± 0.309	0.8837	+0.06	60	2.333 ± 0.333	0.5033
ica:tet	5.692 ± 0.280	0.1909	0.449	55	2.333 ± 0.667	0.5023
			Envelope associated protein genes			
eap	6.530 ± 0.385	0.1217	+0.49	55	1.250 ± 0.412	0.0971
emp	5.540 ± 0.040	0.0576	0.601	20	0.800 ± 0.416	0.0361
			Capsular polysaccharide genes			
capO	6.028 ± 0.579	0.9825	0.113	50	3.000 ± 1.054	0.6035

[a] Means of staphylococcal load calculated as $\log_{10}$ CFU g^{-1} in homogenized renal tissues 5 days following infection in cohorts of fifteen BALB/c mice per challenge strain. Standard error of the means (±SEM) is indicated.

[b] Statistical significance was calculated with the Students t-test and P-values recorded; P-values <0.05 were deemed significant.

[c] Reduction in bacterial load calculated as $\log_{10}$ CFU g^{-1}.

[d] Abscess formation in kidney tissues five days following infection was measured by macroscopic inspection (% positive)

[e] Histopathology of hematoxylene-eosin stained, thin sectioned kidneys from eight to ten animals: the average number of abscesses per kidney was recorded and averaged again for the final mean (±SEM).

[f] Statistical significance was calculated with the Students t-test and P-values recorded, P-values <0.05 were deemed significant.

[0366] Sortase mutants cannot establish abscess lesions and fail to persist. Sortase A is a transpeptidase that immobilizes nineteen surface proteins in the envelope of *S. aureus* strain Newman (Mazmanian et al., 1999; Mazmanian et al., 2000). Earlier work identified sortase A as a virulence factor in multiple animal model systems, however the contributions of this enzyme and its anchored surface proteins to abscess formation or persistence have not yet been revealed (Jonsson et al. 2002; Weiss et al., 2004). Compared to the wild-type parent (Baba et al., 2007), an isogenic srtA variant (ΔsrtA) failed to form abscess lesions on either macroscopic or histopathology examination on days 2, 5 or 15 (FIG. **9**F-J and Table 6). In mice infected with the strA mutant, only 1×10^4 CFU g^{-1} was recovered from kidney tissue on day 5 of infection, which is a 2.046 $\log_{10}$CFU g^{-1} reduction compared to the wild-type parent strain ($P=6.73\times10^{-6}$)(FIG. **9**P). A similar defect was observed for the srtA mutant of MRSA strain USA300 (data not shown). Scanning electron microscopy showed that srtA mutants (arrow heads) were highly dispersed and often associated with leukocytes in otherwise healthy renal tissue (FIG. **10**B). On day fifteen following infection, srtA mutants were cleared from renal tissues, a $\geqq$3.5 $\log_{10}$CFU g_{-1} reduction compared to the wild-type (FIG. **9**P). Thus, sortase A anchored surface proteins enable the formation of abscess lesions and the persistence of bacteria in host tissues, wherein staphylococci replicate as communities embedded in an extracellular matrix and shielded from surrounding leukocytes by an amorphous pseudocapsule.

[0367] Genetic requirements for staphylococcal surface proteins. Sortase A anchors a large spectrum of proteins with LPXTG motif sorting signals to the cell wall envelope, thereby providing for the surface display of many virulence factors (Mazmanian et al., 2002). To identify surface proteins required for staphylococcal abscess formation, bursa aurealis insertions were introduced in 5' coding sequences of genes that encode polypeptides with LPXTG motif proteins (Bae et al., 2004) and transduced these mutations into *S. aureus* Newman. Following intravenous infection of mice and analysis through the renal abscess model, the severity of observed virulence defects was rank ordered as the $\log_{10}$ reduction of the means of staphylococcal CFU g^{-1} (FIG. **11** and Table 6). Mutations in sdrD, isdB, clfB, isdA, clfA, and isdC caused reduced bacterial load (Table 6). The inventors considered mutants <30% or less surface abscesses and histology abscess average $P<0.05$ as significant for defects in abscess formation, which included variants with mutations in sdrD, isdB, and isdA (Table 6). Interestingly, mutations in clfA and clfB exhibited defects in staphylococcal load but not in abscess formation (FIG. **11**). These virulence findings are in agreement with previous studies suggesting that clumping factor proteins mediate fibrinogen binding as well as resistance to phagocytic clearance, attributes required for pathogen survival and dissemination in blood (McDevitt et al., 1994; Ni Eidhin et al. 1998). Protein A impedes phagocytosis by binding the Fc component of immunoglobulin (Uhlen et al., 1984; Jensen et al., 1958), activates platelet aggregation via the von Willebrand factor (Hartleib et al., 2000), functions as a B cell superantigen by capturing the Fab region of VH3 bearing IgM (Roben et al., 1995), and, through its activation of TNFR1, can initiate staphylococcal pneumonia (Gomez et al., 2004). Protein A mutants (spa) exhibited a modest reduction in staphylococcal load (day 5), however, in contrast to wildtype, clfA and clfB strains, the ability of spa variants to form abscesses was diminished (FIG. **11** and Table 6).

[0368] Staphylococcal carbohydrates and envelope associated proteins. *S. aureus* elaborates two carbohydrate structures, capsular polysaccharide (CPS) (Jones 2005) and poly-N-acetylglucosamine (PNAG) (Gotz 2002). *S. aureus* Newman and USA300 synthesize type 5 CPS, which is composed of a repeating trisaccharide subunit [→4)-β-D-ManAcA-(1→4)-α-L-FucNAc(3OAc)-(1→3)-β-D-FucNAc-(1→] (Baba et al., 2007). Nucleotide sequences of the cap5 gene cluster comprise a 16 gene operon (capA-P) and two of its products, CapP and CapO, function as epimerase and dehydrogenase in the synthesis UDP-N-acetylmannosaminuronic acid (UDP-ManNAcA) (O'Riordan and Lee, 2004; Sau et al., 1997). As expected, bursa aurealis insertion into cap0 abrogated CPS5 synthesis (data not shown). PNAG (or PIA), a linear β(1-6)-linked glucosaminoglycan, is composed of 2-deoxy-2-amino-D-glucopyranosyl residues, of which 80-85% are N9 acetylated (Mack et al., 1996); the remaining glucosamine residues are positively charged and promote association of the polysaccharide with the bacterial envelope (Vuong et al., 2004). PNAG is synthesized by products of the intercellular adhesin locus (icaADBC) (Heilmann et al., 1996; Cramton et al., 1999). Both *S. aureus* carbohydrate structures were dispensable for the pathogenesis of animal infections, as mutations in capO as well as icaADBC or the regulator icaR did not affect bacterial load on day 5, the establishment of staphylococcal communities or renal abscess formation (Table 6). The contribution of envelope associated proteins to staphylococcal abscess formation was also examined. The hallmark of envelope associated proteins is that they can be extracted by boiling in hot SDS. This method was used to detect the deposition of two such proteins, Eap and Emp, in the envelope of *S. aureus* Newman. A mutant with bursa aurealis insertion in emp displayed reduced bacterial load in kidney tissue on day 5 of infection in addition to significant defects in the formation of abscesses and in bacterial persistence within host tissues (FIG. **12**, Table 6). No reduction in abscess formation was observed for the eap mutant, whereas the reduced staphylococcal load on day 5 and 15 suggests a defect in bacterial peristence within host tissues (FIG. **12**, Table 6). Expression of Emp and Eap during infection was detected with immunofluorescence experiments (FIG. **12**J-K). Eap was found deposited within the pseudocapsule, whereas Emp was detected in staphylococal abscess communities. These observations support a model whereby Emp contributes to the formation of staphylococcal communities that elicit abscess lesions, whereas Eap deposition in the pseudocapsule promotes bacterial persistence in host tissues.

[0369] Envelope associated proteins as vaccine antigens. Previous work sought to characterize *S. aureus* vaccine antigens by interrogating purified sortase A substrates for their ability to elicit protective immunity towards staphylococcal disease (Stranger-Jones et al., 2006). When used as individual subunit vaccine antigens, surface proteins generated variable degrees of protection; immunization with SdrD, IsdA, IsdB, SdrE, SpA, ClfA as well as ClfB achieved a significant reduction in bacterial load, however none of these vaccines afforded complete protection. In contrast, a combination of four antigens generated much more robust vaccine protection against abscess formation or lethal challenge with several different *S. aureus* strains (Stranger-Jones et al., 2006). Recombinant Eap and Emp was purified from *Escherichia*

coli and used these proteins to immunize BALB/c mice for subsequent challenge with *S. aureus* Newman (FIG. **13**). Following immunization, mice developed humoral immune responses against both envelope associated proteins (FIG. **13**A). Immunization with Emp caused a modest 0.959 $\log_{10}$ CFU g^{-1} reduction in staphylococcal load within kidney tissues (P=0.5114), whereas a significant level of protection was achieved with Eap (1.939 $\log_{10}$CFU g^{-1} reduction in bacterial load, P=0.0079) (FIG. **13**B). To test whether Emp or Eap specific antibodies can provide protection against staphylococcal challenge, rabbits were immunized and Emp-as well as Eap-specific antibodies were purified by affinity chromatography.

[0370] Passive immunization with 5 mg kg^{-1} (85 μg per animal) purified antibodies into the peritoneal cavity of naïve BALB/c mice resulted in low, but detectable levels of serum IgG 24 hours following transfer (antibody titers of 1,000±110 for Eap and 1,124±236 for Emp, FIG. **13**C). In parallel, passively immunized animals were challenged by intravenous inoculation with *S. aureus* Newman, which, when compared to mock controls, resulted in a 1.36 $\log_{10}$CFU g^{-1} reduction in staphylococcal load for Eap immunized animals (n=10) on day 4 (P=0.0085) and a reduction in the number of abscesses formed (mock treated 4.64±1.09 abscesses $kidney^{-1}$ vs. Eap immunized 1.40±0.48, P=0.028, n=14 and 10, FIG. **13**D-E).

[0371] Animals (n=9) that received Emp-specific antibodies displayed a 1.20 $\log_{10}$CFU g^{-1} reduction in staphylococcal load on day 4 (P=0.0132), but only a slightly reduced number of abscesses formed (2.0±0.98, P=0.1362, FIG. **13**D-E). In summary, similar to sortase anchored surface proteins, antibodies against envelope associated factors can generate protection against staphylococcal infection in mice.

B. Materials and Methods

[0372] Bacterial Strains and Growth. Staphylococci were cultured on tryptic soy agar or broth at 37° C. *E. coli* strains DH5a and BL21(DE3) were cultured on Luria agar or broth at 37° C. Ampicillin (100 μg/ml) and erythromycin (10 μg/ml) were used for plasmid and transposon mutant selection, respectively.

[0373] Transposon Mutagenesis. Insertional mutations from the *Phoenix* library were transduced into human clinical isolate *S. aureus* Newman. Each mutant carries the transposon *bursa aurealis* containing an erythromycin resistance cassette in the gene of interest. The mutations were verified as previously described (Bae et al., 2004). Briefly, chromosomal DNA was extracted (Promega Wizard Kit), digested with AciI (NEB), religated with T4 Ligase (Promega) to form individual plasmids, and PCR amplified using primers specific to the transposon bursa aurealis. These products were sequenced to verify the site of transposon insertion in the target gene.

[0374] Cloning, purification, and antibody generation. Coding sequences for Eap and Emp were PCR-amplified using *S. aureus* Newman template DNA (Baba et al., 2007). PCR products were cloned into pET15b to express recombinant proteins with an N-terminal His6 tag fusion. Bacteria were disrupted in a French press, membrane and insoluble components sedimented by ultracentrifugation. His-tagged Emp was purified by affinity chromatography in its native state. Extract containing Eap was solubilized at room temperature in 8 M urea, 50 mM Tris-HCl pH 8.0 for 4-5 hours, then centrifuged at 10,000×g. The supernatant containing the denatured protein was subjected to nickel-nitrilotriacetic acid (Ni-NTA) affinity chromatography (Promega). Protein was eluted in PBS-8M urea containing successively higher concentrations of imidazole (100-500 mM). Eluate fractions positive for Eap were pooled, diluted into PBS-1M Urea and passed over a second Ni-NTA column. Refolded Eap was eluted with PBS buffer containing imidazole. Protein concentration was determined by absorbance at 280 nm. Rabbits (6 month old New-Zealand white, females, Charles River Laboratories) were immunized with 500 μg protein emulsified in CFA (Difco) for initial immunization or IFA for booster immunizations on day 24 and 48. On day 60, rabbits were bled and serum recovered for immunoblotting, immune-fluorescence microscopy or passive transfer experiments.

[0375] Scanning Electron Microscopy. Infected kidneys (right side) were fixed for 24-48 hours in 8% glutaraldehyde at 4° C. and sectioned into 2-5 mm pieces to expose internal tissues or abscesses. These samples were then dehydrated by successive incubations in 25, 50, 75, 90, 100% ethanol, followed by 100% HMDS. Following dehydration, samples were mounted and sputter coated with 80% Pt/20% Pd to 8 nm before viewing under a Fei NovaNano SEM200 scanning electron microscope. For biofilm assays, staphylococci were grown on coverslips in iron depleted RPMI in 5% CO_2 and washed 3 times in PBS. Cover slips were serially dehydrated by incubation in ethanol and HMDS, mounted, and sputter coated prior to viewing under the scanning electron microscope.

[0376] Biofilm formation. *S. aureus* strains were grown in Chelex (Sigma) treated RPMI 1640 (Gibco) supplemented with 10% RPMI 1640 and 1% Casamino acids (Difco). Overnight cultures were grown at 37° C. in 6% CO_2, then inoculated 1:10 in quadruplicate into 96-well flat-bottomed tissue culture plates (Costar) containing fresh media. These plates were incubated statically at 37° C. in 6% CO_2 for 24 hours. Wells were washed three times with 1×PBS, dried for 2 hours at 37° C., and stained with 1% safranin. Absorbance at 450 nm was measured to quantify biofilm formation. Each strain was tested in at least 3 separate experiments and a two-tailed Student t test was used to compare mutants to wild-type.

[0377] Renal Abscess. Overnight cultures of *S. aureus* Newman were inoculated 1:100 into fresh tryptic soy broth and grown for 2 hours at 37° C. Staphylococci were sedimented, washed with 1×PBS, and suspended in a volume of PBS to yield an A600 of 0.6 (3×10^8 CFU/ml). The inoculum was verified by plating and colony enumeration. Mice were anesthetized by intraperitoneal injection of 100 mg/ml of ketamine and 2 mg/ml of xylazine per kilogram of body weight. 6-8 week old female BALB/c mice (Charles River Laboratories) were infected with 100 μl of bacterial suspension (3×10^7 CFU) by retroorbital injection. Cohorts of 10 or 20 mice were infected per staphylococcal strain. On the day 5 following infection, mice were killed by CO_2 inhalation, dissected, and the kidneys were excised and homogenized in 0.01% Triton X-100 using a sonicator. Aliquots (20 μl) were serially diluted and plated for determination of CFU. Three to four right kidneys from each cohort of mice were fixed in 10% formalin for 24 h at room temperature. Tissues were embedded in paraffin, thin-sectioned, stained with hematoxylin and eosin, and examined by microscopy. 3-4 week old female BALB/c mice were used for persistence studies.

[0378] Immunization. BALB/c mice (24-day-old female, 8-10 mice per group, Charles River Laboratories, Wilmington, Mass.) were immunized by intramuscular injection into

the hind leg with purified protein. Antigen (25 μg purified protein per animal) was administered on days 0 (emulsified 1:1 with complete Freund's adjuvant) and 11 (emulsified 1:1 with incomplete Freund's adjuvant). Mice were bled periorbitally on day 20, followed by retro-orbital challenge in the opposite eye with 10^7 CFU/ml bacteria on day 21. Mice were killed on day 25 and processed according to the renal abscess model.

[0379] Immunofluorescence microscopy. Kidneys of infected animals were dissected, placed in 1×PBS on ice, and then flash frozen in Tissue Tek OCT Compound within cryomolds. Samples were thin sliced (4 μm thick), mounted on slides, and stored at −80° C. Prior to staining, slides were warmed to room temperature for 30 minutes, fixed in ice cold acetone for 10 minutes, and washed twice with ice cold PBS. The slides were blocked in 3% BSA, 1:20 Human IgG (Sigma), 1×PBS, 0.1% Tween-80 for 1 hour at room temperature with shaking Specific rabbit antibody (1:2,000) was added to the mixture and slides were allowed to incubate for another hour. The solution was decanted and glass slides were washed 3 times with PBS and 10 minute incubations each. Slides were placed in 3% BSA, 1×PBS, 0.1% Tween-80, 1:200 AlexaFluor-647 mouse anti-rabbit secondary antibody and allowed to incubate at room temperature in the dark, with shaking. The solution was decanted, slides were washed 3 times with PBS, placed in PBS containing 1:1,000 Hoechst dye (Invitrogen) as well as 1 μg/ml BODIPY-vancomycin and allowed to incubate in the dark for 5 minutes with shaking The slides were washed once more with PBS, mounted in Npropylgallate, and viewed under a Leica SP5 AOBS spectral two-photon confocal microscope.

[0380] Active and passive immunization. BALB/c mice (n=15) were immunized with purified Eap or Emp or PBS on day 0, 11. On day 20 following immunization, 5 mice were bled to obtain sera to determine antibody titers and on day 21, all mice were challenged with 1×10^7 CFU *S. aureus* Newman. Five days following infection, kidneys were removed during necropsy and renal tissue analyzed for staphylococcal load or histopathology.

[0381] Rabbit Eap or Emp antibodies were purified by affinity chromatography (purified Eap or Emp covalently linked to sepharose) and transferred by intraperitoneal injection into mice. Passively immunized animals were challenged twenty-four hours later by retroorbital injection with 1×10^7 CFU *S. aureus* Newman. Serum IgG titers of actively or passively immunized animals were analyzed by ELISA. Four days following infection, kidneys were removed during necropsy and renal tissue was analyzed for staphylococcal load or histopathology.

Example 2

Staphylococcus Aureus Synthesizes Adenosine to Escape Host Immune Responses

A. Results

[0382] AdsA is required for staphylococcal survival in blood. To identify staphylococcal genes required for escape from innate immune responses, the ability of *S. aureus* strain Newman to survive in whole blood from BALB/c mice or Sprague-Dawley rats was examined by recording bacterial load at timed intervals via the formation of colonies on agar medium (FIG. **15**). As expected, immune cells within blood of naïve mice and rats, which lack antibodies specific for staphylococci (data not shown), were unable to phagocytose and kill *S. aureus* Newman (FIGS. **15**A and **15**D). In contrast to the wild-type strain, a variant lacking the structural gene for sortase A (srtA) displayed a defect in staphylococcal escape from phagocytic killing ($P<0.05$) (FIGS. **15**A and **15**D). Sortase A anchors a large spectrum of different polypeptides in the staphylococcal envelope, using a transpeptidation mechanism and LPXTG motif sorting signal at the C-terminus of surface proteins (Mazmanian et al., 2002). To examine these surface proteins for their contribution to staphylococcal escape from phagocytic killing, the inventors transduced *bursa aurealis* insertions in surface protein genes (Bae et al., 2004) into wild-type strain *S. aureus* Newman and measured survival of staphylococcal variants in blood (FIGS. **15**B and **15**E). Mutations in clfA and sasH (*Staphylococcus aureus* surface protein), hereafter named adsA, displayed consistent survival defects. The phenotype of clfA mutants represents an expected result, as the encoded clumping factor A (ClfA) product is known to precipitate fibrin and interfere with macrophage and neutrophil phagocytosis (Palmqvist et al., 2004; Higgins et al., 2006). The contribution of AdsA to pathogenesis is not yet known. AdsA harbors a 5'-nucleotidase domain with the two signature sequences ILHTnDiHGrL (residues 124-134) and YdamaVGNHEFD (residues 189-201), suggesting that the protein may catalyze the synthesis of adenosine from 5'-AMP. To further examine the importance of adsA in staphylococcal virulence, the inventors complemented the adsA gene by cloning the entire adsA gene and upstream promoter sequences into expression vector pOS1, generating padsA. Transformation of adsA mutant staphylococci with padsA restored their ability to survive in mouse or rat blood, indicating that the observed virulence defect is indeed caused by the absence of adsA expression (FIGS. **15**C and **15**F, and FIG. **20**). *S. aureus* survival was also examined in blood of human volunteers. As with murine blood, the number of adsA mutant staphylococci was reduced and staphylococcal phagocytosis by neutrophils was increased as compared to wild-type strain *S. aureus* Newman (FIGS. **15**G and **15**H).

[0383] AdsA is required for staphylococci virulence and abscess formation. To investigate the contribution of adsA in invasive staphylococcal disease, BALB/c mice were infected by intravenous inoculation with 10^7 colony forming units (CFU) of wild type *S. aureus* Newman or its isogenic asdA variant. Animals were killed 5 days post-infection and both kidneys were removed. The right kidney was homogenized and staphylococcal load enumerated by plating on agar and colony formation (FIG. **16**A). The left kidney was fixed with glutaraldehyde, embedded in paraffin, thin sectioned and analyzed by histology (FIG. **16**B). As expected, wild-type *S. aureus* Newman formed abscesses in kidney tissue with an average bacterial load of 10^7 CFU per gram of organ tissue. In contrast, adsA mutant staphylococci were unable to form abscesses and displayed a greater than ten-fold reduction in bacterial load, as compared to the wild-type (FIG. **16**A).

[0384] Infections with MRSA strains that were acquired in communities of the United States (CA-MRSA) have been characterized by pulsed-field gel electrophoresis and DNA sequencing. Currently, the major CA-MRSA clone is USA300 (McDougal et al., 2003), the predominant cause of skin and soft tissue infections as well as bacteremia (Carleton et al., 2004). To assess the contribution of adsA towards virulence of USA300, an isogenic adsA mutant was isolated using phage transduction and *S. aureus* strain LAC (USA300) (Bae et al., 2004). BALB/c mice were infected by retro-orbital injection of staphylococci into the blood stream. Five

days following challenge, staphylococci were enumerated in homogenized kidney tissue and the histopathologies of abscesses were visualized in hematoxylin-eosin stained thin sections of this organ (FIG. **16**C). Similar to *S. aureus* Newman, the inventors observed a one-log reduction in CFU recovered from the kidneys of animals infected with the adsA mutant of *S. aureus* USA300. Further, fewer abscesses and smaller lesions were observed in kidneys of mice infected with the adsA variant (FIG. **16**D and FIG. **21**). Together these results document the requirement of adsA for virulence in two clinical isolates, *S. aureus* strains Newman and USA300.

[0385] Differences in abscess formation and recovery of CFUs from kidneys of infected mice may stem from enhanced bacterial clearance in the blood stream, causing fewer bacteria to reach peripheral organ tissues. Alternatively, adsA could play a direct role in the formation of abscesses and infectious foci. To discern between these possibilities, BALB/c mice were infected by retro-orbital inoculation and peripheral blood was sampled at timed intervals by cardiac puncture. In agreement with observations of enhanced clearance of adsA mutant staphylococci in vitro, significantly fewer CFU of adsA mutant staphylococci were retrieved 90 minutes post-infection, as compared to the wild-type parent strain *S. aureus* Newman. Further, transformation of the adsA mutant strain with padsA restored its ability to survive in blood following intravenous challenge (FIG. **16**E). Although we cannot rule out the possibility that adsA contributes also specifically to abscess formation, these data suggest that the reduced virulence of adsA mutant staphylococci results from their decreased survival in blood.

[0386] AdsA-mediated synthesis of adenosine correlates with staphylococcal survival in blood. Given that AdsA harbors a 5'nucleotidase signature sequence, it was asked whether AdsA can synthesize adenosine from AMP. Cell wall peptidoglycan of *S. aureus* wild-type, adsA and isdB (iron surface determinant B, a gene that does not contribute to AMP hydrolysis) (Mazmanian et al., 2003) mutant strains, and the adsA:padsA strain was degraded with lysostaphin (Schindler and Schuhardt, 1964), and cell wall extracts were incubated with radiolabeled [^{14}C]AMP. Production of adenosine was monitored by thin layer chromatography (TLC). Lysostaphin extracts of adsA mutant staphylococci displayed significantly reduced adenosine synthase activity (~25% of wild-type). Adenosine synthase activity was restored to wild-type levels when adsA mutants were transformed with padsA (FIG. **17**A). Disruption of isdB, in contrast, did not affect the generation of adenosine by *S. aureus*.

[0387] To characterize the enzymatic activity of AdsA, we expressed and purified a soluble recombinant form of AdsA from *Escherichia coli*. Purified AdsA cleaved [^{14}C]AMP to generate adenosine and maximal activity (K_M=44 nM) was observed in the presence of 5 mM $MgCl_2$ or 5 mM $MnCl_2$, similar to the metal requirements of other adenosine synthases (Zimmermann, 1992). On the other hand, incubation of AdsA with 5 mM $ZnCl_2$ or 5 mM $CuSO_4$ prior to the addition of [^{14}C]AMP, completely inhibited adenosine synthase activity (FIG. **17**B, lanes 6 and 7). A similar inhibiting effect was observed when EDTA, a divalent metal ion chelator, was added to AdsA, demonstrating that AdsA requires divalent cations for adenosine synthase activity in vitro.

[0388] It was contemplated that staphylococci escape phagocytic clearance in blood by synthesizing adenosine. The survival defect of adsA mutant staphylococci in blood could be rescued by exogenous supplies of adenosine. This was tested, revealing a dose-dependent increase in the survival of adsA mutant staphylococci upon the addition of 1-100 μM adenosine (FIG. **17**F). Under physiological conditions, the concentration of AMP in the extracellular milieu is estimated to be in the nanomolar range. Immunological insult or tissue injury, however, causes release of AMP whose concentration may increase up to 100 μM. It therefore seems plausible that these AMP stores may be converted to adenosine during staphylococcal infection. To assess the relative abundance of adenosine during staphylococcal infection, mouse blood was infected with *S. aureus* for 60 min. Plasma was retrieved, protein removed and samples subjected to reverse phase high pressure liquid chromatography (rpHPLC). For calibration, commercially purified adenosine was separated by rpHPLC and determined its molecular mass in the eluate (FIG. **18**A). Chromatography of uninfected blood revealed the adenosine absorption peak, whose identity was confirmed by mass spectrometry (FIG. **18**A). The adenosine peak in blood was increased ten-fold following infection with *S. aureus* Newman (FIG. **18**C), whereas infection with the isogenic adsA mutant produced less than a two-fold increase in adenosine (FIG. **18**D). Of note, extracellular adenosine is imported rapidly by blood cells (half life <1 min) (Thiel et al., 2003). In view of this, the observed ten-fold increase of adenosine in blood during *S. aureus* infection represents a substantial accumulation of this signaling molecule and an important virulence strategy whereby staphylococci combat host immunity.

[0389] *Bacillus anthracis* survives in blood and synthesizes adenosine. To investigate whether other pathogenic bacteria also employ adenosine synthase to promote escape from phagocytic clearance, bacterial genome sequences were searched for products harboring the adenosine synthase domain of AdsA and several different genes were identified (Table 3). The genome of *B. anthracis* encodes BasA (*Bacillus anthracis* surface protein, NCBI locus tag BAS4031) with a 5'-nucleotidase signature sequence (YdvisLGNHEFN, residues 131-142) and a C-terminal LPXTG sorting signal, indicating that this surface protein is also deposited by sortase A in the cell wall envelope (Gaspar et al. 2005). To determine whether BasA functions as an adenosine synthase and contributes to escape from innate immune responses, we constructed a deletion mutant of basA by allelic replacement (FIG. **19**). Mutanolysin, a muralytic enzyme that cleaves N-acetylmuramyl-(β1→4)-N-acetylglucosamine within peptidoglycan (Yokigawa et al., 1974), was used to generate cell wall lysates. Cell wall extracts from wild-type bacilli harbored adenosine synthase activity, however extracts derived from basA mutant bacilli displayed a reduction in this activity (FIG. **19**A). Deletion of the structural gene basA abolished expression (FIG. **19**B) and surface display of BasA in *B. anthracis* (FIG. **19**C) and reduced the ability of bacilli to synthesize adenosine (FIG. **19**A). Residual amounts of AMP hydrolysis may be attributable to other phosphatases, for example alkaline phosphatase. The inventors expressed and affinity purified tagged BasA from *E. coli*. Similar to *S. aureus* AdsA, optimal adenosine synthase activity of BasA was observed in the presence of 5 mM $MnCl_2$ (K_M=2.01 nM), whereas 5 mM $MgCl_2$ showed reduced activity (FIG. **19**D). When inoculated into mouse blood, increased phagocytic clearance of the basA mutant was observed, as compared to the wild-type parent *B. anthracis* Sterne (FIG. **19**E). Together these experiments suggest that, similar to staphylococci, *B. anthracis* also employs AdsA to synthesize adenosine and escape innate immune responses.

TABLE 7

Other microbes with putative 5'-nucleotidases

Organism	Function	Pubmed Accession
Parasites		
Trichinella spiralis	Secreted 5'-nucleotidase	Q8MQS9
Giardia lamblia	Putative uncharacterized protein	A8BZM2
Gram Positive bacteria		
Bacillus anthracis	2',3'-cyclic-nucleotide 2'-phospodiesterase	Q6HTQ7
Bacillus cereus	5'-nucleotidase domain protein	A7GMX9
Clostridium perfringens	5'-nucleotidase family protein	B1BIR2
Enterococcus faecalis	5'-nucleotidase family protein	Q839U0
Listeria monocytogenes	Putative uncharacterized protein	A3FTX4L
Listeria monocytogenes	Putative uncharacterized protein	A4DAM1
Staphylococcus aureus str. MW2	Putative 5'-nucleotidase	Q8NYQ6
Staphylococcus epidermis	5'-nucleotidase family protein	Q5HQE0
Streptococcus pyogenes	Putative surface-anchored 5'-nucleotidase	A2RF30
Streptococcus mutans	Putative 5'-nucleotidase	Q8CVC5
Streptococcus gordonii	5'-nucleotidase family protein	A8AXM1
Streptococcus suis	Putative 5'-nucleotidase	A4VV27
Gram Negative bacteria		
Aeromonas salmonicida	Putative 5'-nucleotidase	A4SNE6
Burkholderia dolosa	5'-nucleotidase/2',3'-cyclic phosphodiesterase	A2W738
Bacteroides fragilis	Possible secreted 5'-nucleotidase	A5ZBW1
Bacteroides caccai	Putative uncharacterized protein	Q5LHW0
Enterobacter	5'-nucleotidase domain protein	A4W7G3
Escherichia coli str. UTI89	Putative uncharacterized protein	Q1R3X2
Haemophilus parasuis	Putative uncharacterized protein	B0QT39
Haemophilus influenzae	Probable 5'-nucleotidase precursor	P44569
Klebsiella pneumoniae	Putative 5'-nucleotidase precursor	A6TGD1
Salmonella choleraesuis	UDP-sugar hydrolase 5'-nucleotidase	Q57S69
Salmonella typhimurium	Putative 5'-nucleotidase	Q7CR96
Salmonella paratyphi A	Putative secreted 5'-nucleotidase	Q5PDK6
Trepenoma denticola	Phosphatase/5'-nucleotidase	Q73PC9
Vibrio cholerae	5'-nucleotidase precursor	Q9KQ30
Vibrio parahaemolyticus	5'-nucleotidase precursor	P22848
Yersenia pestis str *Antiqua*	5'-nucleotidase precursor	Q1C4S3

[0390] Other microbes with putative 5'-nucleotidases represent well known pathogens (Table 7) and we sought to analyze their ability to synthesize adenosine. Similar to cell wall extracts from *S. aureus* and *B. anthracis, Enterococcus faecilis* and *Staphylococcus epidermidis* both synthesized adenosine from AMP, whereas the non-pathogenic microbe *Bacillus subtilis* did not (data not shown). The inventors conclude that the ability of bacterial pathogens to synthesize adenosine and release this immunosuppressive compound into host tissues may represent a universal virulence strategy.

B. Materials and Methods

[0391] Bacterial Strains. *S. aureus* strains were grown in TSB at 37° C. *S. aureus* strain USA300 was obtained through the Network on Antimicrobial Resistance in *S. aureus* (NARSA, NIAID). All mutants used in this study were obtained from the *Phoenix* (SNE) library (Bae et al., 2004). Each *Phoenix* isolate is a derivative of the clinical isolate Newman (Duthie and Lorenz, 1952) or USA300 (Carleton et al., 2004) as indicated. All bursa aurealis insertions were transduced into wild-type *S. aureus* Newman or USA300 using bacteriophage ϕ85 and verified by PCR analysis. Chloramphenicol was used at 10 mg l^{-1} for plasmid and allele selection with padsA. Erythromycin was used at 10 mg l^{-1} for allele selection in *S. aureus* Newman and at 50 mg l^{-1} for allele selection in USA300. Mutants of *B. anthracis* strain Sterne were generated with pLM4, containing a thermosensitive origin of replication. Plasmids with 1 kb DNA sequence flanking each side of the mutation were transformed into *B. anthracis* and transformants grown at 30° C. (permissive temperature) in LB broth (20 μg ml^{-1} kanamycin). Cultures were diluted 1:100 and plated on LB agar (20 μg ml^{-1} kanamycin) at 43° C. overnight (restrictive temperature). Single colonies were inoculated into LB broth without antibiotics and grown overnight at 30° C. To ensure loss of pLM4-based plasmid, these cultures were diluted four times into fresh LB broth without antibiotic pressure and propagated at 30° C. Cultures were diluted and plated on LB agar and colonies examined for kanamycin resistance. DNA from kanamycin-sensitive colonies was analyzed by PCR for the presence or absence of mutant alleles.

[0392] Plasmids. The following primers were employed for PCR amplification reactions P55 (5'-TTTCCCGGGACGATCCAGCTCTAATCGCTG-3') (SEQ ID NO:42), P56 (5'-TTTGAGCTCAAAGCAAATAGATAATCGAGAAATATAAAAAG-3) (SEQ ID NO:43), P57 (5'-TTTGAGCTCAGTTGCTCCAGCCAGCAT T-3') (SEQ ID NO:44), P58 (5'-TTTGAATTCAAACGGATTCATTCCAGCC-3') (SEQ ID NO:45), FP10 (5'-TACGAATTCGACTTGGCAGGCAATTGAAAA-3') (SEQ ID NO:46), RP10 (5'-TGTGAATTCTTAGCTAGCTTTTCTACGTCG-3') (SEQ ID NO:47), FP3C (5'-TCGGGATCCGCTGAG-

CAGCATACACCAATG-3') (SEQ ID NO:48), RPB (5'-TGTGGATCCTTATTGATTAATTTGTTCAGCTAATGC-3') (SEQ ID NO:49). Ligation of FP10/RP10 (adsA+700 bp upstream from start site) PCR products into pOS1 (EcoRI) generated padsA. Insertion of P55/P56 (basA 1 kb 5' flanking sequence) and P57/P58 (basA 1 kb 3' flanking sequence) PCR products into pLM4 (EcoRI, SacI, and XmaI sites) generated pJK34. This plasmid was used to delete the basA coding sequence. Ligation products were transformed into *E. coli* DH5α, and plasmid DNA into *E. coli* K1077 (dam^-, dcm^-) and purified (non-methylated) plasmid DNA was transformed into *B. anthracis* following a previously developed protocol (Gaspar et al., 2005). Ligation of FP3C/RPB (1.2 kb truncation of adsA starting 5' after the signal peptide) PCR products into pGEX-2T (GE Healthcare) generated the adsA expression vector pVT1 and this plasmid was transformed into *E. coli* BL21.

[0393] Animal experiments. All experimental protocols were reviewed, approved and performed under regulatory supervision of The University of Chicago's Institutional Biosafety Committee (IBC) and Institutional Animal Care and Use Committee (IACUC). BALB/c mice were purchased from Charles River Laboratories and Sprague-Dawley rats were purchased from Harlan. Overnight cultures of *S. aureus* strains were diluted 1:100 into fresh TSB and grown for 3 h at 37° C. Staphylococci were centrifuged, washed twice and diluted in PBS to yield an OD_{600} of 0.5 (1×10^8 CFU ml^{-1}). Viable staphylococci were enumerated by colony formation on tryptic soy agar plates to quantify the infectious dose. Mice were anaesthetized by intraperitoneal injection of 80-120 mg of ketamine and 3-6 mg of xylazine per kilogram of body weight. One hundred microliters of bacterial suspension (1×10^7 CFU) were administered intravenously via retro-orbital injection into BALB/c mice (6-wk old female). On day 5, mice were killed by compressed CO_2 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 Prizm software. For histopathology, kidney tissue was incubated at room temperature in 10% formalin for 24 h. Tissues were embedded in paraffin, thin-sectioned, stained with haematoxylin-eosin and examined by microscopy.

[0394] To measure staphylococcal survival in blood, 6-week old female BALB/c mice were infected with 1×10^7 CFU of staphylococci by retro-orbital injection. At 30 or 90 minutes, mice were killed by compressed CO_2 inhalation and blood was collected by cardiac puncture using a 25 gauge needle. Aliquots were incubated on ice for 30 minutes in a final concentration of 0.5% saponin/PBS to lyse host eukaryotic cells. Dilutions were plated on TSA for enumeration of surviving CFU at the two different time points.

[0395] Chemicals. Mutanolysin (Sigma) was suspended at a concentration of 5,000 units ml^{-1} in 100 mM sodium phosphate, pH 6.0, containing 1 mM PMSF and stored at −20 C. [^{14}C]AMP and [^{14}C]adenosine were purchased from Moravek Biochemicals. Lysostaphin was purchased from AMBI and purified adenosine was purchased from Sigma.

[0396] Bacterial survival in blood. Overnight cultures of *S. aureus* strains were diluted 1:100 into fresh TSB and grown for 3 h at 37° C. Staphylococci were centrifuged, washed twice and diluted in PBS to yield an OD_{600} of 0.5 (1×10^8 CFU ml^{-1}). Whole blood was collected by cardiac puncture of Sprague-Dawley rats or BALB/c mice and 5 μg ml^{-1} of lepirudin anticoagulant immediately added. 100 μl of 10^5 CFU ml^{-1} of bacteria were mixed with 900 μl of rat or mouse blood. For human blood studies, 100 μl of 10^8 CFU ml^{-1} of bacteria was mixed with 900 μl of freshly drawn human blood. The tubes were then incubated at 37° C. with slow rotation for the indicated time points, at which time aliquots were incubated on ice for 30 minutes in a final concentration of 0.5% saponin/PBS to lyse eukaryotic cells. Dilutions of staphylococci were plated on TSA for enumeration of surviving CFU. Experiments with blood from human volunteers involved protocols that were reviewed, approved and performed under regulatory supervision of The University of Chicago's Institutional Review Board (IRB).

[0397] Adenosine synthase activity. Overnight cultures of *S. aureus* strains were diluted 1:100 into fresh TSB and grown for 3 h at 37° C. Staphylococci were centrifuged and washed twice with PBS. 3 ml of cells were spun down and resuspended in 100 μL TSM buffer (50 mM Tris-HCL pH 7.5, 10 mM $MgCl_2$, and 0.5 M sucrose); 2 μl of lysostaphin was then added and allowed to incubate for 30 min at 37° C. The solution was then spun down for 5 min at 10 k rpm and supernatants containing released cell surface proteins collected. 15 μl of lysostaphin extracts were then incubated with 3 μCi [^{14}C]AMP for 30 minutes at 37° C. Samples were then spotted on a silica plate followed by separation by TLC using a (75:25 isopropanol: ddH2O) 0.2 M ammonia bicarbonate solvent. For cell wall extracts of *S. aureus, E. faecilis, B. anthracis* and *S. epidermidis* digested with mutanolysin, mutanolysin was substituted for lysostaphin and used per the manufacturer's recommended conditions. When assayed with purified proteins, 2 μM of purified AdsA or BasA was incubated in a final volume of 15 μl with 3 μCi [^{14}C]AMP in the presence of the indicated metal cations in TSM buffer.

[0398] Adenosine concentration in blood. Whole blood killing assay with staphylococci was performed as described above. Extraction of plasma was performed as described (Mo and Ballard, 2001). Briefly, after conclusion of the whole blood killing assay, blood samples were centrifuged at 13 k rpm for 5 minutes and non-cellular plasma was collected. 600 μl of plasma was then extracted with 75 μl perchloric acid (1.5 M) and 1 mM EDTA. The supernatant (500 μl) was withdrawn after centrifugation for 5 min at 13 k rpm and neutralized with 29 μl 4 M KOH. After ice cooling for 10 min, the sample was again centrifuged at 13 k rpm for 5 min. The pH of the supernatant was finally adjusted to 6-7, diluted 1:4 with PBS, filtered with a 0.22 μm syringe filter prior to reverse phase high performance liquid chromatography (rpHPLC).

[0399] HPLC and mass spectrometry. Presence of adenosine production was determined by rpHPLC. Samples were chromatographed on a 250 mm×3 mm column (BDS Hypersil C18, 5 μm particle size, Thermoscientific). The mobile phase consisted of solution A (dH_20: 0.1% trifluoroacetic acid) and solution B (acetonitrile: 0.1% trifluoroacetic acid). Adenosine was eluted with a solvent B gradient from 1 to 100%, run from 5 to 50 min. The solvent flow rate was 0.5 ml/min. Peaks were detected by their UV absorbance at 280 nm. The peak of adenosine in the HPLC chromatogram was identified by comparison of its retention time to the retention time of purified adenosine (Sigma) used as a standard sample. Fractions containing adenosine were then co-spotted with matrix (α-cyano-4-hydroxycinnamic acid) and subjected to MALDI-MS under reflector positive conditions.

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[0400] 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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Gln Ile Met Asn Ser Asn His Ala Lys Ala Ser Val Thr Glu Ser Val
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aag cat ttt gtt gct aaa ggc cca gaa gta aat aga ttt att acg caa      432
Lys His Phe Val Ala Lys Gly Pro Glu Val Asn Arg Phe Ile Thr Gln
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aac aaa gta aac cac cac ttc att act acg caa acc cac tac aag aaa      480
Asn Lys Val Asn His His Phe Ile Thr Thr Gln Thr His Tyr Lys Lys
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gtt att act tca tac aaa tca aca cat gta cat aaa cat gta aat cat      528
Val Ile Thr Ser Tyr Lys Ser Thr His Val His Lys His Val Asn His
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Ala Lys Asp Ser Ile Asn Lys His Phe Ile Val Lys Pro Ser Glu Ser
            180                 185                 190

cct aga tat aca cat cca tct caa tct tta att atc aag cat cat ttt      624
Pro Arg Tyr Thr His Pro Ser Gln Ser Leu Ile Ile Lys His His Phe
        195                 200                 205

gca gtt cct gga tat cac gcg cat aaa ttt gtt aca cca ggg cat gct      672
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Thr Asp Asn Lys Asn Phe Val Ala Ser Glu Asp Lys Leu Asn Lys Ile
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Ala Asp Ser Ser Ala Ala Ser Lys Ile Val Asp Lys Asn Phe Val Val
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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
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Asn Lys Val Asn His His Phe Ile Thr Thr Gln Thr His Tyr Lys Lys
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Val Ile Thr Ser Tyr Lys Ser Thr His Val His Lys His Val Asn His
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Ala Lys Asp Ser Ile Asn Lys His Phe Ile Val Lys Pro Ser Glu Ser
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Pro Arg Tyr Thr His Pro Ser Gln Ser Leu Ile Ile Lys His His Phe
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Val Lys Lys Tyr Phe Ser Phe Ser Gln Ser Asn Gly Tyr Lys Ile Gly
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Ala Ser Thr Gly Ala Asn Phe Asn Asn Asn Glu Ala Ser Ala Ala Ala
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Lys Pro Leu Asp Lys Ser Ser Ser Ser Leu His His Gly Tyr Ser Lys
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Val His Val Pro Tyr Ala Ile Thr Val Asn Gly Thr Ser Gln Asn Ile
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tta tca agc tta aca ttt aat aag aat caa aat att agt tat aaa gat      240
Leu Ser Ser Leu Thr Phe Asn Lys Asn Gln Asn Ile Ser Tyr Lys Asp
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Ala Asp Leu Ile Asn Thr Ser Glu Ile Lys Ala Ile Asn Ile Asn Val
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Ser Asn Leu Thr Phe Asn Lys Asn Gln Asn Ile Ser Tyr Lys Asp Leu
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gag gat aaa gtt aaa tca gtt tta gaa tca aat aga ggt att acc gat      624
Glu Asp Lys Val Lys Ser Val Leu Glu Ser Asn Arg Gly Ile Thr Asp
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gtt gat tta aga tta tcg aag caa gcg aaa tat aca gtt aat ttt aaa      672
Val Asp Leu Arg Leu Ser Lys Gln Ala Lys Tyr Thr Val Asn Phe Lys
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Asn Leu Ile Asn Ser Ser Asp Ile Lys Ser Ile Asn Ile Asn Val Asp
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Thr Lys Lys His Ile Glu Asn Lys Ala Lys Arg Asn Tyr Gln Val Pro
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Tyr Ser Ile Asn Leu Asn Gly Thr Ser Thr Asn Ile Leu Ser Asn Leu
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Ser Phe Ser Asn Lys Pro Trp Thr Asn Tyr Lys Asn Leu Thr Ser Gln
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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
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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

Lys Tyr Ala Lys Lys Ala Tyr Tyr Thr Val Tyr Phe Lys Asn Gly Gly
                325                 330                 335

Lys Arg Ile Leu Gln Leu Asn Ser Lys Asn Tyr Thr Ala Asn Leu Val
            340                 345                 350

His Ala Lys Asp Val Lys Arg Ile Glu Ile Thr Val Lys Thr Gly Thr
        355                 360                 365

Lys Ala Lys Ala Asp Arg Tyr Val Pro Tyr Thr Ile Ala Val Asn Gly
    370                 375                 380

Thr Ser Thr Pro Ile Leu Ser Asp Leu Lys Phe Thr Gly Asp Pro Arg
385                 390                 395                 400

Val Gly Tyr Lys Asp Ile Ser Lys Lys Val Lys Ser Val Leu Lys His
                405                 410                 415

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

Tyr Thr Val His Phe Lys Asn Gly Thr Lys Lys Val Ile Asn Ile Asn
        435                 440                 445

Ser Asn Ile Ser Gln Leu Asn Leu Leu Tyr Val Gln Asp Ile Lys Lys
    450                 455                 460

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

Val Pro Tyr Thr Ile Ala Val Asn Gly Thr Ser Thr Pro Ile Leu Ser
                485                 490                 495

Lys Leu Lys Ile Ser Asn Lys Gln Leu Ile Ser Tyr Lys Tyr Leu Asn
            500                 505                 510

Asp Lys Val Lys Ser Val Leu Lys Ser Glu Arg Gly Ile Ser Asp Leu
        515                 520                 525

Asp Leu Lys Phe Ala Lys Gln Ala Lys Tyr Thr Val Tyr Phe Lys Asn
    530                 535                 540

Gly Lys Lys Gln Val Val Asn Leu Lys Ser Asp Ile Phe Thr Pro Asn
545                 550                 555                 560

Leu Phe Ser Ala Lys Asp Ile Lys Lys Ile Asp Ile Asp Val Lys Gln
                565                 570                 575

Tyr Thr Lys Ser Lys Lys Asn Lys
            580
```

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<210> SEQ ID NO 5
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Staphylococcus sp.
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(294)

<400> SEQUENCE: 5

```
atg gca atg att aag atg agt cca gag gaa atc aga gca aaa tcg caa       48
Met Ala Met Ile Lys Met Ser Pro Glu Glu Ile Arg Ala Lys Ser Gln
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
Asp Ala Val Gln Glu Gln Asp Gln Gln Leu Ser Asn Asn Phe Gly Leu
                85                  90                  95

caa taa                                                             294
Gln
```

<210> SEQ ID NO 6
<211> LENGTH: 97
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 6

```
Met Ala Met Ile Lys Met Ser Pro Glu Glu Ile Arg Ala Lys Ser Gln
1               5                  10                  15

Ser Tyr Gly Gln Gly Ser Asp Gln Ile Arg Gln Ile Leu Ser Asp Leu
            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
    50                  55                  60

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

Asp Ala Val Gln Glu Gln Asp Gln Gln Leu Ser Asn Asn Phe Gly Leu
                85                  90                  95

Gln
```

<210> SEQ ID NO 7
<211> LENGTH: 307
<212> TYPE: DNA
<213> ORGANISM: Staphylococcus sp.
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(306)

<400> SEQUENCE: 7

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```
atg ggt gga tat aaa ggg att aaa gca gat ggt ggc aag gtg aat caa       48
Met Gly Gly Tyr Lys Gly Ile Lys Ala Asp Gly Gly Lys Val Asn Gln
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

caa gga ctt gat agg gtg a                                           307
Gln Gly Leu Asp Arg Val
            100


<210> SEQ ID NO 8
<211> LENGTH: 102
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 8

Met Gly Gly Tyr Lys Gly Ile Lys Ala Asp Gly Gly Lys Val Asn Gln
1               5                   10                  15

Ala Lys Gln Leu Ala Ala Lys Ile Ala Lys Asp Ile Glu Ala Cys Gln
            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
                85                  90                  95

Gln Gly Leu Asp Arg Val
            100


<210> SEQ ID NO 9
<211> LENGTH: 4158
<212> TYPE: DNA
<213> ORGANISM: Staphylococcus sp.
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(4158)

<400> SEQUENCE: 9

atg cta aac aga gaa aat aaa acg gca ata aca aga aaa ggc atg gta       48
Met Leu Asn Arg Glu Asn Lys Thr Ala Ile Thr Arg Lys Gly Met Val
1               5                   10                  15

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
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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
    210                 215                 220

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
Leu Thr Val Val Asp Ala Asp Asn Ser Lys Thr Ile Val Pro Ala Gln
            260                 265                 270

gat tat tta tca tta aaa tca caa att aca gtt gat gac aaa gtt aaa      864
Asp Tyr Leu Ser Leu Lys Ser Gln Ile Thr Val Asp Asp Lys Val Lys
        275                 280                 285

tca ggt gat tat ttc aca att aaa tac tca gat aca gta caa gta tat      912
Ser Gly Asp Tyr Phe Thr Ile Lys Tyr Ser Asp Thr Val Gln Val Tyr
    290                 295                 300

gga ttg aat ccg gaa gat att aaa aat att ggt gat att aaa gat cca      960
Gly Leu Asn Pro Glu Asp Ile Lys Asn Ile Gly Asp Ile Lys Asp Pro
305                 310                 315                 320

aat aat ggt gaa aca att gcg act gca aaa cat gat act gca aat aat     1008
Asn Asn Gly Glu Thr Ile Ala Thr Ala Lys His Asp Thr Ala Asn Asn
                325                 330                 335
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tta att aca tat aca ttt aca gat tat gtt gat cga ttt aat tca gta     1056
Leu Ile Thr Tyr Thr Phe Thr Asp Tyr Val Asp Arg Phe Asn Ser Val
            340                 345                 350

aaa atg ggt att aat tac tca att tat atg gat gca gat aca att cct     1104
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

aca act aca aca gca gat atc act tat ccg gct tat aaa gaa gct gac     1200
Thr Thr Thr Thr Ala Asp Ile Thr Tyr Pro Ala Tyr Lys Glu Ala Asp
385                 390                 395                 400

aat aat tca ata gga tca gct ttt aca gag aca gtt tct cat gta gga     1248
Asn Asn Ser Ile Gly Ser Ala Phe Thr Glu Thr Val Ser His Val Gly
                405                 410                 415

aat gtt gaa gac cct ggt tac tat aac cag gta gta tat gtt aat cct     1296
Asn Val Glu Asp Pro Gly Tyr Tyr Asn Gln Val Val Tyr Val Asn Pro
            420                 425                 430

atg gat aag gat tta aaa ggt gct aag tta aaa gtt gaa gcg tac cat     1344
Met Asp Lys Asp Leu Lys Gly Ala Lys Leu Lys Val Glu Ala Tyr His
        435                 440                 445

ccg aaa tat cca act aat att ggt caa att aat caa aat gtt aca aat     1392
Pro Lys Tyr Pro Thr Asn Ile Gly Gln Ile Asn Gln Asn Val Thr Asn
    450                 455                 460

ata aaa ata tat cgt gtt cct gaa gga tat aca ttg aat aaa gga tat     1440
Ile Lys Ile Tyr Arg Val Pro Glu Gly Tyr Thr Leu Asn Lys Gly Tyr
465                 470                 475                 480

gac gtt aat act aat gat ttg gta gac gta act gat gaa ttt aaa aat     1488
Asp Val Asn Thr Asn Asp Leu Val Asp Val Thr Asp Glu Phe Lys Asn
                485                 490                 495

aaa atg acg tat gga tca aat caa agt gtt aat ctt gat ttt ggt gat     1536
Lys Met Thr Tyr Gly Ser Asn Gln Ser Val Asn Leu Asp Phe Gly Asp
            500                 505                 510

att aca tca gca tat gtt gta atg gtt aat aca aaa ttc caa tat aca     1584
Ile Thr Ser Ala Tyr Val Val Met Val Asn Thr Lys Phe Gln Tyr Thr
        515                 520                 525

aat agc gaa agc cca aca ctt gtt caa atg gct act tta tct tca aca     1632
Asn Ser Glu Ser Pro Thr Leu Val Gln Met Ala Thr Leu Ser Ser Thr
    530                 535                 540

ggt aat aaa tcc gtt tct act ggc aat gct tta gga ttt act aat aac     1680
Gly Asn Lys Ser Val Ser Thr Gly Asn Ala Leu Gly Phe Thr Asn Asn
545                 550                 555                 560

caa agt ggc gga gct ggt caa gaa gta tat aaa att ggt aac tac gta     1728
Gln Ser Gly Gly Ala Gly Gln Glu Val Tyr Lys Ile Gly Asn Tyr Val
                565                 570                 575

tgg gaa gat act aat aaa aac ggt gtt caa gaa tta gga gaa aaa ggc     1776
Trp Glu Asp Thr Asn Lys Asn Gly Val Gln Glu Leu Gly Glu Lys Gly
            580                 585                 590

gtt ggc aat gta act gta act gta ttt gat aat aat aca aat aca aaa     1824
Val Gly Asn Val Thr Val Thr Val Phe Asp Asn Asn Thr Asn Thr Lys
        595                 600                 605

gta gga gaa gca gtt act aaa gaa gat ggg tca tac ttg att cca aac     1872
Val Gly Glu Ala Val Thr Lys Glu Asp Gly Ser Tyr Leu Ile Pro Asn
    610                 615                 620

tta cct aat gga gat tac cgt gta gaa ttt tca aac tta cca aaa ggt     1920
Leu Pro Asn Gly Asp Tyr Arg Val Glu Phe Ser Asn Leu Pro Lys Gly
625                 630                 635                 640
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tat gaa gta acc cct tca aaa caa ggt aat aac gaa gaa tta gat tca     1968
Tyr Glu Val Thr Pro Ser Lys Gln Gly Asn Asn Glu Glu Leu Asp Ser
                645                 650                 655

aac ggc tta tct tca gtt att aca gtt aat ggc aaa gat aac tta tct     2016
Asn Gly Leu Ser Ser Val Ile Thr Val Asn Gly Lys Asp Asn Leu Ser
            660                 665                 670

gca gac tta ggt att tac aaa cct aaa tac aac tta ggt gac tat gtc     2064
Ala Asp Leu Gly Ile Tyr Lys Pro Lys Tyr Asn Leu Gly Asp Tyr Val
        675                 680                 685

tgg gaa gat aca aat aaa aat ggt atc caa gac caa gat gaa aaa ggt     2112
Trp Glu Asp Thr Asn Lys Asn Gly Ile Gln Asp Gln Asp Glu Lys Gly
    690                 695                 700

ata tct ggc gta acg gta aca tta aaa gat gaa aac ggt aac gtg tta     2160
Ile Ser Gly Val Thr Val Thr Leu Lys Asp Glu Asn Gly Asn Val Leu
705                 710                 715                 720

aaa aca gtt aca aca gac gca gat ggc aaa tat aaa ttt act gat tta     2208
Lys Thr Val Thr Thr Asp Ala Asp Gly Lys Tyr Lys Phe Thr Asp Leu
                725                 730                 735

gat aat ggt aat tat aaa gtt gaa ttt act aca cca gaa ggc tat aca     2256
Asp Asn Gly Asn Tyr Lys Val Glu Phe Thr Thr Pro Glu Gly Tyr Thr
            740                 745                 750

ccg act aca gta aca tct ggt agc gac att gaa aaa gac tct aat ggt     2304
Pro Thr Thr Val Thr Ser Gly Ser Asp Ile Glu Lys Asp Ser Asn Gly
        755                 760                 765

tta aca aca aca ggt gtt att aat ggt gct gat aac atg aca tta gat     2352
Leu Thr Thr Thr Gly Val Ile Asn Gly Ala Asp Asn Met Thr Leu Asp
    770                 775                 780

agt gga ttc tac aaa aca cca aaa tat aat tta ggt aat tat gta tgg     2400
Ser Gly Phe Tyr Lys Thr Pro Lys Tyr Asn Leu Gly Asn Tyr Val Trp
785                 790                 795                 800

gaa gat aca aat aaa gat ggt aag cag gat tca act gaa aaa ggt att     2448
Glu Asp Thr Asn Lys Asp Gly Lys Gln Asp Ser Thr Glu Lys Gly Ile
                805                 810                 815

tca ggc gta aca gtt aca ttg aaa aat gaa aac ggt gaa gtt tta caa     2496
Ser Gly Val Thr Val Thr Leu Lys Asn Glu Asn Gly Glu Val Leu Gln
            820                 825                 830

aca act aaa aca gat aaa gat ggt aaa tat caa ttt act gga tta gaa     2544
Thr Thr Lys Thr Asp Lys Asp Gly Lys Tyr Gln Phe Thr Gly Leu Glu
        835                 840                 845

aat gga act tat aaa gtt gaa ttc gaa aca cca tca ggt tac aca cca     2592
Asn Gly Thr Tyr Lys Val Glu Phe Glu Thr Pro Ser Gly Tyr Thr Pro
    850                 855                 860

aca caa gta ggt tca gga act gat gaa ggt ata gat tca aat ggt aca     2640
Thr Gln Val Gly Ser Gly Thr Asp Glu Gly Ile Asp Ser Asn Gly Thr
865                 870                 875                 880

tca aca aca ggt gtc att aaa gat aaa gat aac gat act att gac tct     2688
Ser Thr Thr Gly Val Ile Lys Asp Lys Asp Asn Asp Thr Ile Asp Ser
                885                 890                 895

ggt ttc tac aaa ccg act tac aac tta ggt gac tat gta tgg gaa gat     2736
Gly Phe Tyr Lys Pro Thr Tyr Asn Leu Gly Asp Tyr Val Trp Glu Asp
            900                 905                 910

aca aat aaa aac ggt gtt caa gat aaa gat gaa aag ggt att tca ggt     2784
Thr Asn Lys Asn Gly Val Gln Asp Lys Asp Glu Lys Gly Ile Ser Gly
        915                 920                 925

gta aca gtt acg tta aaa gat gaa aac gac aaa gtt tta aaa aca gtt     2832
Val Thr Val Thr Leu Lys Asp Glu Asn Asp Lys Val Leu Lys Thr Val
    930                 935                 940
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aca aca gat gaa aat ggt aaa tat caa ttc act gat tta aac aat gga     2880
Thr Thr Asp Glu Asn Gly Lys Tyr Gln Phe Thr Asp Leu Asn Asn Gly
945                 950                 955                 960

act tat aaa gtt gaa ttc gag aca cca tca ggt tat aca cca act tca     2928
Thr Tyr Lys Val Glu Phe Glu Thr Pro Ser Gly Tyr Thr Pro Thr Ser
                965                 970                 975

gta act tct gga aat gat act gaa aaa gat tct aat ggt tta aca aca     2976
Val Thr Ser Gly Asn Asp Thr Glu Lys Asp Ser Asn Gly Leu Thr Thr
            980                 985                 990

aca ggt gtc att aaa gat gca gat aac atg aca tta gac agt ggt ttc     3024
Thr Gly Val Ile Lys Asp Ala Asp Asn Met Thr Leu Asp Ser Gly Phe
        995                 1000                1005

tat aaa aca cca aaa tat agt tta ggt gat tat gtt tgg tac gac agt     3072
Tyr Lys Thr Pro Lys Tyr Ser Leu Gly Asp Tyr Val Trp Tyr Asp Ser
    1010                1015                1020

aat aaa gac ggc aaa caa gat tca act gaa aaa ggt atc aaa gat gtt     3120
Asn Lys Asp Gly Lys Gln Asp Ser Thr Glu Lys Gly Ile Lys Asp Val
1025                1030                1035                1040

aaa gtt att tta tta aat gaa aaa ggc gaa gta att gga aca act aaa     3168
Lys Val Ile Leu Leu Asn Glu Lys Gly Glu Val Ile Gly Thr Thr Lys
                1045                1050                1055

aca gat gaa aat ggt aaa tac cgc ttt gat aat tta gat agc ggt aaa     3216
Thr Asp Glu Asn Gly Lys Tyr Arg Phe Asp Asn Leu Asp Ser Gly Lys
            1060                1065                1070

tac aaa gtt att ttt gaa aag cct act ggc tta aca caa aca ggt aca     3264
Tyr Lys Val Ile Phe Glu Lys Pro Thr Gly Leu Thr Gln Thr Gly Thr
        1075                1080                1085

aat aca act gaa gat gat aaa gat gcc gat ggt ggc gaa gtt gat gta     3312
Asn Thr Thr Glu Asp Asp Lys Asp Ala Asp Gly Gly Glu Val Asp Val
    1090                1095                1100

aca att acg gat cat gat gat ttc aca ctt gat aat ggc tac tac gaa     3360
Thr Ile Thr Asp His Asp Asp Phe Thr Leu Asp Asn Gly Tyr Tyr Glu
1105                1110                1115                1120

gaa gaa aca tca gat agc gac tca gat tcg gac agc gat tca gac tca     3408
Glu Glu Thr Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
                1125                1130                1135

gac agc gat tca gac tca gat agt gat tca gat tca gat agt gat tca     3456
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
            1140                1145                1150

gat tca gat agt gat tca gat tca gac agc gac tca gac tca gat agt     3504
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
        1155                1160                1165

gac tca gac tca gat agc gat tca gat tca gat agc gat tca gac tca     3552
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
    1170                1175                1180

gac agc gat tca gat tca gac agc gac tca gac tca gat agc gac tca     3600
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
1185                1190                1195                1200

gat tcg gac agc gat tca gac tca gat agc gac tca gac tca gac agc     3648
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
                1205                1210                1215

gat tca gac tca gat agc gac tca gac tca gat agc gat tca gat tca     3696
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
            1220                1225                1230

gac agc gat tca gat tca gac agt gat tca gat tca gac agc gac tca     3744
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
        1235                1240                1245
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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
            1300                1305                1310

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
    1330                1335                1340

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
                1365                1370                1375

ttc ggt cgt cgt aaa aaa caa aat aaa taa                             4158
Phe Gly Arg Arg Lys Lys Gln Asn Lys
            1380                1385


<210> SEQ ID NO 10
<211> LENGTH: 1385
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 10

Met Leu Asn Arg Glu Asn Lys Thr Ala Ile Thr Arg Lys Gly Met Val
1               5                   10                  15

Ser Asn Arg Leu Asn Lys Phe Ser Ile Arg Lys Tyr Thr Val Gly Thr
            20                  25                  30

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

Leu Glu Asn Lys Ser Val Val Asn Val Gln Pro Thr Asn Glu Glu Asn
                165                 170                 175
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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
            580                 585                 590

Val Gly Asn Val Thr Val Thr Val Phe Asp Asn Asn Thr Asn Thr Lys
        595                 600                 605

Val Gly Glu Ala Val Thr Lys Glu Asp Gly Ser Tyr Leu Ile Pro Asn
    610                 615                 620

Leu Pro Asn Gly Asp Tyr Arg Val Glu Phe Ser Asn Leu Pro Lys Gly
625                 630                 635                 640

Tyr Glu Val Thr Pro Ser Lys Gln Gly Asn Asn Glu Glu Leu Asp Ser
                645                 650                 655

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
                805                 810                 815

Ser Gly Val Thr Val Thr Leu Lys Asn Glu Asn Gly Glu Val Leu Gln
            820                 825                 830

Thr Thr Lys Thr Asp Lys Asp Gly Lys Tyr Gln Phe Thr Gly Leu Glu
        835                 840                 845

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
                885                 890                 895

Gly Phe Tyr Lys Pro Thr Tyr Asn Leu Gly Asp Tyr Val Trp Glu Asp
            900                 905                 910

Thr Asn Lys Asn Gly Val Gln Asp Lys Asp Glu Lys Gly Ile Ser Gly
        915                 920                 925

Val Thr Val Thr Leu Lys Asp Glu Asn Asp Lys Val Leu Lys Thr Val
    930                 935                 940

Thr Thr Asp Glu Asn Gly Lys Tyr Gln Phe Thr Asp Leu Asn Asn Gly
945                 950                 955                 960

Thr Tyr Lys Val Glu Phe Glu Thr Pro Ser Gly Tyr Thr Pro Thr Ser
                965                 970                 975

Val Thr Ser Gly Asn Asp Thr Glu Lys Asp Ser Asn Gly Leu Thr Thr
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           980                 985                 990

Thr Gly Val Ile Lys Asp Ala Asp Asn Met Thr Leu Asp Ser Gly Phe
        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

Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
        1155                1160                1165

Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
    1170                1175                1180

Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
1185                1190                1195                1200

Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
                1205                1210                1215

Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
            1220                1225                1230

Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
        1235                1240                1245

Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
    1250                1255                1260

Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
1265                1270                1275                1280

Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
                1285                1290                1295

Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
            1300                1305                1310

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

Ala Thr Leu Phe Gly Gly Leu Phe Ala Ala Leu Gly Ser Leu Leu Leu
                1365                1370                1375

Phe Gly Arg Arg Lys Lys Gln Asn Lys
            1380                1385
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<210> SEQ ID NO 11
<211> LENGTH: 3426
<212> TYPE: DNA
<213> ORGANISM: Staphylococcus sp.
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(3426)

<400> SEQUENCE: 11

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atg att aac agg gat aat aaa aag gca ata aca aaa aag ggt atg att   48
Met Ile Asn Arg Asp Asn Lys Lys Ala Ile Thr Lys Lys Gly Met Ile
1               5                  10                  15

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
50                  55                  60

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
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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
Gly Asp Gly Lys Asp Asn Val Ala Ala Ala His Asp Gly Lys Asp Ile
290                 295                 300

gaa tat gat aca gag ttt aca att gac aat aaa gtc aaa aaa ggc gat   960
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 ggt 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
405                 410                 415

gat tat caa gac cca atg gtt cat ggt 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

ggt agt caa gta gat gat tat gga aat att aaa cta gga aat ggt 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 ggt 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
530                 535                 540

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
545                 550                 555                 560
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caa ggt act agt atg aga aca act gat aaa tat ggt tat tat aat tat   1728
Gln Gly Thr Ser Met Arg Thr Thr Asp Lys Tyr Gly Tyr Tyr Asn Tyr
565                 570                 575

gca gga tat tca aac ttc atc gta act tct aat gac act ggc ggt ggc   1776
Ala Gly Tyr Ser Asn Phe Ile Val Thr Ser Asn Asp Thr Gly Gly Gly
580                 585                 590

gac ggt act gtt aaa cct gaa gaa aag tta tac aaa att ggt gac tat   1824
Asp Gly Thr Val Lys Pro Glu Glu Lys Leu Tyr Lys Ile Gly Asp Tyr
595                 600                 605

gta tgg gaa gac gtt gat aaa gac ggt gtc caa ggt aca gat tcg aaa   1872
Val Trp Glu Asp Val Asp Lys Asp Gly Val Gln Gly Thr Asp Ser Lys
610                 615                 620

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

gtt 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
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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

gga tac ttc gaa gaa gat aca tca gac agt gat tca gac tca gac agt   2832
Gly Tyr Phe Glu Glu Asp Thr Ser Asp Ser Asp Ser Asp Ser Asp Ser
930                 935                 940

gat tca gac tca gac agc gac tca gat tca gac agt gat tca gac tca   2880
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
945                 950                 955                 960

gat agc gat tca gat tca gac agc gac tca gac tca gat agc gac tca   2928
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
965                 970                 975

gac tca gac agc gac tca gac tca gat agc gac tca gat tcg gac agc   2976
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
980                 985                 990

gat tca gac tca gat agc gac tca gat tca gac agc gat tca gac tca   3024
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
995                1000                1005

gat agc gac tca gat tca gac agt gac tca gac tca gat agc gac tca   3072
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
1010                1015                1020

gac tca gac agt gac tca gac tca gac agc gat tca gat tca gat agc   3120
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
1025               1030                1035                1040

gac tca gat tcg gac agt gat tca gac tca gat agc gac tca gat tca   3168
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
1045                1050                1055

gac agc gac tca gac tca gat agc gac tca gac tca gac agt gat tca   3216
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
1060                1065                1070

gac tca gat agc gat tcg gac tcg gat gca gga aaa cat aca cct gtt   3264
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ala Gly Lys His Thr Pro Val
1075                1080                1085

aaa cca atg agt act act aaa gac cat cac aat aaa gca aaa gca tta   3312
Lys Pro Met Ser Thr Thr Lys Asp His His Asn Lys Ala Lys Ala Leu
1090                1095                1100

cca gaa aca ggt agt gaa aat aac ggc tca aat aac gca acg tta ttt   3360
Pro Glu Thr Gly Ser Glu Asn Asn Gly Ser Asn Asn Ala Thr Leu Phe
1105               1110                1115                1120

ggt gga tta ttt gca gca tta ggt tca tta ttg tta ttc ggt cgt cgc   3408
Gly Gly Leu Phe Ala Ala Leu Gly Ser Leu Leu Leu Phe Gly Arg Arg
1125                1130                1135

aaa aaa caa aac aaa taa                                          3426
Lys Lys Gln Asn Lys
1140
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<210> SEQ ID NO 12
<211> LENGTH: 1141
<212> TYPE: PRT

-continued

<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 12

```
Met Ile Asn Arg Asp Asn Lys Lys Ala Ile Thr Lys Lys Gly Met Ile
1               5                  10                  15

Ser Asn Arg Leu Asn Lys Phe Ser Ile Arg Lys Tyr Thr Val Gly Thr
            20                  25                  30

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

Asn Ser Thr Thr Glu Asn Asp Ser Thr Asn Pro Ile Lys Lys Glu Thr
                85                  90                  95

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

Thr Gln Gln Gln Gln Asn Asn Val Thr Ala Thr Thr Glu Thr Lys Pro
        115                 120                 125

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

Thr Glu Asp Thr Ser Val Ile Leu Glu Glu Lys Lys Ala Pro Asn Tyr
145                 150                 155                 160

Thr Asn Asn Asp Val Thr Thr Lys Pro Ser Thr Ser Glu Ile Gln Thr
                165                 170                 175

Lys Pro Thr Thr Pro Gln Glu Ser Thr Asn Ile Glu Asn Ser Gln Pro
            180                 185                 190

Gln Pro Thr Pro Ser Lys Val Asp Asn Gln Val Thr Asp Ala Thr Asn
        195                 200                 205

Pro Lys Glu Pro Val Asn Val Ser Lys Glu Glu Leu Lys Asn Asn Pro
    210                 215                 220

Glu Lys Leu Lys Glu Leu Val Arg Asn Asp Asn Asn Thr Asp Arg Ser
225                 230                 235                 240

Thr Lys Pro Val Ala Thr Ala Pro Thr Ser Val Ala Pro Lys Arg Leu
                245                 250                 255

Asn Ala Lys Met Arg Phe Ala Val Ala Gln Pro Ala Ala Val Ala Ser
            260                 265                 270

Asn Asn Val Asn Asp Leu Ile Thr Val Thr Lys Gln Thr Ile Lys Val
        275                 280                 285

Gly Asp Gly Lys Asp Asn Val Ala Ala Ala His Asp Gly Lys Asp Ile
    290                 295                 300

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

Thr Met Thr Ile Asn Tyr Asp Lys Asn Val Ile Pro Ser Asp Leu Thr
                325                 330                 335

Asp Lys Asn Asp Pro Ile Asp Ile Thr Asp Pro Ser Gly Glu Val Ile
            340                 345                 350

Ala Lys Gly Thr Phe Asp Lys Ala Thr Lys Gln Ile Thr Tyr Thr Phe
        355                 360                 365

Thr Asp Tyr Val Asp Lys Tyr Glu Asp Ile Lys Ala Arg Leu Thr Leu
    370                 375                 380
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Tyr Ser Tyr Ile Asp Lys Gln Ala Val Pro Asn Glu Thr Ser Leu Asn
385                 390                 395                 400

Leu Thr Phe Ala Thr Ala Gly Lys Glu Thr Ser Gln Asn Val Ser Val
                405                 410                 415

Asp Tyr Gln Asp Pro Met Val His Gly Asp Ser Asn Ile Gln Ser Ile
            420                 425                 430

Phe Thr Lys Leu Asp Glu Asn Lys Gln Thr Ile Glu Gln Gln Ile Tyr
        435                 440                 445

Val Asn Pro Leu Lys Lys Thr Ala Thr Asn Thr Lys Val Asp Ile Ala
    450                 455                 460

Gly Ser Gln Val Asp Asp Tyr Gly Asn Ile Lys Leu Gly Asn Gly Ser
465                 470                 475                 480

Thr Ile Ile Asp Gln Asn Thr Glu Ile Lys Val Tyr Lys Val Asn Pro
                485                 490                 495

Asn Gln Gln Leu Pro Gln Ser Asn Arg Ile Tyr Asp Phe Ser Gln Tyr
            500                 505                 510

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
                645                 650                 655

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
            740                 745                 750

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
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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                 860

Gly Thr Thr Lys Thr Asp Glu Asn Gly Lys Tyr Arg Phe Asp Asn Leu
865                 870                 875                 880

Asp Ser Gly Lys Tyr Lys Val Ile Phe Glu Lys Pro Ala Gly Leu Thr
                885                 890                 895

Gln Thr Val Thr Asn Thr Thr Glu Asp Asp Lys Asp Ala Asp Gly Gly
            900                 905                 910

Glu Val Asp Val Thr Ile Thr Asp His Asp Asp Phe Thr Leu Asp Asn
        915                 920                 925

Gly Tyr Phe Glu Glu Asp Thr Ser Asp Ser Asp Ser Asp Ser Asp Ser
    930                 935                 940

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
            1060                1065                1070

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
                1125                1130                1135

Lys Lys Gln Asn Lys
            1140


<210> SEQ ID NO 13
<211> LENGTH: 1052
<212> TYPE: DNA
<213> ORGANISM: Staphylococcus sp.
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(1050)
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<400> SEQUENCE: 13

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atg aca aaa cat tat tta aac agt aag tat caa tca gaa caa cgt tca   48
Met Thr Lys His Tyr Leu Asn Ser Lys Tyr Gln Ser Glu Gln Arg Ser
1               5                  10                  15

tca gct atg aaa aag att aca atg ggt aca gca tct atc att tta ggt   96
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   144
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 gtt tct caa gca   192
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   240
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 ggt aaa gta att aaa   288
Lys Ser His Met Asp Asp Tyr Met Gln His Pro Gly Lys Val Ile Lys
85                  90                  95

caa aat aat aaa tat tat ttc caa acc gtg tta aac aat gca tca ttc   336
Gln Asn Asn Lys Tyr Tyr Phe Gln Thr Val Leu Asn Asn Ala Ser Phe
100                 105                 110

tgg 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
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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
Gly Ser Leu Ser Leu Leu Leu Phe Lys Arg Lys Glu Ser Lys
340                 345                 350


<210> SEQ ID NO 14
<211> LENGTH: 350
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 14

Met Thr Lys His Tyr Leu Asn Ser Lys Tyr Gln Ser Glu Gln Arg Ser
1               5                   10                  15

Ser Ala Met Lys Lys Ile Thr Met Gly Thr Ala Ser Ile Ile Leu Gly
            20                  25                  30

Ser Leu Val Tyr Ile Gly Ala Asp Ser Gln Gln Val Asn Ala Ala Thr
        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
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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 15
<211> LENGTH: 1938
<212> TYPE: DNA
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 15

ttagttttta cgttttctag gtaatacgaa tgcaacgatg ctacttaaag ctagtaatgc 60

cattaatggt aatgtcatat ctttatttga ttcttcacca gtttgtggta atgattttgc 120

tttatttttct tgtgtatttt tattgttttg gctttgagtg tgtccatcat ttgtgttttt 180

aatgtttgct ttttgtaatg gagcactatc ttttgcttcg ctagaacctg ctgaagtttg 240

aacaacatct tttgttgttt ttgatgaagc agttgttggt tttgcaacat tttgagtcgt 300

agatactacc ttagttggag ttgtactact tgattctact tcacctttag ttggttttgt 360

agcaggcgtt ttgtctttac ctgactcact agatgcgtca ttttcttttt caacacttgg 420

taattgttta ttgtcatctt tttggctgtc ttgtttttgt gattcttttt caacaggtga 480

tggtgttggt ttgctaggcg tagctggagt agcttccttc ttagctgagt tatcttgttg 540

ttctttttttg ttagatttat cggtattggc ttttgtaaat gcttctttat caacgattct 600

gacatggtat tgtccatcat aatcaatcgt ttttacgtga actttaacga tagcatcata 660

tagagtttta ccttcaacat atgggaaaat aattgttcta gtattatttt tagcatcttt 720

gcttatagtt ctaacacgtt gaccttcaac catgaaatct ttccagtaat cgtcattagt 780

agtttccatg accatatatt ttttgccgtt aagcatacct gttttaatag ggtgtttaac 840

aaaagtatcc atcatagatt cgttattctc aacactttca taaacaacat attttgtatc 900

ttgtaaatca gtcatttttt catttgttgg ttgtacattt tggaattcag taatagctga 960

tttcacttgc tcatctaaag ctttctttgt atcctctaat ttcttcttgt actcagcctt 1020

taatttttca ggaagtttat cttgaatttt atttaattca taaacttgtc tttctagtgt 1080

tttcgctttt ttatatggcg ctaataattt ttcagcttta taatcttctt cagttttgaa 1140

tttatctgca ctgttataaa ttggttgtgc gaattccatt aatgtgtaat cgtatttttc 1200

ttctttgtta ttgaagtgag ttgaacttac aattttaacg gcttttgttc catttgaaac 1260

agagaagcga atgtaagcgt aatctttaac agtatcgtat gatactaatt taattggcaa 1320

ctttttgtca ccttcataaa cttcaaattt tctccaaaat tgacctgatt gtaatcctaa 1380

ttcaatttct ggttttgaat cagtgaaaat aactctagca ggtttaacag agctggcata 1440

atgataaaat tgttgctcac cattttcttt tttcatttca aaatcaattg gacgagagtt 1500

tggtgcgcta tgatctttat cttttattgc agggttttta atcgcttctc taagttcctg 1560

attcaaaata ggatatgtat tgttagtggc ttttgctgct ggtttaactg cttttgtttc 1620

cttaggggct ttaacttctt taacttcttt agcttctttt gtttcagaag taggggcctc 1680

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aacttcttta ttagatactg agacagcatt agctactggt ttagtttctg gagctttttc 1740

agatgttgtt gttggacttg caactgcttc agtttttggt tgtgcttctg tatttgtacc 1800

acctgtttct tcagctgctg cttgtgcttc gccatttgac attaataata aaagtgtact 1860

aatcgctaca gatgcaacgc ctagtgatga ctttctaatt gaataaaatg atttaaattc 1920

tttttgctgt ttgttcat 1938

<210> SEQ ID NO 16
<211> LENGTH: 645
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 16

Met Asn Lys Gln Gln Lys Glu Phe Lys Ser Phe Tyr Ser Ile Arg Lys
1 5 10 15

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

Met Ser Asn Gly Glu Ala Gln Ala 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

Lys Glu Val Lys Glu Val Lys Ala Pro Lys Glu Thr Lys Ala Val Lys
100 105 110

Pro Ala Ala Lys Ala Thr Asn Asn Thr Tyr Pro Ile Leu Asn Gln Glu
115 120 125

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

Ala Pro Asn Ser Arg Pro Ile Asp Phe Glu Met Lys Lys Glu Asn Gly
145 150 155 160

Glu Gln Gln Phe Tyr His Tyr Ala Ser Ser Val Lys Pro Ala Arg Val
165 170 175

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

Gln Phe Trp Arg Lys Phe Glu Val Tyr Glu Gly Asp Lys Lys Leu Pro
195 200 205

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

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

His Phe Asn Asn Lys Glu Glu Lys Tyr Asp Tyr Thr Leu Met Glu Phe
245 250 255

Ala Gln Pro Ile Tyr Asn Ser Ala Asp Lys Phe Lys Thr Glu Glu Asp
260 265 270

Tyr Lys Ala Glu Lys Leu Leu Ala Pro Tyr Lys Lys Ala Lys Thr Leu
275 280 285

Glu Arg Gln Val Tyr Glu Leu Asn Lys Ile Gln Asp Lys Leu Pro Glu
290 295 300

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Lys Leu Lys Ala Glu Tyr Lys Lys Lys Leu Glu Asp Thr Lys Lys Ala
305                 310                 315                 320

Leu Asp Glu Gln Val Lys Ser Ala Ile Thr Glu Phe Gln Asn Val Gln
                325                 330                 335

Pro Thr Asn Glu Lys Met Thr Asp Leu Gln Asp Thr Lys Tyr Val Val
            340                 345                 350

Tyr Glu Ser Val Glu Asn Asn Glu Ser Met Met Asp Thr Phe Val Lys
        355                 360                 365

His Pro Ile Lys Thr Gly Met Leu Asn Gly Lys Lys Tyr Met Val Met
    370                 375                 380

Glu Thr Thr Asn Asp Asp Tyr Trp Lys Asp Phe Met Val Glu Gly Gln
385                 390                 395                 400

Arg Val Arg Thr Ile Ser Lys Asp Ala Lys Asn Asn Thr Arg Thr Ile
                405                 410                 415

Ile Phe Pro Tyr Val Glu Gly Lys Thr Leu Tyr Asp Ala Ile Val Lys
            420                 425                 430

Val His Val Lys Thr Ile Asp Tyr Asp Gly Gln Tyr His Val Arg Ile
        435                 440                 445

Val Asp Lys Glu Ala Phe Thr Lys Ala Asn Thr Asp Lys Ser Asn Lys
    450                 455                 460

Lys Glu Gln Gln Asp Asn Ser Ala Lys Lys Glu Ala Thr Pro Ala Thr
465                 470                 475                 480

Pro Ser Lys Pro Thr Pro Ser Pro Val Glu Lys Glu Ser Gln Lys Gln
                485                 490                 495

Asp Ser Gln Lys Asp Asp Asn Lys Gln Leu Pro Ser Val Glu Lys Glu
            500                 505                 510

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 17
<211> LENGTH: 1353
<212> TYPE: DNA
<213> ORGANISM: Staphylococcus sp.
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(1353)

<400> SEQUENCE: 17
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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
Glu Gln Gln Asn Ala Phe Tyr Glu Ile Leu Asn Met Pro Asn Leu Asn
165                 170                 175

gaa gaa caa cgc aat ggt 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
225                 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                 250                 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                 265                 270

aac aaa aaa cct ggt 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
275                 280                 285

ggc aac aag cct ggt aaa gaa gac aac aaa aaa cct ggt aaa gaa gac   912
Gly Asn Lys Pro Gly Lys Glu Asp Asn Lys Lys Pro Gly Lys Glu Asp
290                 295                 300
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ggc aac aag cct ggt 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
305                 310                 315                 320

ggc aac aag cct ggt aaa gaa gac aac aac aag cct ggt aaa gaa gac   1008
Gly Asn Lys Pro Gly Lys Glu Asp Asn Asn Lys Pro Gly Lys Glu Asp
325                 330                 335

ggc aac aag cct ggt aaa gaa gac ggc aac aaa cct ggt aaa gaa gac   1056
Gly Asn Lys Pro Gly Lys Glu Asp Gly Asn Lys Pro Gly Lys Glu Asp
340                 345                 350

ggc aac gga gta cat gtc gtt aaa cct ggt gat aca gta aat gac att   1104
Gly Asn Gly Val His Val Val Lys Pro Gly Asp Thr Val Asn Asp Ile
355                 360                 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                 375                 380

tta gct gat aaa aac atg atc aaa cct ggt caa gaa ctt gtt gtt gat   1200
Leu Ala Asp Lys Asn Met Ile Lys Pro Gly Gln Glu Leu Val Val Asp
385                 390                 395                 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                 410                 415

cca gaa act ggt gaa gaa aat cca ttc atc ggt aca act gta ttt ggt   1296
Pro Glu Thr Gly Glu Glu Asn Pro Phe Ile Gly Thr Thr Val Phe Gly
420                 425                 430

gga tta tca tta gcc tta ggt 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                 440                 445

gaa cta taa                                                     1353
Glu Leu
450
```

<210> SEQ ID NO 18
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 18

```
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
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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

Lys Lys Gln Pro Ala Asn His Ala Asp Ala Asn Lys Ala Gln Ala Leu
                405                 410                 415

Pro Glu Thr Gly Glu Glu Asn Pro Phe Ile Gly Thr Thr Val Phe Gly
            420                 425                 430

Gly Leu Ser Leu Ala Leu Gly Ala Ala Leu Leu Ala Gly Arg Arg Arg
        435                 440                 445

Glu Leu
    450


<210> SEQ ID NO 19
<211> LENGTH: 2634
<212> TYPE: DNA
<213> ORGANISM: Staphylococcus sp.
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(2634)

<400> SEQUENCE: 19

ttg aaa aaa aga att gat tat ttg tcg aat aag cag aat aag tat tcg   48
Met Lys Lys Arg Ile Asp Tyr Leu Ser Asn Lys Gln Asn Lys Tyr Ser
1               5                  10                  15

att aga cgt ttt aca gta ggt acc aca tca gta ata gta ggg gca act   96
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Ile Arg Arg Phe Thr Val Gly Thr Thr Ser Val Ile Val Gly Ala Thr
20                  25                  30

ata cta ttt ggg ata ggc aat cat caa gca caa gct tca gaa caa tcg   144
Ile Leu Phe Gly Ile Gly Asn His Gln Ala Gln Ala Ser Glu Gln Ser
35                  40                  45

aac gat aca acg caa tct tcg aaa aat aat gca agt gca gat tcc gaa   192
Asn Asp Thr Thr Gln Ser Ser Lys Asn Asn Ala Ser Ala Asp Ser Glu
50                  55                  60

aaa aac aat atg ata gaa aca cct caa tta aat aca acg gct aat gat   240
Lys Asn Asn Met Ile Glu Thr Pro Gln Leu Asn Thr Thr Ala Asn Asp
65                  70                  75                  80

aca tct gat att agt gca aac aca aac agt gcg aat gta gat agc aca   288
Thr Ser Asp Ile Ser Ala Asn Thr Asn Ser Ala Asn Val Asp Ser Thr
85                  90                  95

aca aaa cca atg tct aca caa acg agc aat acc act aca aca gag cca   336
Thr Lys Pro Met Ser Thr Gln Thr Ser Asn Thr Thr Thr Thr Glu Pro
100                 105                 110

gct tca aca aat gaa aca cct caa ccg acg gca att aaa aat caa gca   384
Ala Ser Thr Asn Glu Thr Pro Gln Pro Thr Ala Ile Lys Asn Gln Ala
115                 120                 125

act gct gca aaa atg caa gat caa act gtt cct caa gaa gca aat tct   432
Thr Ala Ala Lys Met Gln Asp Gln Thr Val Pro Gln Glu Ala Asn Ser
130                 135                 140

caa gta gat aat aaa aca acg aat gat gct aat agc ata gca aca aac   480
Gln Val Asp Asn Lys Thr Thr Asn Asp Ala Asn Ser Ile Ala Thr Asn
145                 150                 155                 160

agt gag ctt aaa aat tct caa aca tta gat tta cca caa tca tca cca   528
Ser Glu Leu Lys Asn Ser Gln Thr Leu Asp Leu Pro Gln Ser Ser Pro
165                 170                 175

caa acg att tcc aat gcg caa gga act agt aaa cca agt gtt aga acg   576
Gln Thr Ile Ser Asn Ala Gln Gly Thr Ser Lys Pro Ser Val Arg Thr
180                 185                 190

aga gct gta cgt agt tta gct gtt gct gaa ccg gta gta aat gct gct   624
Arg Ala Val Arg Ser Leu Ala Val Ala Glu Pro Val Val Asn Ala Ala
195                 200                 205

gat gct aaa ggt aca aat gta aat gat aaa gtt acg gca agt aat ttc   672
Asp Ala Lys Gly Thr Asn Val Asn Asp Lys Val Thr Ala Ser Asn Phe
210                 215                 220

aag tta gaa aag act aca ttt gac cct aat caa agt ggt aac aca ttt   720
Lys Leu Glu Lys Thr Thr Phe Asp Pro Asn Gln Ser Gly Asn Thr Phe
225                 230                 235                 240

atg gcg gca aat ttt aca gtg aca gat aaa gtg aaa tca ggg gat tat   768
Met Ala Ala Asn Phe Thr Val Thr Asp Lys Val Lys Ser Gly Asp Tyr
245                 250                 255

ttt aca gcg aag tta cca gat agt tta act ggt aat gga gac gtg gat   816
Phe Thr Ala Lys Leu Pro Asp Ser Leu Thr Gly Asn Gly Asp Val Asp
260                 265                 270

tat tct aat tca aat aat acg atg cca att gca gac att aaa agt acg   864
Tyr Ser Asn Ser Asn Asn Thr Met Pro Ile Ala Asp Ile Lys Ser Thr
275                 280                 285

aat ggc gat gtt gta gct aaa gca aca tat gat atc ttg act aag acg   912
Asn Gly Asp Val Val Ala Lys Ala Thr Tyr Asp Ile Leu Thr Lys Thr
290                 295                 300

tat aca ttt gtc ttt aca gat tat gta aat aat aaa gaa aat att aac   960
Tyr Thr Phe Val Phe Thr Asp Tyr Val Asn Asn Lys Glu Asn Ile Asn
305                 310                 315                 320

gga caa ttt tca tta cct tta ttt aca gac cga gca aag gca cct aaa   1008
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Gly Gln Phe Ser Leu Pro Leu Phe Thr Asp Arg Ala Lys Ala Pro Lys
325                 330                 335

tca gga aca tat gat gcg aat att aat att gcg gat gaa atg ttt aat   1056
Ser Gly Thr Tyr Asp Ala Asn Ile Asn Ile Ala Asp Glu Met Phe Asn
340                 345                 350

aat aaa att act tat aac tat agt tcg cca att gca gga att gat aaa   1104
Asn Lys Ile Thr Tyr Asn Tyr Ser Ser Pro Ile Ala Gly Ile Asp Lys
355                 360                 365

cca aat ggc gcg aac att tct tct caa att att ggt gta gat aca gct   1152
Pro Asn Gly Ala Asn Ile Ser Ser Gln Ile Ile Gly Val Asp Thr Ala
370                 375                 380

tca ggt caa aac aca tac aag caa aca gta ttt gtt aac cct aag caa   1200
Ser Gly Gln Asn Thr Tyr Lys Gln Thr Val Phe Val Asn Pro Lys Gln
385                 390                 395                 400

cga gtt tta ggt aat acg tgg gtg tat att aaa ggc tac caa gat aaa   1248
Arg Val Leu Gly Asn Thr Trp Val Tyr Ile Lys Gly Tyr Gln Asp Lys
405                 410                 415

atc gaa gaa agt agc ggt aaa gta agt gct aca gat aca aaa ctg aga   1296
Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
420                 425                 430

att ttt gaa gtg aat gat aca tct aaa tta tca gat agc tac tat gca   1344
Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
435                 440                 445

gat cca aat gac tct aac ctt aaa gaa gta aca gac caa ttt aaa aat   1392
Asp Pro Asn Asp Ser Asn Leu Lys Glu Val Thr Asp Gln Phe Lys Asn
450                 455                 460

aga atc tat tat gag cat cca aat gta gct agt att aaa ttt ggt gat   1440
Arg Ile Tyr Tyr Glu His Pro Asn Val Ala Ser Ile Lys Phe Gly Asp
465                 470                 475                 480

att act aaa aca tat gta gta tta gta gaa ggg cat tac gac aat aca   1488
Ile Thr Lys Thr Tyr Val Val Leu Val Glu Gly His Tyr Asp Asn Thr
485                 490                 495

ggt aag aac tta aaa act cag gtt att caa gaa aat gtt gat cct gta   1536
Gly Lys Asn Leu Lys Thr Gln Val Ile Gln Glu Asn Val Asp Pro Val
500                 505                 510

aca aat aga gac tac agt att ttc ggt tgg aat aat gag aat gtt gta   1584
Thr Asn Arg Asp Tyr Ser Ile Phe Gly Trp Asn Asn Glu Asn Val Val
515                 520                 525

cgt tat ggt ggt gga agt gct gat ggt gat tca gca gta aat ccg aaa   1632
Arg Tyr Gly Gly Gly Ser Ala Asp Gly Asp Ser Ala Val Asn Pro Lys
530                 535                 540

gac cca act cca ggg ccg ccg gtt gac cca gaa cca agt cca gac cca   1680
Asp Pro Thr Pro Gly Pro Pro Val Asp Pro Glu Pro Ser Pro Asp Pro
545                 550                 555                 560

gaa cca gaa cca acg cca gat cca gaa cca agt cca gac cca gaa ccg   1728
Glu Pro Glu Pro Thr Pro Asp Pro Glu Pro Ser Pro Asp Pro Glu Pro
565                 570                 575

gaa cca agc cca gac ccg gat ccg gat tcg gat tca gac agt gac tca   1776
Glu Pro Ser Pro Asp Pro Asp Pro Asp Ser Asp Ser Asp Ser Asp Ser
580                 585                 590

ggc tca gac agc gac tca ggt tca gat agc gac tca gaa tca gat agc   1824
Gly Ser Asp Ser Asp Ser Gly Ser Asp Ser Asp Ser Glu Ser Asp Ser
595                 600                 605

gat tcg gat tca gac agt gat tca gat tca gac agc gac tca gaa tca   1872
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Glu Ser
610                 615                 620

gat agc gat tca gaa tca gat agc gac tca gat tca gat agc gat tca   1920
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Asp Ser Asp Ser Glu Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
625                 630                 635                 640

gat tca gat agc gat tca gaa tca gat agc gat tcg gat tca gac agt   1968
Asp Ser Asp Ser Asp Ser Glu Ser Asp Ser Asp Ser Asp Ser Asp Ser
645                 650                 655

gat tca gat tca gac agc gac tca gaa tca gat agc gac tca gaa tca   2016
Asp Ser Asp Ser Asp Ser Asp Ser Glu Ser Asp Ser Asp Ser Glu Ser
660                 665                 670

gat agt gag tca gat tca gac agt gac tcg gac tca gac agt gat tca   2064
Asp Ser Glu Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
675                 680                 685

gac tca gat agc gat tca gac tca gat agc gat tca gac tca gac agc   2112
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
690                 695                 700

gat tca gat tca gac agc gac tca gaa tca gac agc gac tca gac tca   2160
Asp Ser Asp Ser Asp Ser Asp Ser Glu Ser Asp Ser Asp Ser Asp Ser
705                 710                 715                 720

gat agc gac tca gac tca gac agc gac tca gat tca gat agc gat tca   2208
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
725                 730                 735

gac tca gac agc gac tca gac tca gac agc gac tca gac tca gat agc   2256
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
740                 745                 750

gat tca gac tca gac agc gac tca gat tca gat agc gat tcg gac tca   2304
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
755                 760                 765

gac agc gat tca gat tca gac agc gac tca gac tcg gat agc gat tca   2352
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
770                 775                 780

gat tca gac agc gac tca gac tcg gat agc gac tcg gat tca gat agt   2400
Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
785                 790                 795                 800

gac tcc gat tca aga gtt aca cca cca aat aat gaa cag aaa gca cca   2448
Asp Ser Asp Ser Arg Val Thr Pro Pro Asn Asn Glu Gln Lys Ala Pro
805                 810                 815

tca aat cct aaa ggt gaa gta aac cat tct aat aag gta tca aaa caa   2496
Ser Asn Pro Lys Gly Glu Val Asn His Ser Asn Lys Val Ser Lys Gln
820                 825                 830

cac aaa act gat gct tta cca gaa aca gga gat aag agc gaa aac aca   2544
His Lys Thr Asp Ala Leu Pro Glu Thr Gly Asp Lys Ser Glu Asn Thr
835                 840                 845

aat gca act tta ttt ggt gca atg atg gca tta tta gga tca tta cta   2592
Asn Ala Thr Leu Phe Gly Ala Met Met Ala Leu Leu Gly Ser Leu Leu
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 20
<211> LENGTH: 877
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 20

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Ile Glu Glu Ser Ser Gly Lys Val Ser Ala Thr Asp Thr Lys Leu Arg
            420                 425                 430
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```
Ile Phe Glu Val Asn Asp Thr Ser Lys Leu Ser Asp Ser Tyr Tyr Ala
        435                 440                 445

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

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

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

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

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

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

Asp Pro Thr Pro Gly Pro Pro Val Asp Pro Glu Pro Ser Pro Asp Pro
545                 550                 555                 560

Glu Pro Glu Pro Thr Pro Asp Pro Glu Pro Ser Pro Asp Pro Glu Pro
                565                 570                 575

Glu Pro Ser Pro Asp Pro Asp Pro Asp Ser Asp Ser Asp Ser Asp Ser
            580                 585                 590

Gly Ser Asp Ser Asp Ser Gly Ser Asp Ser Asp Ser Glu Ser Asp Ser
        595                 600                 605

Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Glu Ser
    610                 615                 620

Asp Ser Asp Ser Glu Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
625                 630                 635                 640

Asp Ser Asp Ser Asp Ser Glu Ser Asp Ser Asp Ser Asp Ser Asp Ser
                645                 650                 655

Asp Ser Asp Ser Asp Ser Asp Ser Glu Ser Asp Ser Asp Ser Glu Ser
            660                 665                 670

Asp Ser Glu Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
        675                 680                 685

Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser
    690                 695                 700

Asp Ser Asp Ser Asp Ser Asp Ser Glu Ser Asp Ser Asp 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 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
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        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 21
<211> LENGTH: 684
<212> TYPE: DNA
<213> ORGANISM: Staphylococcus sp.
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(684)

<400> SEQUENCE: 21

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

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
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Asn Val Glu
225


<210> SEQ ID NO 22
<211> LENGTH: 227
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 22

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


<210> SEQ ID NO 23
<211> LENGTH: 1908
<212> TYPE: DNA
<213> ORGANISM: Staphylococcus sp.
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(1908)

<400> SEQUENCE: 23

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
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
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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 ggc 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
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
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Ile Leu Glu Ser Ile Phe Asn Lys Asp Glu Ala Asp Lys Ile Leu Lys
340                 345                 350

gat ata cgt gtt gat ggt 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 tgg 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 ggt 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 ggt aaa ggt 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

ggt aat gta tct ttg cct aaa gcg ggg gaa acg ata aaa gaa cat tgg   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 ggt gca atg ggt gta cta atg att tgg   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 24
<211> LENGTH: 635
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 24

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

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Thr Arg His Ile Asp Gln Leu Ser Leu Thr Thr Ser Asp Asp Leu Leu
    370                 375                 380

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 25
<211> LENGTH: 2862
<212> TYPE: DNA
<213> ORGANISM: Staphylococcus sp.
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(2862)

<400> SEQUENCE: 25

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
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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

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
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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
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
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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
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
945                 950
```

<210> SEQ ID NO 26

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<211> LENGTH: 953
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 26

Met Asn Asn Lys Lys Thr Ala Thr Asn Arg Lys Gly Met Ile Pro Asn
1 5 10 15

Arg Leu Asn Lys Phe Ser Ile Arg Lys Tyr Ser Val Gly Thr Ala Ser
            20 25 30

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

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

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    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

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 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
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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
                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
    930                 935                 940

Phe Gly Arg Arg Lys Lys Gln Asn Lys
945                 950


<210> SEQ ID NO 27
<211> LENGTH: 2970
<212> TYPE: DNA
<213> ORGANISM: Staphylococcus sp.
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(2970)

<400> SEQUENCE: 27

atg aat atg aag aaa aaa gaa aaa cac gca att cgg aaa aaa tcg att   48
Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1               5                  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
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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
210                 215                 220

gca ccg gca gct ggc aca gat att acg aat cag ttg aca gat gtg aaa   720
Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asp Val Lys
225                 230                 235                 240

gtt act att gac tct ggt acg act gtg tat ccg cac caa gca ggt tat   768
Val Thr Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr
245                 250                 255

gtc aaa ctg aat tat ggt ttt tca gtg cct aat tct gct gtt aaa ggt   816
Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly
260                 265                 270

gac aca ttc aaa ata act gta cct aaa gaa tta aac tta aat ggt gta   864
Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
275                 280                 285

act tca act gct aaa gtg cca cca att atg gct gga gat caa gta ttg   912
Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
290                 295                 300

gca aat ggt gta atc gat agt gat ggt aat gtt att tat aca ttt aca   960
Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305                 310                 315                 320

gac tat gtt gat aat aaa gaa aat gta aca gct aat att act atg cca   1008
Asp Tyr Val Asp Asn Lys Glu Asn Val Thr Ala Asn Ile Thr Met Pro
325                 330                 335

gct tat att gac cct gaa aat gtt aca aag aca ggt aat gtg aca ttg   1056
Ala Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu
340                 345                 350

aca act ggc ata gga acc aat act gct agt aag aca gta tta atc gac   1104
Thr Thr Gly Ile Gly Thr Asn Thr Ala Ser Lys Thr Val Leu Ile Asp
355                 360                 365

tat gag aaa tat gga caa ttc cat aat tta tca att aaa ggt acg att   1152
Tyr Glu Lys Tyr Gly Gln Phe His Asn Leu Ser Ile Lys Gly Thr Ile
370                 375                 380

gat caa atc gat aaa aca aat aat acg tat cgc caa aca att tat gtc   1200
Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385                 390                 395                 400

aat cca agc gga gat aac gtt gtg tta cct gcc tta aca ggt aat tta   1248
Asn Pro Ser Gly Asp Asn Val Val Leu Pro Ala Leu Thr Gly Asn Leu
405                 410                 415

att cct aat aca aag agt aat gcg tta ata gat gca aaa aac act gat   1296
Ile Pro Asn Thr Lys Ser Asn Ala Leu Ile Asp Ala Lys Asn Thr Asp
420                 425                 430
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att aaa gtt tat aga gtc gat aat gct aat gat tta tct gaa agt tat   1344
Ile Lys Val Tyr Arg Val Asp Asn Ala Asn Asp Leu Ser Glu Ser Tyr
435                 440                 445

tat gtg aat cct agc gat ttt gaa gat gta act aat caa gtt aga att   1392
Tyr Val Asn Pro Ser Asp Phe Glu Asp Val Thr Asn Gln Val Arg Ile
450                 455                 460

tca ttt cca aat gct aat caa tac aaa gta gaa ttt cct acg gac gat   1440
Ser Phe Pro Asn Ala Asn Gln Tyr Lys Val Glu Phe Pro Thr Asp Asp
465                 470                 475                 480

gac caa att aca aca ccg tat att gta gtt gtt aat ggc cat att gat   1488
Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Val Asn Gly His Ile Asp
485                 490                 495

cct gct agt aca ggt gat tta gca cta cgt tcg aca ttt tat ggt tat   1536
Pro Ala Ser Thr Gly Asp Leu Ala Leu Arg Ser Thr Phe Tyr Gly Tyr
500                 505                 510

gat tct aat ttt ata tgg aga tct atg tca tgg gac aac gaa gta gca   1584
Asp Ser Asn Phe Ile Trp Arg Ser Met Ser Trp Asp Asn Glu Val Ala
515                 520                 525

ttt aat aac gga tca ggt tct ggt gac ggt atc gat aaa cca gtt gtt   1632
Phe Asn Asn Gly Ser Gly Ser Gly Asp Gly Ile Asp Lys Pro Val Val
530                 535                 540

cct gaa caa cct gat gag cct ggt gaa att gaa cca att cca gag gat   1680
Pro Glu Gln Pro Asp Glu Pro Gly Glu Ile Glu Pro Ile Pro Glu Asp
545                 550                 555                 560

tca gat tct gac cca ggt tca gat tct ggc agc gat tct aat tca gat   1728
Ser Asp Ser Asp Pro Gly Ser Asp Ser Gly Ser Asp Ser Asn Ser Asp
565                 570                 575

agc ggt tca gat tct ggc agt gat tct aca tca gat agt ggt tca gat   1776
Ser Gly Ser Asp Ser Gly Ser Asp Ser Thr Ser Asp Ser Gly Ser Asp
580                 585                 590

tca gcg agt gat tca gat tca gca agt gat tca gac tca gcg agt gat   1824
Ser Ala Ser Asp Ser Asp Ser Ala Ser Asp Ser Asp Ser Ala Ser Asp
595                 600                 605

tca gat tca gca agt gat tca gat tca gca agt gat tca gat tca gca   1872
Ser Asp Ser Ala Ser Asp Ser Asp Ser Ala Ser Asp Ser Asp Ser Ala
610                 615                 620

agt gat tca gac tca gca agt gat tca gat tca gca agt gat tca gat   1920
Ser Asp Ser Asp Ser Ala Ser Asp Ser Asp Ser Ala Ser Asp Ser Asp
625                 630                 635                 640

tca gca agc gat tca gat tca gcg agc gat tca gat tca gcg agc gat   1968
Ser Ala Ser Asp Ser Asp Ser Ala Ser Asp Ser Asp Ser Ala Ser Asp
645                 650                 655

tca gat tca gcg agt gat tcc gac tca gcg agc gat tca gac tca gat   2016
Ser Asp Ser Ala Ser Asp Ser Asp Ser Ala Ser Asp Ser Asp Ser Asp
660                 665                 670

agt gac tca gat tcc gat agc gat tcc gac tca gat agc gac tca gat   2064
Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
675                 680                 685

tca gac agc gat tct gac tca gac agc gat tct gac tca gac agt gac   2112
Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
690                 695                 700

tca gat tcc gat agc gat tcc gac tca gac agt gac tca gat tcc gat   2160
Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
705                 710                 715                 720

agc gat tcc gac tca gac agt gac tca gat tcc gat agc gat tca gat   2208
Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
725                 730                 735
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tcc gac agt gat tcc gac tca gat agc gat tcc gac tca gat agc gac   2256
Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
740                 745                 750

tca gat tca gac agc gat tca gat tca gac agc gat tct gac tca gac   2304
Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
755                 760                 765

agt gac tca gat tcc gat agc gat tca gat tca gac agt gat tca gac   2352
Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
770                 775                 780

tca gat agc gat tca gat tcc gac agt gac tca gac tca gac agc gat   2400
Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
785                 790                 795                 800

tca gat tcc gat agc gat tca gat tcc gac agt gac tca gat tcc gat   2448
Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
805                 810                 815

agt gac tcg gat tca gcg agt gat tca gat tca gat agc gat tca gaa   2496
Ser Asp Ser Asp Ser Ala Ser Asp Ser Asp Ser Asp Ser Asp Ser Glu
820                 825                 830

tca gat agt gac tca gac tca gac agt gat tca gat tca gat agt gac   2544
Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp Ser Asp
835                 840                 845

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 28
<211> LENGTH: 989
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 28

Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1               5                   10                  15
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Gly Val Ala Ser Val Leu Val Gly Thr Leu Ile Gly Phe Gly Leu Leu
            20                  25                  30

Ser Ser Lys Glu Ala Asp Ala Ser Glu Asn Ser Val Thr Gln Ser Asp
        35                  40                  45

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Ser Ala
    50                  55                  60

Ala Pro Lys Thr Asp Asp Thr Asn Val Ser Asp Thr Lys Thr Ser Ser
65                  70                  75                  80

Asn Thr Asn Asn Gly Glu Thr Ser Val Ala Gln Asn Pro Ala Gln Gln
                85                  90                  95

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

Val Thr Gly Glu Ala Thr Thr Thr Thr Thr Asn Gln Ala Asn Thr Pro
        115                 120                 125

Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln
    130                 135                 140

Thr Ser Asn Glu Thr Thr Ser Asn Asp Thr Asn Thr Val Ser Ser Val
145                 150                 155                 160

Asn Ser Pro Gln Asn Ser Thr Asn Ala Glu Asn Val Ser Thr Thr Gln
                165                 170                 175

Asp Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln
            180                 185                 190

Asn Thr Asp Ala Ser Asn Lys Asp Val Val Ser Gln Ala Val Asn Pro
        195                 200                 205

Ser Thr Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
    210                 215                 220

Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asp Val Lys
225                 230                 235                 240

Val Thr Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr
                245                 250                 255

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

Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
        275                 280                 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
    290                 295                 300

Ala Asn Gly Val Ile Asp Ser Asp Gly Asn Val Ile Tyr Thr Phe Thr
305                 310                 315                 320

Asp Tyr Val Asp Asn Lys Glu Asn Val Thr Ala Asn Ile Thr Met Pro
                325                 330                 335

Ala Tyr Ile Asp Pro Glu Asn Val Thr Lys Thr Gly Asn Val Thr Leu
            340                 345                 350

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

Tyr Glu Lys Tyr Gly Gln Phe His Asn Leu Ser Ile Lys Gly Thr Ile
    370                 375                 380

Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385                 390                 395                 400

Asn Pro Ser Gly Asp Asn Val Val Leu Pro Ala Leu Thr Gly Asn Leu
                405                 410                 415

Ile Pro Asn Thr Lys Ser Asn Ala Leu Ile Asp Ala Lys Asn Thr Asp
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           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

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
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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


<210> SEQ ID NO 29
<211> LENGTH: 243
<212> TYPE: DNA
<213> ORGANISM: Staphylococcus sp.
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(240)

<400> SEQUENCE: 29

atg aat cag cac gta aaa gta aca ttt gat ttt act aat tat aat tac       48
Met Asn Gln His Val Lys Val Thr Phe Asp Phe Thr Asn Tyr Asn Tyr
1               5                   10                  15

ggc aca tat gac tta gca gta cca gca tat tta ccg ata aaa aac tta       96
Gly Thr Tyr Asp Leu Ala Val Pro Ala Tyr Leu Pro Ile Lys Asn Leu
20                  25                  30

ata gct tta gta ttg gat agt ttg gac att tca ata ttt gat gtc aat      144
Ile Ala Leu Val Leu Asp Ser Leu Asp Ile Ser Ile Phe Asp Val Asn
35                  40                  45

aca caa att aaa gtg atg acg aaa ggt caa tta ctt gtt gaa aat gat      192
Thr Gln Ile Lys Val Met Thr Lys Gly Gln Leu Leu Val Glu Asn Asp
50                  55                  60

cga ctc att gat tat caa atc gct gat gga gat att ttg aag tta cta      240
Arg Leu Ile Asp Tyr Gln Ile Ala Asp Gly Asp Ile Leu Lys Leu Leu
65                  70                  75                  80

tag                                                                 243


<210> SEQ ID NO 30
<211> LENGTH: 80
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 30

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
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-continued

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            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


<210> SEQ ID NO 31
<211> LENGTH: 393
<212> TYPE: DNA
<213> ORGANISM: Staphylococcus sp.
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(393)

<400> SEQUENCE: 31

atg aat ttt aat gat att gaa aca atg gtt aag tcg aaa ttt aaa gat       48
Met Asn Phe Asn Asp Ile Glu Thr Met Val Lys Ser Lys Phe Lys Asp
1               5                   10                  15

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
115                 120                 125

atg aat taa                                                         393
Met Asn
130


<210> SEQ ID NO 32
<211> LENGTH: 130
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 32

Met Asn Phe Asn Asp Ile Glu Thr Met Val Lys Ser Lys Phe Lys Asp
1               5                   10                  15

Ile Lys Lys His Ala Glu Glu Ile Ala His Glu Ile Glu Val Arg Ser
            20                  25                  30

Gly Tyr Leu Arg Lys Ala Glu Gln Tyr Lys Arg Leu Glu Phe Asn Leu
        35                  40                  45

Ser Phe Ala Leu Asp Asp Ile Glu Ser Thr Ala Lys Asp Val Gln Thr
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    50                  55                  60

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
            100                 105                 110

Ala Lys Glu Ile Ala Gly Glu Lys Ala Ser Glu Tyr Phe Asn Lys Ala
        115                 120                 125

Met Asn
    130


<210> SEQ ID NO 33
<211> LENGTH: 462
<212> TYPE: DNA
<213> ORGANISM: Staphylococcus aureus
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(462)

<400> SEQUENCE: 33

gca gaa att aat aaa caa aca aca tca caa ggt gtc aca act gaa aaa       48
Ala Glu Ile Asn Lys Gln Thr Thr Ser Gln Gly Val Thr Thr Glu Lys
1               5                   10                  15

aat aat ggt atc gca gtg tta gaa caa gat gtg att aca cca aca gtt       96
Asn Asn Gly Ile Ala Val Leu Glu Gln Asp Val Ile Thr Pro Thr Val
20                  25                  30

aaa cct caa gcg aaa caa gat att atc caa gca gtt aca act cgt aaa      144
Lys Pro Gln Ala Lys Gln Asp Ile Ile Gln Ala Val Thr Thr Arg Lys
35                  40                  45

caa caa att aaa aag tca aat gca tca tta caa gat gaa aaa gat gta      192
Gln Gln Ile Lys Lys Ser Asn Ala Ser Leu Gln Asp Glu Lys Asp Val
50                  55                  60

gca aat gat aaa att ggt aaa att gaa aca aag gca att aaa gat att      240
Ala Asn Asp Lys Ile Gly Lys Ile Glu Thr Lys Ala Ile Lys Asp Ile
65                  70                  75                  80

gat gca gca aca aca aat gca caa gta gaa gcc att aaa aca aaa gca      288
Asp Ala Ala Thr Thr Asn Ala Gln Val Glu Ala Ile Lys Thr Lys Ala
85                  90                  95

atc aat gat att aat caa act aca cct gct aca aca gct aaa gca gca      336
Ile Asn Asp Ile Asn Gln Thr Thr Pro Ala Thr Thr Ala Lys Ala Ala
100                 105                 110

gct ctt gaa gaa ttt gac gaa gtt gtt caa gca caa att gat caa gca      384
Ala Leu Glu Glu Phe Asp Glu Val Val Gln Ala Gln Ile Asp Gln Ala
115                 120                 125

cct tta aat cct gat aca aca aat gaa gaa gta gcg gaa gct att gaa      432
Pro Leu Asn Pro Asp Thr Thr Asn Glu Glu Val Ala Glu Ala Ile Glu
130                 135                 140

cgt att aat gca gct aaa gtt tct ggt gtt                             462
Arg Ile Asn Ala Ala Lys Val Ser Gly Val
145                 150


<210> SEQ ID NO 34
<211> LENGTH: 154
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 34
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Ala Glu Ile Asn Lys Gln Thr Thr Ser Gln Gly Val Thr Thr Glu Lys
1               5                   10                  15

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

Lys Pro Gln Ala Lys Gln Asp Ile Ile Gln Ala Val Thr Thr Arg Lys
        35                  40                  45

Gln Gln Ile Lys Lys Ser Asn Ala Ser Leu Gln Asp Glu Lys Asp Val
    50                  55                  60

Ala Asn Asp Lys Ile Gly Lys Ile Glu Thr Lys Ala Ile Lys Asp Ile
65                  70                  75                  80

Asp Ala Ala Thr Thr Asn Ala Gln Val Glu Ala Ile Lys Thr Lys Ala
                85                  90                  95

Ile Asn Asp Ile Asn Gln Thr Thr Pro Ala Thr Thr Ala Lys Ala Ala
            100                 105                 110

Ala Leu Glu Glu Phe Asp Glu Val Val Gln Ala Gln Ile Asp Gln Ala
        115                 120                 125

Pro Leu Asn Pro Asp Thr Thr Asn Glu Glu Val Ala Glu Ala Ile Glu
    130                 135                 140

Arg Ile Asn Ala Ala Lys Val Ser Gly Val
145                 150


<210> SEQ ID NO 35
<211> LENGTH: 2319
<212> TYPE: DNA
<213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 35

atgaaagctt tattacttaa aacaagtgta tggctcgttt tgctttttag tgtaatggga     60

ttatggcaag tctcgaacgc ggctgagcag catacaccaa tgaaagcaca tgcagtaaca    120

acgatagaca aagcaacaac agataagcaa caagtaccgc caacaaagga agcggctcat    180

cattctggca aagaagcggc aaccaacgta tcagcatcag cgcagggaac agctgatgat    240

acaaacagca aagtaacatc caacgcacca tctaacaaac catctacagt agtttcaaca    300

aaagtaaacg aaacacgcga cgtagataca caacaagcct caacacaaaa accaactcac    360

acagcaacgt tcaaattatc aaatgctaaa acagcatcac tttcaccacg aatgtttgct    420

gctaatgcac cacaaacaac aacacataaa atattacata caaatgatat ccatggccga    480

ctagccgaag aaaaagggcg tgtcatcggt atggctaaat taaaaacagt aaaagaacaa    540

gaaaagcctg atttaatgtt agacgcagga gacgccttcc aaggtttacc actttcaaac    600

cagtctaaag gtgaagaaat ggctaaagca atgaatgcag taggttatga tgctatggca    660

gtcggtaacc atgaatttga ctttggatac gatcagttga aaaagttaga gggtatgtta    720

gacttcccga tgctaagtac taacgtttat aaagatggaa aacgcgcgtt taagccttca    780

acgattgtaa caaaaaatgg tattcgttat ggaattattg gtgtaacgac accagaaaca    840

aagacgaaaa caagacctga aggcattaaa ggcgttgaat ttagagatcc attacaaagt    900

gtgacagcgg aaatgatgcg tatttataaa gacgtagata catttgttgt tatatcacat    960

ttaggaattg atccttcaac acaagaaaca tggcgtggtg attacttagt gaaacaatta   1020

agtcaaaatc cacaattgaa gaaacgtatt acagttattg atggtcattc acatacagta   1080

cttcaaaatg gtcaaattta taacaatgat gcattggcac aaacaggtac agcacttgcg   1140
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aatatcggta agattacatt taattatcgc aatggagagg tatcgaatat taaaccgtca   1200

ttgattaatg ttaaagacgt tgaaaatgta acaccgaaca aagcattagc tgaacaaatt   1260

aatcaagctg atcaaacatt tagagcacaa actgcagagg taattattcc aaacaatacc   1320

attgatttca aaggagaaag agatgacgtt agaacgcgtg aaacaaattt aggaaacgcg   1380

attgcagatg ctatggaagc gtatggcgtt aagaatttct ctaaaaagac tgactttgcc   1440

gtgacaaatg gtggaggtat tcgtgcctct atcgcaaaag gtaaggtgac acgctatgat   1500

ttaatctcag tattaccatt tggaaatacg attgcgcaaa ttgatgtaaa aggttcagac   1560

gtctggacgg ctttcgaaca tagtttaggc gcaccaacaa cacaaaagga cggtaagaca   1620

gtgttaacag cgaatggcgg tttactacat atctctgatt caatccgtgt ttactatgat   1680

ataaataaac cgtctggcaa acgaattaat gctattcaaa ttttaaataa agagacaggt   1740

aagtttgaaa atattgattt aaaacgtgta tatcacgtaa cgatgaatga cttcacagca   1800

tcaggtggcg acggatatag tatgttcggt ggtcctagag aagaaggtat ttcattagat   1860

caagtactag caagttattt aaaaacagct aacttagcta agtatgatac gacagaacca   1920

caacgtatgt tattaggtaa accagcagta agtgaacaac cagctaaagg acaacaaggt   1980

agcaaaggta gtaagtctgg taaagataca caaccaattg gtgacgacaa agtgatggat   2040

ccagcgaaaa aaccagctcc aggtaaagtt gtattgttgc tagcgcatag aggaactgtt   2100

agtagcggta cagaaggttc tggtcgcaca atagaaggag ctactgtatc aagcaagagt   2160

gggaaacaat tggctagaat gtcagtgcct aaaggtagcg cgcatgagaa acagttacca   2220

aaaactggaa ctaatcaaag ttcaagccca gaagcgatgt ttgtattatt agcaggtata   2280

ggtttaatcg cgactgtacg acgtagaaaa gctagctaa                          2319
```

<210> SEQ ID NO 36
<211> LENGTH: 745
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 36

```
Ala Glu Gln His Thr Pro Met Lys Ala His Ala Val Thr Thr Ile Asp
1               5                   10                  15

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                  80

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

Ala Lys Leu Lys Thr Val Lys Glu Gln Glu Lys Pro Asp Leu Met Leu
```

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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
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Lys Arg Val Tyr His Val Thr Met Asn Asp Phe Thr Ala Ser Gly Gly
                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                 640

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                 720

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 37
<211> LENGTH: 322
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 37

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
```

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                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

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 38
<211> LENGTH: 10419
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 38

Met Asn Tyr Arg Asp Lys Ile Gln Lys Phe Ser Ile Arg Lys Tyr Thr
1               5                   10                  15

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

Asn Thr Ser Gln Ala His Ala Ala Glu Thr Asn Gln Pro Ala Ser Val
        35                  40                  45

Val Lys Gln Lys Gln Gln Ser Asn Asn Glu Gln Thr Glu Asn Arg Glu
    50                  55                  60

Ser Gln Val Gln Asn Ser Gln Asn Ser Gln Asn Gly Gln Ser Leu Ser
65                  70                  75                  80

Ala Thr His Glu Asn Glu Gln Pro Asn Ile Ser Gln Ala Asn Leu Val
                85                  90                  95

Asp Gln Lys Val Ala Gln Ser Ser Thr Thr Asn Asp Glu Gln Pro Ala
            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
```

-continued

```
        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

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
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```
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

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
```

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```
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
    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
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    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

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
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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

Thr Gln  Ala Ser Gly Tyr Ala  His Met Gln Asn Ala  Thr Gly Leu
    2135                2140                2145
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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
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Ala Thr  Ile Arg Gln Asn Val  Thr Ala Ala Asn Ala  Ala Lys Ser
    2915                2920                2925

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
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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

Asn Asp  Ile Ile Asn Gly Asn  Ala Gln His Pro Val  Ile Thr Pro
    3320                3325                3330

Ser Asp  Val Asn Asn Ala Leu  Ser Asn Val Thr Ser  Lys Glu His
    3335                3340                3345

Ala Leu  Asn Gly Glu Ala Lys  Leu Asn Ala Ala Lys  Gln Glu Ala
    3350                3355                3360

Asn Thr  Ala Leu Gly His Leu  Asn Asn Leu Asn Asn  Ala Gln Arg
    3365                3370                3375

Gln Asn  Leu Gln Ser Gln Ile  Asn Gly Ala His Gln  Ile Asp Ala
    3380                3385                3390

Val Asn  Thr Ile Lys Gln Asn  Ala Thr Asn Leu Asn  Ser Ala Met
    3395                3400                3405

Gly Asn  Leu Arg Gln Ala Val  Ala Asp Lys Asp Gln  Val Lys Arg
    3410                3415                3420

Thr Glu  Asp Tyr Ala Asp Ala  Asp Thr Ala Lys Gln  Asn Ala Tyr
    3425                3430                3435

Asn Ser  Ala Val Ser Ser Ala  Glu Thr Ile Ile Asn  Gln Thr Thr
    3440                3445                3450

Asn Pro  Thr Met Ser Val Asp  Asp Val Asn Arg Ala  Thr Ser Ala
    3455                3460                3465

Val Thr  Ser Asn Lys Asn Ala  Leu Asn Gly Tyr Glu  Lys Leu Ala
    3470                3475                3480

Gln Ser  Lys Thr Asp Ala Ala  Arg Ala Ile Asp Ala  Leu Pro His
    3485                3490                3495

Leu Asn  Asn Ala Gln Lys Ala  Asp Val Lys Ser Lys  Ile Asn Ala
    3500                3505                3510

Ala Ser  Asn Ile Ala Gly Val  Asn Thr Val Lys Gln  Gln Gly Thr
    3515                3520                3525

Asp Leu  Asn Thr Ala Met Gly  Asn Leu Gln Gly Ala  Ile Asn Asp
    3530                3535                3540

Glu Gln  Thr Thr Leu Asn Ser  Gln Asn Tyr Gln Asp  Ala Thr Pro
    3545                3550                3555

Ser Lys  Lys Thr Ala Tyr Thr  Asn Ala Val Gln Ala  Ala Lys Asp
    3560                3565                3570

Ile Leu  Asn Lys Ser Asn Gly  Gln Asn Lys Thr Lys  Asp Gln Val
    3575                3580                3585

Thr Glu  Ala Met Asn Gln Val  Asn Ser Ala Lys Asn  Asn Leu Asp
    3590                3595                3600

Gly Thr  Arg Leu Leu Asp Gln  Ala Lys Gln Thr Ala  Lys Gln Gln
    3605                3610                3615

Leu Asn  Asn Met Thr His Leu  Thr Thr Ala Gln Lys  Thr Asn Leu
    3620                3625                3630

Thr Asn  Gln Ile Asn Ser Gly  Thr Thr Val Ala Gly  Val Gln Thr
    3635                3640                3645

Val Gln  Ser Asn Ala Asn Thr  Leu Asp Gln Ala Met  Asn Thr Leu
    3650                3655                3660

Arg Gln  Ser Ile Ala Asn Lys  Asp Ala Thr Lys Ala  Ser Glu Asp
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    3665                3670                3675

Tyr Val  Asp Ala Asn Asn Asp  Lys Gln Thr Ala Tyr  Asn Asn Ala
    3680                3685                3690

Val Ala  Ala Ala Glu Thr Ile  Ile Asn Ala Asn Ser  Asn Pro Glu
    3695                3700                3705

Met Asn  Pro Ser Thr Ile Thr  Gln Lys Ala Glu Gln  Val Asn Ser
    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
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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

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
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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

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
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    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
    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
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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

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
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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

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
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    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
    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
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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

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
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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

Lys Gln  Ala Leu Asn Gly Asp  Arg Lys Val Thr Asp  Ala Lys Asn
    6875                 6880                 6885

Asn Ala  Asn Gln Thr Leu Ser  Thr Leu Asp Asn Leu  Asn Asn Ala
    6890                 6895                 6900

Gln Lys  Gly Ala Val Thr Gly  Asn Ile Asn Gln Ala  His Thr Val
    6905                 6910                 6915

Ala Glu  Val Thr Gln Ala Ile  Gln Thr Ala Gln Glu  Leu Asn Thr
    6920                 6925                 6930

Ala Met  Gly Asn Leu Lys Asn  Ser Leu Asn Asp Lys  Asp Thr Thr
    6935                 6940                 6945

Leu Gly  Ser Gln Asn Phe Ala  Asp Ala Asp Pro Glu  Lys Lys Asn
    6950                 6955                 6960

Ala Tyr  Asn Glu Ala Val His  Asn Ala Glu Asn Ile  Leu Asn Lys
    6965                 6970                 6975

Ser Thr  Gly Thr Asn Val Pro  Lys Asp Gln Val Glu  Ala Ala Met
    6980                 6985                 6990

Asn Gln  Val Asn Ala Thr Lys  Ala Ala Leu Asn Gly  Thr Gln Asn
    6995                 7000                 7005

Leu Glu  Lys Ala Lys Gln His  Ala Asn Thr Ala Ile  Asp Gly Leu
    7010                 7015                 7020

Ser His  Leu Thr Asn Ala Gln  Lys Glu Ala Leu Lys  Gln Leu Val
    7025                 7030                 7035

Gln Gln  Ser Thr Thr Val Ala  Glu Ala Gln Gly Asn  Glu Gln Lys
    7040                 7045                 7050

Ala Asn  Asn Val Asp Ala Ala  Met Asp Lys Leu Arg  Gln Ser Ile
    7055                 7060                 7065

Ala Asp  Asn Ala Thr Thr Lys  Gln Asn Gln Asn Tyr  Thr Asp Ala
    7070                 7075                 7080

Ser Gln  Asn Lys Lys Asp Ala  Tyr Asn Asn Ala Val  Thr Thr Ala
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    7085                7090                7095

Gln Gly  Ile Ile Asp Gln Thr  Thr Ser Pro Thr Leu  Asp Pro Thr
    7100                7105                7110

Val Ile  Asn Gln Ala Ala Gly  Gln Val Ser Thr Thr  Lys Asn Ala
    7115                7120                7125

Leu Asn  Gly Asn Glu Asn Leu  Glu Ala Ala Lys Gln  Gln Ala Ser
    7130                7135                7140

Gln Ser  Leu Gly Ser Leu Asp  Asn Leu Asn Asn Ala  Gln Lys Gln
    7145                7150                7155

Thr Val  Thr Asp Gln Ile Asn  Gly Ala His Thr Val  Asp Glu Ala
    7160                7165                7170

Asn Gln  Ile Lys Gln Asn Ala  Gln Asn Leu Asn Thr  Ala Met Gly
    7175                7180                7185

Asn Leu  Lys Gln Ala Ile Ala  Asp Lys Asp Ala Thr  Lys Ala Thr
    7190                7195                7200

Val Asn  Phe Thr Asp Ala Asp  Gln Ala Lys Gln Gln  Ala Tyr Asn
    7205                7210                7215

Thr Ala  Val Thr Asn Ala Glu  Asn Ile Ser Lys Ala  Asn Gly Asn
    7220                7225                7230

Ala Thr  Gln Ala Glu Val Glu  Gln Ala Ile Lys Gln  Val Asn Ala
    7235                7240                7245

Ala Lys  Gln Ala Leu Asn Gly  Asn Ala Asn Val Gln  His Ala Lys
    7250                7255                7260

Asp Glu  Ala Thr Ala Leu Ile  Asn Ser Ser Asn Asp  Leu Asn Gln
    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
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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

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
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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

Thr Ala  Thr Ser Leu Asp Gln  Ala Met Asp Gln Leu  Ser Gln Ala
    8060                 8065                 8070

Ile Asn  Asp Lys Ala Gln Thr  Leu Ala Asp Gly Asn  Tyr Leu Asn
    8075                 8080                 8085

Ala Asp  Pro Asp Lys Gln Asn  Ala Tyr Lys Gln Ala  Val Ala Lys
    8090                 8095                 8100

Ala Glu  Ala Leu Leu Asn Lys  Gln Ser Gly Thr Asn  Glu Val Gln
    8105                 8110                 8115

Ala Gln  Val Glu Ser Ile Thr  Asn Glu Val Asn Ala  Ala Lys Gln
    8120                 8125                 8130

Ala Leu  Asn Gly Asn Asp Asn  Leu Ala Asn Ala Lys  Gln Gln Ala
    8135                 8140                 8145

Lys Gln  Gln Leu Ala Asn Leu  Thr His Leu Asn Asp  Ala Gln Lys
    8150                 8155                 8160

Gln Ser  Phe Glu Ser Gln Ile  Thr Gln Ala Pro Leu  Val Thr Asp
    8165                 8170                 8175

Val Thr  Thr Ile Asn Gln Lys  Ala Gln Thr Leu Asp  His Ala Met
    8180                 8185                 8190

Glu Leu  Leu Arg Asn Ser Val  Ala Asp Asn Gln Thr  Thr Leu Ala
    8195                 8200                 8205

Ser Glu  Asp Tyr His Asp Ala  Thr Ala Gln Arg Gln  Asn Asp Tyr
    8210                 8215                 8220

Asn Gln  Ala Val Thr Ala Ala  Asn Asn Ile Ile Asn  Gln Thr Thr
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    8225                8230                8235

Ser Pro  Thr Met Asn Pro Asp  Asp Val Asn Gly Ala  Thr Thr Gln
    8240                8245                8250

Val Asn  Asn Thr Lys Val Ala  Leu Asp Gly Asp Glu  Asn Leu Ala
    8255                8260                8265

Ala Ala  Lys Gln Gln Ala Asn  Asn Arg Leu Asp Gln  Leu Asp His
    8270                8275                8280

Leu Asn  Asn Ala Gln Lys Gln  Gln Leu Gln Ser Gln  Ile Thr Gln
    8285                8290                8295

Ser Ser  Asp Ile Ala Ala Val  Asn Gly His Lys Gln  Thr Ala Glu
    8300                8305                8310

Ser Leu  Asn Thr Ala Met Gly  Asn Leu Ile Asn Ala  Ile Ala Asp
    8315                8320                8325

His Gln  Ala Val Glu Gln Arg  Gly Asn Phe Ile Asn  Ala Asp Thr
    8330                8335                8340

Asp Lys  Gln Thr Ala Tyr Asn  Thr Ala Val Asn Glu  Ala Ala Ala
    8345                8350                8355

Met Ile  Asn Lys Gln Thr Gly  Gln Asn Ala Asn Gln  Thr Glu Val
    8360                8365                8370

Glu Gln  Ala Ile Thr Lys Val  Gln Thr Thr Leu Gln  Ala Leu Asn
    8375                8380                8385

Gly Asp  His Asn Leu Gln Val  Ala Lys Thr Asn Ala  Thr Gln Ala
    8390                8395                8400

Ile Asp  Ala Leu Thr Ser Leu  Asn Asp Pro Gln Lys  Thr Ala Leu
    8405                8410                8415

Lys Asp  Gln Val Thr Ala Ala  Thr Leu Val Thr Ala  Val His Gln
    8420                8425                8430

Ile Glu  Gln Asn Ala Asn Thr  Leu Asn Gln Ala Met  His Gly Leu
    8435                8440                8445

Arg Gln  Ser Ile Gln Asp Asn  Ala Ala Thr Lys Ala  Asn Ser Lys
    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
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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

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
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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

Gln Asn  Leu Thr Ala Lys Gln  Val Ile Lys Leu Asn  Asp Ala Val
    9245                 9250                 9255

Thr Ala  Ala Lys Lys Ala Leu  Asn Gly Glu Glu Arg  Leu Asn Asn
    9260                 9265                 9270

Arg Lys  Ala Glu Ala Leu Gln  Arg Leu Asp Gln Leu  Thr His Leu
    9275                 9280                 9285

Asn Asn  Ala Gln Arg Gln Leu  Ala Ile Gln Gln Ile  Asn Asn Ala
    9290                 9295                 9300

Glu Thr  Leu Asn Lys Ala Ser  Arg Ala Ile Asn Arg  Ala Thr Lys
    9305                 9310                 9315

Leu Asp  Asn Ala Met Gly Ala  Val Gln Gln Tyr Ile  Asp Glu Gln
    9320                 9325                 9330

His Leu  Gly Val Ile Ser Ser  Thr Asn Tyr Ile Asn  Ala Asp Asp
    9335                 9340                 9345

Asn Leu  Lys Ala Asn Tyr Asp  Asn Ala Ile Ala Asn  Ala Ala His
    9350                 9355                 9360

Glu Leu  Asp Lys Val Gln Gly  Asn Ala Ile Ala Lys  Ala Glu Ala
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    9365                9370                9375

Glu Gln  Leu Lys Gln Asn Ile  Ile Asp Ala Gln Asn  Ala Leu Asn
    9380                9385                9390

Gly Asp  Gln Asn Leu Ala Asn  Ala Lys Asp Lys Ala  Asn Ala Phe
    9395                9400                9405

Val Asn  Ser Leu Asn Gly Leu  Asn Gln Gln Gln Gln  Asp Leu Ala
    9410                9415                9420

His Lys  Ala Ile Asn Asn Ala  Asp Thr Val Ser Asp  Val Thr Asp
    9425                9430                9435

Ile Val  Asn Asn Gln Ile Asp  Leu Asn Asp Ala Met  Glu Thr Leu
    9440                9445                9450

Lys His  Leu Val Asp Asn Glu  Ile Pro Asn Ala Glu  Gln Thr Val
    9455                9460                9465

Asn Tyr  Gln Asn Ala Asp Asp  Asn Ala Lys Thr Asn  Phe Asp Asp
    9470                9475                9480

Ala Lys  Arg Leu Ala Asn Thr  Leu Leu Asn Ser Asp  Asn Thr Asn
    9485                9490                9495

Val Asn  Asp Ile Asn Gly Ala  Ile Gln Ala Val Asn  Asp Ala Ile
    9500                9505                9510

His Asn  Leu Asn Gly Asp Gln  Arg Leu Gln Asp Ala  Lys Asp Lys
    9515                9520                9525

Ala Ile  Gln Ser Ile Asn Gln  Ala Leu Ala Asn Lys  Leu Lys Glu
    9530                9535                9540

Ile Glu  Ala Ser Asn Ala Thr  Asp Gln Asp Lys Leu  Ile Ala Lys
    9545                9550                9555

Asn Lys  Ala Glu Glu Leu Ala  Asn Ser Ile Ile Asn  Asn Ile Asn
    9560                9565                9570

Lys Ala  Thr Ser Asn Gln Ala  Val Ser Gln Val Gln  Thr Ala Gly
    9575                9580                9585

Asn His  Ala Ile Glu Gln Val  His Ala Asn Glu Ile  Pro Lys Ala
    9590                9595                9600

Lys Ile  Asp Ala Asn Lys Asp  Val Asp Lys Gln Val  Gln Ala Leu
    9605                9610                9615

Ile Asp  Glu Ile Asp Arg Asn  Pro Asn Leu Thr Asp  Lys Glu Lys
    9620                9625                9630

Gln Ala  Leu Lys Asp Arg Ile  Asn Gln Ile Leu Gln  Gln Gly His
    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
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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

Glu Ala   Ile Ala Lys Leu Asn   Gln Leu Lys Glu Gln   Ala Ile Gln
    10040                10045                10050

Ala Ile   Gln Arg Ala Gln Ser   Ile Asp Glu Ile Ser   Glu Gln Leu
    10055                10060                10065

Glu Gln   Phe Lys Ala Gln Met   Lys Ala Ala Asn Pro   Thr Ala Lys
    10070                10075                10080

Glu Leu   Ala Lys Arg Lys Gln   Glu Ala Ile Ser Arg   Ile Lys Asp
    10085                10090                10095

Phe Ser   Asn Glu Lys Ile Asn   Ser Ile Arg Asn Ser   Glu Ile Gly
    10100                10105                10110

Thr Ala   Asp Glu Lys Gln Ala   Ala Met Asn Gln Ile   Asn Glu Ile
    10115                10120                10125
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Val Leu   Glu Thr Ile Arg Asp   Ile Asn Asn Ala His   Thr Leu Gln
    10130                 10135                 10140

Gln Val   Glu Ala Ala Leu Asn   Asn Gly Ile Ala Arg   Ile Ser Ala
    10145                 10150                 10155

Val Gln   Ile Val Thr Ser Asp   Arg Ala Lys Gln Ser   Ser Ser Thr
    10160                 10165                 10170

Gly Asn   Glu Ser Asn Ser His   Leu Thr Ile Gly Tyr   Gly Thr Ala
    10175                 10180                 10185

Asn His   Pro Phe Asn Ser Ser   Thr Ile Gly His Lys   Lys Lys Leu
    10190                 10195                 10200

Asp Glu   Asp Asp Asp Ile Asp   Pro Leu His Met Arg   His Phe Ser
    10205                 10210                 10215

Asn Asn   Phe Gly Asn Val Ile   Lys Asn Ala Ile Gly   Val Val Gly
    10220                 10225                 10230

Ile Ser   Gly Leu Leu Ala Ser   Phe Trp Phe Phe Ile   Ala Lys Arg
    10235                 10240                 10245

Arg Arg   Lys Glu Asp Glu Glu   Glu Glu Leu Glu Ile   Arg Asp Asn
    10250                 10255                 10260

Asn Lys   Asp Ser Ile Lys Glu   Thr Leu Asp Asp Thr   Lys His Leu
    10265                 10270                 10275

Pro Leu   Leu Phe Ala Lys Arg   Arg Arg Lys Glu Asp   Glu Glu Asp
    10280                 10285                 10290

Val Thr   Val Glu Glu Lys Asp   Ser Leu Asn Asn Gly   Glu Ser Leu
    10295                 10300                 10305

Asp Lys   Val Lys His Thr Pro   Phe Phe Leu Pro Lys   Arg Arg Arg
    10310                 10315                 10320

Lys Glu   Asp Glu Glu Asp Val   Glu Val Thr Asn Glu   Asn Thr Asp
    10325                 10330                 10335

Glu Lys   Val Leu Lys Asp Asn   Glu His Ser Pro Leu   Leu Phe Ala
    10340                 10345                 10350

Lys Arg   Arg Lys Asp Lys Glu   Glu Asp Val Glu Thr   Thr Thr Ser
    10355                 10360                 10365

Ile Glu   Ser Lys Asp Glu Asp   Val Pro Leu Leu Leu   Ala Lys Lys
    10370                 10375                 10380

Lys Asn   Gln Lys Asp Asn Gln   Ser Lys Asp Lys Lys   Ser Ala Ser
    10385                 10390                 10395

Lys Asn   Thr Ser Lys Lys Val   Ala Ala Lys Lys Lys   Lys Lys Lys
    10400                 10405                 10410

Ala Lys   Lys Asn Lys Lys
    10415
```

<210> SEQ ID NO 39
<211> LENGTH: 636
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 39

```
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
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```
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
                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
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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                 480

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                 560

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 40
<211> LENGTH: 628
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus sp.

<400> SEQUENCE: 40

Met Ser Asp Arg Phe Ile Lys Phe Asn Asp Glu Gln Leu Asp Ala Lys
1               5                   10                  15

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                  80

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                 160

Tyr Leu Glu His Ala Phe Leu Ser Gln Asp Phe Phe Asp Ile Pro Ser
                165                 170                 175
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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
                565                 570                 575
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Val Phe Asn Val Phe Leu Ser Gln Asp Pro Ile Thr Glu Asp Val Glu
            580                 585                 590

Gln Thr Ile His Asn Ile Tyr Gly Gln Tyr Ala Ile Phe Val Glu Gly
        595                 600                 605

Val Ala His Leu Pro Gly His Leu Ser Pro Leu Leu Lys Lys Leu Leu
    610                 615                 620

Leu Lys Ser Leu
625


<210> SEQ ID NO 41
<211> LENGTH: 780
<212> TYPE: PRT
<213> ORGANISM: Bacillus anthracis

<400> SEQUENCE: 41

Met Lys Lys Ser Lys Lys Met Leu Ala Gly Ala Thr Leu Ala Ile Gly
1               5                   10                  15

Val Met Ala Pro Gln Val Leu Pro Ala Thr Ala His Ala Asp Glu Lys
            20                  25                  30

Thr Gly Glu Ser Thr Val Asn Leu Arg Ile Leu Glu Thr Ser Asp Ile
        35                  40                  45

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

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

Glu Ala Lys Asn Ser Val Leu Phe Asp Asp Gly Asp Ala Leu Gln Gly
                85                  90                  95

Thr Pro Leu Gly Asp Tyr Val Ala Asn Lys Ile Asn Asp Pro Lys Lys
            100                 105                 110

Pro Val Asp Pro Ser Tyr Thr His Pro Leu Tyr Arg Leu Met Asn Leu
        115                 120                 125

Met Lys Tyr Asp Val Ile Ser Leu Gly Asn His Glu Phe Asn Tyr Gly
    130                 135                 140

Leu Asp Tyr Leu Asn Lys Val Ile Ser Lys Thr Glu Phe Pro Val Ile
145                 150                 155                 160

Asn Ser Asn Val Tyr Lys Asp Asp Lys Asp Asn Asn Glu Glu Asn Asp
                165                 170                 175

Gln Asn Tyr Phe Lys Pro Tyr His Val Phe Glu Lys Glu Val Glu Asp
            180                 185                 190

Glu Ser Gly Gln Lys Gln Lys Val Lys Ile Gly Val Met Gly Phe Val
        195                 200                 205

Pro Pro Gln Val Met Asn Trp Asp Lys Ala Asn Leu Glu Gly Lys Val
    210                 215                 220

Lys Ala Lys Asp Ile Val Glu Thr Ala Lys Lys Met Val Pro Lys Met
225                 230                 235                 240

Lys Ala Glu Gly Ala Asp Val Ile Val Ala Leu Ala His Ser Gly Val
                245                 250                 255

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

Thr Glu Val Pro Gly Val Asp Ala Val Leu Met Gly His Ser His Thr
        275                 280                 285

Glu Val Lys Asp Val Phe Asn Gly Val Pro Val Val Met Pro Gly Val
    290                 295                 300
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Phe Gly Ser Asn Leu Gly Ile Ile Asp Met Gln Leu Lys Lys Val Asn
305                 310                 315                 320

Gly Lys Trp Glu Val Gln Lys Glu Gln Ser Lys Pro Gln Leu Arg Pro
                325                 330                 335

Ile Ala Asp Ser Lys Gly Asn Pro Leu Val Gln Ser Asp Gln Asn Leu
            340                 345                 350

Val Asn Glu Ile Lys Asp Asp His Gln Ala Thr Ile Asp Tyr Val Asn
        355                 360                 365

Thr Ala Val Gly Lys Thr Thr Ala Pro Ile Asn Ser Tyr Phe Ser Leu
    370                 375                 380

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

Tyr Val Glu Lys Leu Phe Ala Glu Asn Gly Gln Tyr Ser Lys Tyr Lys
                405                 410                 415

Gly Ile Pro Val Leu Ser Ala Gly Ala Pro Phe Lys Ala Gly Gly Arg
            420                 425                 430

Asn Gly Ala Thr Tyr Tyr Thr Asp Ile Pro Ala Gly Thr Leu Ala Ile
        435                 440                 445

Lys Asn Val Ala Asp Leu Tyr Val Tyr Pro Asn Thr Leu Tyr Ala Val
    450                 455                 460

Lys Val Asn Gly Ala Gln Val Lys Glu Trp Leu Glu Met Ser Ala Gly
465                 470                 475                 480

Gln Phe Asn Gln Ile Asp Pro Lys Lys Thr Glu Glu Gln Pro Leu Val
                485                 490                 495

Asn Ile Gly Tyr Pro Thr Tyr Asn Phe Asp Ile Leu Asp Gly Leu Lys
            500                 505                 510

Tyr Glu Ile Asp Val Thr Gln Pro Ala Lys Tyr Asp Lys Asp Gly Lys
        515                 520                 525

Val Val Asn Ala Asn Thr Asn Arg Ile Ile Asn Met Thr Tyr Glu Gly
    530                 535                 540

Lys Pro Val Ala Asp Asn Gln Glu Phe Ile Val Ala Thr Asn Asn Tyr
545                 550                 555                 560

Arg Gly Ser Ser Gln Thr Phe Pro Gly Val Ser Lys Gly Glu Val Val
                565                 570                 575

Tyr Gln Ser Gln Asp Glu Thr Arg Gln Ile Ile Val Lys Tyr Met Gln
            580                 585                 590

Glu Thr Pro Val Ile Asp Pro Ala Ala Asp Lys Asn Trp Ala Phe Lys
        595                 600                 605

Pro Ile Val Ala Asp Lys Leu Asn Thr Thr Phe Asp Ser Ser Pro Asn
    610                 615                 620

Ala Gln Lys Tyr Ile Lys Lys Asp Gly Asn Ile Ser Tyr Val Gly Pro
625                 630                 635                 640

Ser Glu Asn Glu Phe Ala Lys Tyr Ala Ile Asp Ile Thr Lys Lys Asn
                645                 650                 655

Asp Asp Asp Lys Glu Thr Gly Gly Glu Asn Pro Thr Ile Pro Pro Thr
            660                 665                 670

Gly Glu Gly Asp Asn Gly Glu Asn Pro Thr Thr Pro Pro Thr Gly Glu
        675                 680                 685

Gly Asn Asn Gly Glu Asn Pro Thr Thr Pro Pro Thr Gly Glu Gly Asn
    690                 695                 700
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Asn Gly Gly Asn Pro Thr Thr Pro Ser Thr Asp Glu Gly Asn Asn Ala
705                 710                 715                 720

Gly Ser Gly Gln Thr Thr Thr Asp Asn Gln Asn Ser Lys Glu Thr Thr
                725                 730                 735

Thr Val Ser Glu Asn Lys Glu Glu Arg Asp Leu Pro Lys Thr Gly Thr
            740                 745                 750

Asn Val Ala Ser Thr Ile Gly Ala Gly Leu Ala Phe Ile Gly Ala Gly
        755                 760                 765

Phe Leu Leu Leu Phe Arg Arg Lys Lys Ala Asn Arg
    770                 775                 780


<210> SEQ ID NO 42
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic primer

<400> SEQUENCE: 42

tttcccggga cgatccagct ctaatcgctg                                    30


<210> SEQ ID NO 43
<211> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic primer

<400> SEQUENCE: 43

tttgagctca aagcaaatag ataatcgaga aatataaaaa g                       41


<210> SEQ ID NO 44
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic primer

<400> SEQUENCE: 44

tttgagctca gttgctccag ccagcat                                       27


<210> SEQ ID NO 45
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic primer

<400> SEQUENCE: 45

tttgaattca aacggattca ttccagcc                                      28


<210> SEQ ID NO 46
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic primer

<400> SEQUENCE: 46

tacgaattcg acttggcagg caattgaaaa                                    30
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<210> SEQ ID NO 47
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic primer

<400> SEQUENCE: 47

tgtgaattct tagctagctt ttctacgtc 29

<210> SEQ ID NO 48
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic primer

<400> SEQUENCE: 48

tcgggatccg ctgagcagca tacaccaatg 30

<210> SEQ ID NO 49
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic primer

<400> SEQUENCE: 49

tgtggatcct tattgattaa tttgttcagc taatgc 36

<210> SEQ ID NO 50
<211> LENGTH: 340
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 50

Met Lys Lys Lys Leu Leu Val Leu Thr Met Ser Thr Leu Phe Ala Thr
1 5 10 15

Gln Leu Ile Asn Ser Asn His Ala Asn 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

Thr Tyr Asn Glu Phe Lys Lys Ala Pro Lys Val Asn Val Ser Asn Leu
50 55 60

Thr Asp Asn Lys Asn Phe Val Ala Ser Glu Asp Lys Leu Lys Lys Ile
65 70 75 80

Ser Asp Pro 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

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Ala Thr Asp Ser Ile Asn Lys His Phe Ile Val Lys Pro Ser Glu Ala
            180                 185                 190

Pro Arg Tyr Thr His Pro Ser Gln Ser Leu Met Ile Asn His Tyr 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 Asn Tyr Val Pro Glu Phe Lys Gly Ser Leu Pro
                325                 330                 335

Ala Pro Arg Val
            340


<210> SEQ ID NO 51
<211> LENGTH: 339
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 51

Met Lys Lys Lys Leu Phe Val Leu Thr Met Ser Thr Leu Phe Ala Thr
1               5                   10                  15

Gln Leu Ile Asn Ser Asn His Ala Asn Ala Ser Thr Glu Ser Val Asp
            20                  25                  30

Lys Asn Phe Val Val Pro Glu Ser Gly Ile Asn Lys Ile Ile Pro Thr
        35                  40                  45

Tyr Asp Glu Phe Lys Lys Ala Pro Lys Val Asn Val Gly Ser Leu Ala
    50                  55                  60

Asp Asn Lys Asn Phe Val Ala Ser Glu Asp Lys Leu Ser Lys Ile Ala
65                  70                  75                  80

Asp Pro Ser Ala Ala Ser Lys Ile Val Asp Lys Asn Phe Val Val Pro
                85                  90                  95

Glu Ser Lys Leu Gly Asn Ile Val Pro Glu Tyr Lys Glu Ile Asn Asn
            100                 105                 110

Arg Val Asn Val Ala Thr Asn Asn Pro Ala Ser Gln Gln Val Asp Lys
        115                 120                 125

His Phe Val Ala Lys Gly Pro Glu Val Asn Arg Phe Ile Thr Gln Asn
    130                 135                 140

Lys Val Asn His Pro Phe Ile Thr Thr Gln Thr His Tyr Lys Lys Val
145                 150                 155                 160

Ile Thr Ser Tyr Lys Ser Thr His Val His Lys His Val Asn His Ala
                165                 170                 175

Thr Gly Ser Ile Asn Lys His Phe Ile Val Lys Pro Ser Glu Ala Pro
            180                 185                 190
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```
Arg Tyr Thr Gln Pro Ser Gln Ser Leu Met Ile Asn His Tyr Phe Ala
        195                 200                 205

Val Pro Gly Tyr His Ala His Lys Phe Val Thr Pro Gly His Ala Ser
    210                 215                 220

Ile Lys Ile Asn His Phe Cys Val Val Pro Gln Ile Asn Ser Phe Lys
225                 230                 235                 240

Val Ile Pro Pro Tyr Gly His Asn Ser His Arg Met His Val Pro Ser
                245                 250                 255

Phe Gln Asn Asn Thr Thr Ala Thr His Gln Asn Ala Lys Val Lys Lys
            260                 265                 270

Ala Tyr Asp Tyr Lys Tyr Phe Tyr Ser Tyr Lys Val Val Lys Gly Val
        275                 280                 285

Lys Lys Tyr Phe Ser Phe Ser Gln Ser Asn Gly Tyr Lys Ile Gly Glu
    290                 295                 300

Pro Ser Leu Asn Ile Lys Asn Val Asn Tyr Gln Tyr Ala Val Pro Ser
305                 310                 315                 320

Tyr Ser Pro Thr His Tyr Val Pro Glu Phe Lys Gly Ser Ile Pro Ala
                325                 330                 335

Pro Arg Val


<210> SEQ ID NO 52
<211> LENGTH: 340
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 52

Met Lys Lys Lys Leu Leu Val Leu Thr Met Ser Thr Leu Phe Ala Thr
1               5                   10                  15

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

Val Asp Ser Ser Ala Ala Ser Lys Ile Val Asp Lys Asn Phe Ala 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
```

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```
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


<210> SEQ ID NO 53
<211> LENGTH: 340
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 53

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

Thr Tyr Asn Glu Phe Lys Lys Ala Pro Lys Val Asn Val Gly Asn Leu
    50                  55                  60

Ala Asp Asn Lys Asn Phe Val Ala Ser Glu Asp Lys Leu Asn Lys Ile
65                  70                  75                  80

Val Asp Ser Ser Ala Ala Ser Lys Ile Val Asp Lys Asn Phe Ala 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
```

-continued

```
    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
```

1. An antigen composition comprising:

(a) an isolated Emp antigen, or an immunogenic fragment thereof; and

(b) at least one additional staphylococcal antigen selected from a group consisting of an isolated ClfA, ClfB, Eap, EsaB, EsxA, EsxB, EsaC, IsdA, IsdB, IsdC, SasF, SasB, SdrC, SdrD, SdrE, SasH, Ebh, Coa, vWa, Hla and SpA antigen, or an immunogenic fragment thereof,

wherein the antigens are comprised in a pharmaceutically acceptable composition capable of stimulating an immune response in a subject in need thereof.

2. The composition of claim **1**, further comprising one or more of a type V capsular saccharide, a type VIII capsular saccharide, and/or a polysaccharide intracellular adhesin (PIA).

3. (canceled)

4. (canceled)

5. The composition of claim **1**, wherein the at least one additional staphylococcal antigen is selected from the group consisting of an isolated ClfB, Eap, EsxA, EsxB, IsdA, and SrdD.

6. The composition of claim **1**, wherein the at least one additional staphylococcal antigen is an isolated IsdA antigen.

7. The composition of claim **6**, further comprising one or more additional staphylococcal antigens selected from the group consisting of ClfB, Eap, EsxA, EsxB, Hla, and SdrD.

8. The composition of claim **7**, further comprising one or more of a type V capsular saccharide, a type VIII capsular saccharide, and/or a polysaccharide intracellular adhesin (PIA).

9. (canceled)

10. (canceled)

11. The composition of claim **1**, wherein the composition comprises less than a 1% weight/weight contamination with other staphylococcal bacterial components.

12. The composition of claim **1**, wherein one or more isolated antigens are coupled to an adjuvant.

13. The composition of claim **1**, wherein the Emp antigen comprises at least 5, 10, 15, or 20 consecutive amino acids of SEQ ID NO:2.

14. The composition of claim **1**, wherein the Emp antigen is at least 70%, 80%, 90%, 95%, or 98% identical to SEQ ID NO:2.

15. (canceled)

16. (canceled)

17. The composition of claim **1**, wherein the Emp antigen comprises the amino acid sequence of SEQ ID NO:2.

18. (canceled)

19. An antigen comprising two or more of a ClfA, ClfB, Eap, Emp, EsaB, EsxA, EsxB, EsaC, IsdA, IsdB, IsdC, SasF, SasH, Ebh, Coa, vWa, Hla, SasB, SdrC, SdrD, SdrE, and SpA antigen, wherein the two or more antigens are coupled forming a multimeric antigen.

20-30. (canceled)

31. A method for eliciting an immune response against a *staphylococcus* bacterium in a subject comprising administering to the subject an effective amount of a composition comprising:

(a) an isolated Emp antigen, or an immunogenic fragment thereof, and

(b) at least one additional staphylococcal antigen selected from a group consisting of an isolated ClfA, ClfB, Eap, EsaB, EsxA, EsxB, EsaC, Hla, SasB, SasH, Ebh, Coa, vWa, IsdA, IsdB, IsdC, SasF, SdrC, SdrD, SdrE, and SpA antigen, or an immunogenic fragment thereof.

32. The method of claim **31**, wherein the subject is provided with an effective amount of an isolated antigen by administering to the subject a composition comprising:

i) the isolated antigen, or

ii) at least one isolated recombinant nucleic acid molecule encoding the antigen.

33. The method of claim **31**, where the subject is also administered an adjuvant.

34. (canceled)

35. (canceled)

36. The method of claim **31**, wherein the Emp antigen comprises at least 5, 10, 15, or 20 consecutive amino acids of SEQ ID NO:2.

37. The method of claim **31**, wherein the Emp antigen is at least 70%, 80%, 90%, 95%, or 98% identical to SEQ ID NO:2.

38. (canceled)

39. (canceled)

40. The method of claim **31**, wherein the Emp antigen comprises the amino acid sequence of SEQ ID NO:2.

41. The method of claim **31**, wherein the staphylococcus bacterium is a *S. aureus* bacterium.

42. The method of claim **31**, wherein the stapylococcus bacterium is a drug resistant bacterium.

43-52. (canceled)

53. The method of claim **31**, wherein the composition includes a recombinant, non-staphylococcus bacterium expressing an isolated Emp antigen, or an immunogenic fragment thereof, and at least one additional staphylococcal antigen selected from a group consisting of an isolated ClfA, ClfB, Eap, EsaB, EsxA, EsxB, EsaC, Hla, SasB, SasH, Ebh, Coa, vWa, IsdA, IsdB, IsdC, SasF, SdrC, SdrD, SdrE, and SpA antigen, or an immunogenic fragment thereof.

54. (canceled)

55. (canceled)

56. The method of claim **31**, wherein the subject is human.

57. The method of claim **31**, wherein the immune response is a protective immune response.

58-71. (canceled)

72. A method for limiting staphylococcal abscess formation and/or persistence in a subject comprising providing to a subject having or suspected of having or at risk of developing a staphylococcal infection an effective amount of an isolated Emp antigen or an immunogenic fragment thereof, and at least one additional staphylococcal antigen selected from a group consisting of an isolated ClfA, ClfB, Eap, EsaB, EsaC, EsxA, EsxB, IsdA, IsdB, IsdC, SasB, SasH, Ebh, Coa, vWa, SasF, SdrC, SdrD, SdrE, Hla and SpA antigen, or an immunogenic fragment thereof.

73-97. (canceled)

98. A method for eliciting an immune response against a staphylococcus bacterium in a subject comprising administering to the subject an effective amount of a composition comprising:

(a) an isolated Eap antigen, or an immunogenic fragment thereof, and

(b) at least one additional staphylococcal antigen selected from a group consisting of an isolated ClfA, ClfB, Emp, EsaB, EsaC, EsxA, EsxB, IsdA, IsdB, IsdC, SasF, SasH, Ebh, Coa, vWa, SasB, SdrC, SdrD, SdrE, Hla and SpA antigen, or an immunogenic fragment thereof.

99-162. (canceled)

163. A method for eliciting an immune response against a staphylococcus bacterium in a subject comprising administering to the subject an effective amount of a composition comprising an isolated AdsA peptide, or an immunogenic fragment thereof.

164-215. (canceled)

* * * * *