

US00RE48137E

(19) **United States**  
 (12) **Reissued Patent**  
**Shirtliff et al.**

(10) **Patent Number: US RE48,137 E**  
 (45) **Date of Reissued Patent: Aug. 4, 2020**

(54) **MULTIVALENT VACCINE PROTECTION FROM *STAPHYLOCOCCUS AUREUS* INFECTION**

FOREIGN PATENT DOCUMENTS

WO 2007/113222 10/2007

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(21) Appl. No.: **15/903,831**

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(22) Filed: **Feb. 23, 2018**

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Reissue of:

(64) Patent No.: **9,265,820**  
 Issued: **Feb. 23, 2016**  
 Appl. No.: **14/382,837**  
 PCT Filed: **Mar. 5, 2013**  
 PCT No.: **PCT/US2013/029053**  
 § 371 (c)(1),  
 (2) Date: **Sep. 4, 2014**  
 PCT Pub. No.: **WO2013/134225**  
 PCT Pub. Date: **Sep. 12, 2013**

Japanese Office Action, dated Nov. 15, 2016 in corresponding Japanese patent application No. 2014-561022, with English language translation.

U.S. Applications:

(60) Provisional application No. 61/606,750, filed on Mar. 5, 2012.

Extended European Search Report, dated Nov. 30, 2015 in corresponding European Patent Application No. 13757330.9.

(51) **Int. Cl.**

**A61K 39/09** (2006.01)  
**A61K 38/14** (2006.01)  
**A61K 39/085** (2006.01)  
**A61K 39/00** (2006.01)

Shao et al., "Immunogenicity and Reactogenicity of Diphtheria-Tetanus-Acellular Pertussis-Hepatitis B-Inactivated Poliovirus and *Haemophilus influenzae* Type B Vaccines Administered Concomitantly to Infants as a Three-dose Primary Course", *Journal of the Formosan Medical Association*, 110(5): 336-341 (2011).

(52) **U.S. Cl.**

CPC ..... **A61K 39/092** (2013.01); **A61K 38/14** (2013.01); **A61K 39/085** (2013.01); **A61K 2039/70** (2013.01)

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(58) **Field of Classification Search**

CPC .. **A61K 39/395**; **A61K 39/085**; **A61K 39/116**;  
**A61K 39/09**; **A61K 39/092**; **A61K 2039/70**

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See application file for complete search history.

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(57) **ABSTRACT**

Vaccine formulations effective against *Staphylococcus aureus*, including methicillin-resistant *Staphylococcus aureus* (MRSA) are disclosed, as well as methods of using the vaccine formulations in the treatment and prevention of *Staphylococcus aureus* infections in a subject.

**18 Claims, 3 Drawing Sheets****Specification includes a Sequence Listing.**



Figure 1

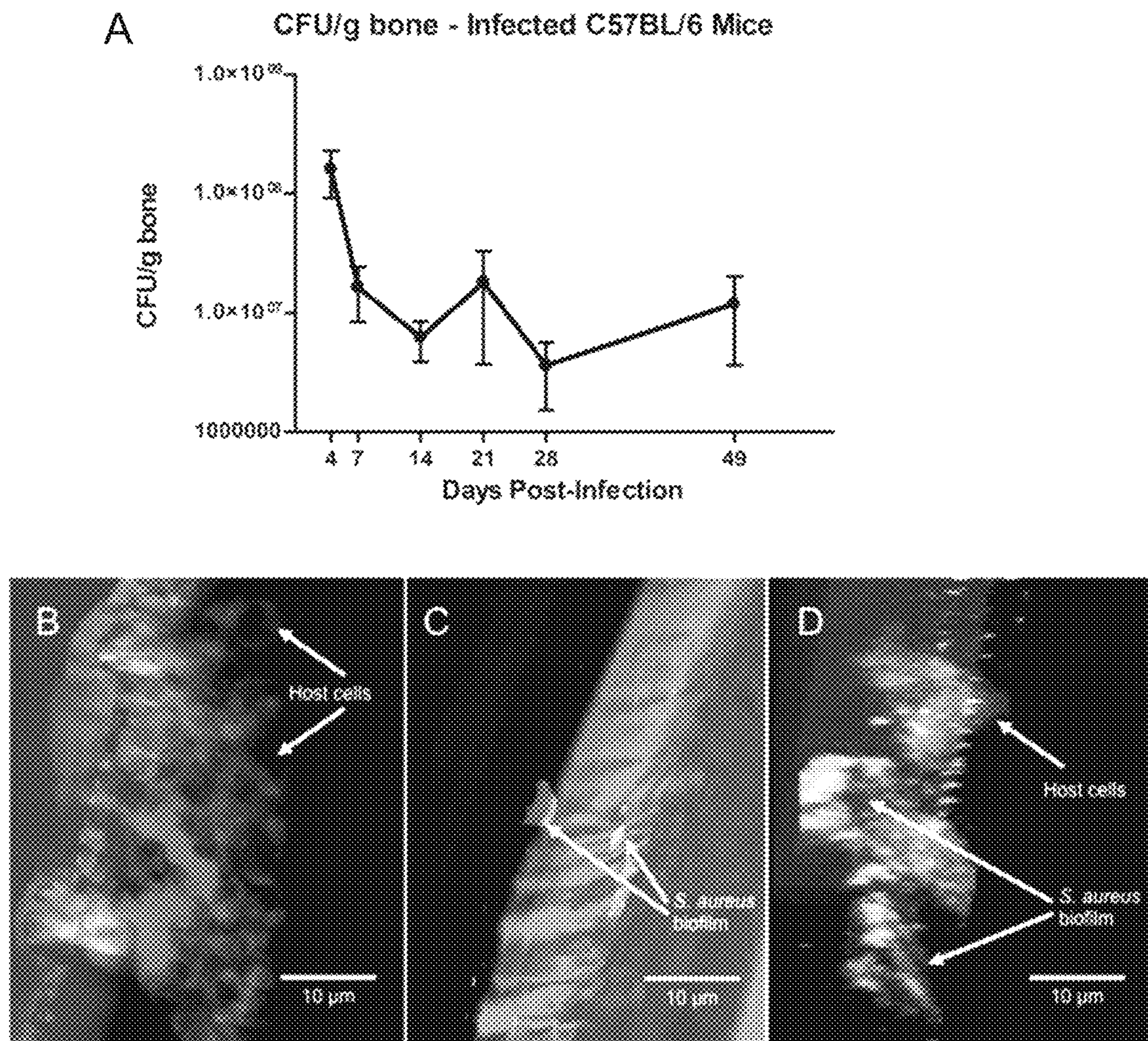


Figure 2

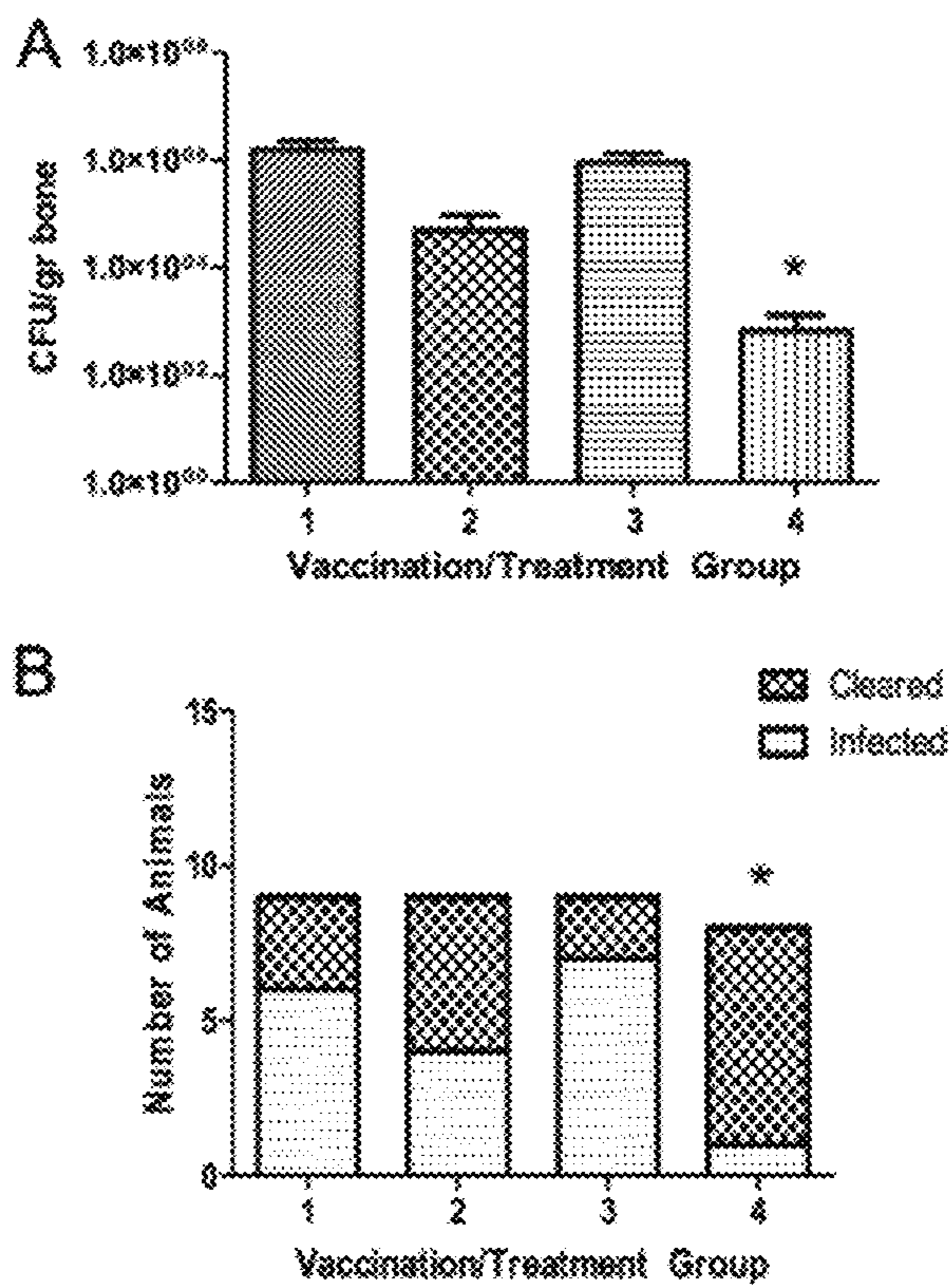
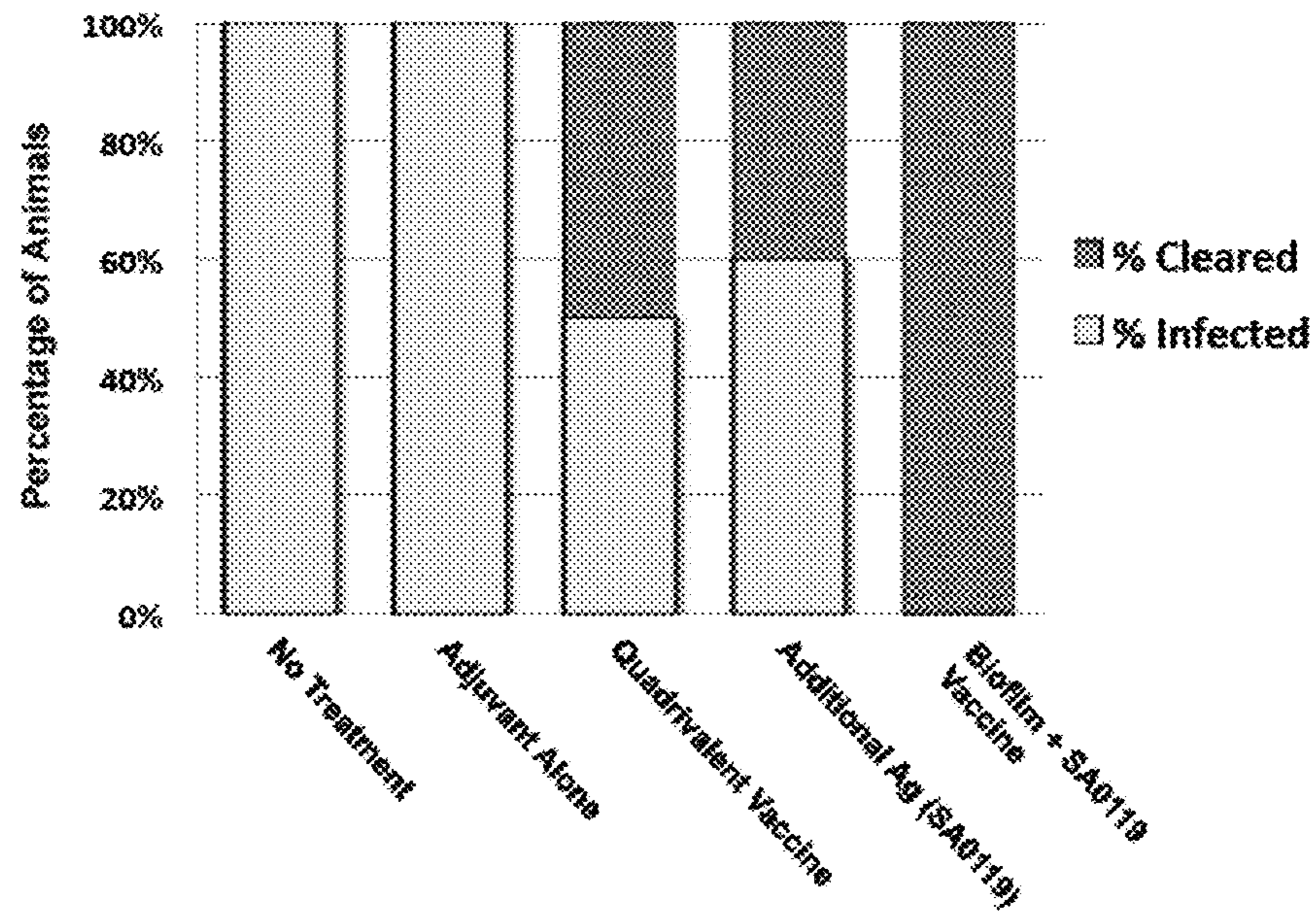




Figure 3





**MULTIVALENT VACCINE PROTECTION  
FROM *STAPHYLOCOCCUS AUREUS*  
INFECTION**

**Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue; a claim printed with strikethrough indicates that the claim was canceled, disclaimed, or held invalid by a prior post-patent action or proceeding.**

STATEMENT OF GOVERNMENTAL INTEREST

This invention was made with government support under Grant Number AI069568 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

1. Field of the Invention

The present invention relates to multivalent vaccine formulations effective against *Staphylococcus aureus*, including both biofilm and planktonic types of bacterial infections, and to methods of using the formulations in the treatment and prevention of *S. aureus* infections in subjects.

2. Related Art

One of the most common and costly problems for the U.S. healthcare system is nosocomial infections (26), with *S. aureus* being the second-leading cause of such infections (4). Methicillin-resistant *S. aureus* (MRSA) is responsible for 40-60% of all nosocomially-acquired *S. aureus* infections, and these resistant strains are now considered to be endemic in the hospital setting (36). Community-associated *S. aureus* strains may also acquire methicillin-resistance (CA-MRSA) and the modern emergence of such strains is of great concern (24, 31, 64).

Recent studies indicate that *S. aureus* is also the major mediator of prosthetic implant infection (1, 54). The increasing involvement of *S. aureus* in foreign body-related infections, the rapid development of resistance to multiple antibiotics by these organisms, and the propensity of these infections to change from an acute infection to one that is persistent, chronic and recurrent have led to this organism once again receiving significant attention.

Treating prosthetic implant infections is a complicated process, and a number of staphylococcal defense mechanisms may be responsible for this difficulty as well as the capacity of *S. aureus* to evade clearance by the host immune response. One of the most important mechanisms utilized by *S. aureus* to thwart the host immune response and develop into a persistent infection is through the formation of a highly-developed biofilm. A biofilm is defined as a microbe-derived community in which bacterial cells are attached to a hydrated surface and embedded in a polysaccharide matrix (13). Bacteria in a biofilm exhibit an altered phenotype in their growth, gene expression, and protein production (17), and prosthetic medical devices are often a site of chronic infection, because they present a suitable substrate for bacterial adherence, colonization, and biofilm formation. Biofilm formation by *S. aureus* during prosthetic implant infection makes eradication of this bacteria extremely difficult, due in part to the dramatically increased resistance of bacteria in a biofilm to host defenses (21) and to antibiotics (46, 51), compared to their planktonic counterparts.

Previous vaccine studies have evaluated the efficacy of bacterial polysaccharides, e.g. polysaccharide capsules, exopolysaccharide, and peptidoglycan (10, 20, 38, 41), as well as recombinant protein subunit vaccines (2, 8, 9, 27, 29, 30, 33, 57, 65) against *S. aureus* infection, but none have demonstrated complete eradication of *S. aureus* in experimental animal models (2, 8, 9, 27, 29, 30, 33, 57, 65) or passed the rigors of phase III clinical testing (56, 59). Most vaccines evaluated to date do not account for biological redundancy of *S. aureus* virulence factors, differential protein expression during different modes of growth (exponential growth versus stationary) or type of infection (planktonic versus biofilm), and the lack of antigen conservation amongst relevant clinical isolates. Indeed, a polysaccharide vaccine (StaphVAX) developed using the *S. aureus* capsular polysaccharide 5 (CP5) and capsular polysaccharide 8 (CP8) conjugated to the *Pseudomonas aeruginosa* exotoxin A failed to provide protection in phase III clinical trials against *S. aureus*-mediated bacteremia in two different cohorts of 1804 and 3600 hemodialysis patients (59). Factors contributing to this failure are the existence of non-encapsulated strains (CP5 and CP8 strains account for 75-80% of isolates) (12) and differential expression as extrapolated from in vitro data indicating that capsular polysaccharide expression is limited to the stationary mode of growth and the absence of CP5 expression in *S. aureus* bound to endothelial cells (48). The efficacy of the StaphVAX vaccine would, therefore, be limited to planktonic-type infections and ineffective at targeting the humoral response to a *S. aureus* biofilm.

Similar to the findings with the CP5/CP8 vaccine (20), subunit vaccines developed against the clumping factor A (C1fA) (2, 27), clumping factor B (C1fB) (57), fibronectin binding protein (FnBP) (65),  $\alpha$ -Hemolysin (9, 29), Pantovallentine leukocidin (PVL) (8), and the iron-regulated surface determinant B (IsdB) (30, 33) mediate partial protection in experimental animal models. These subunit vaccines did not provide complete protection, despite the candidate proteins being highly immunogenic in vivo (25, 33, 57) and the resultant antibodies promoting opsonic killing of *S. aureus* (65). One deficiency of these approaches was relying on a monovalent vaccine to promote protection against the pathogen. *S. aureus* has nearly 70 virulence factors and functional redundancy amongst these factors may abrogate the effect of neutralizing one factor. Arguably, *S. aureus* expresses multiple iron acquisition systems: siderophores staphyloferrin A and B transport transferrin to receptors HtsA and SirA (14, 43), an ABC transporter Fhu imports  $\text{Fe}^{3+}$  hydroxamates (58), and iron-regulated surface determinant (Isd) B and IsdH receptors that bind hemoglobin/haptoglobin complexes (18, 62), therefore the overall effectiveness of anti-IsdB antibodies that block IsdB-mediated hemoglobin binding may be only a modest effect on iron uptake and the organism's pathogenicity (30). The validity of this argument is exemplified by the cessation of phase III clinical trials of Merck's IsdB vaccine (V710) that failed to provide complete protection (16), despite promising immunogenicity and opsonic killing data from phase II trials (25, 52).

Efficacy of a monovalent vaccine can also be compromised by differential expression of the targeted protein during the course of infection. While *S. aureus* initiates colonization by binding host extracellular ligands using its adhesin proteins called microbial surface components recognizing adhesive matrix molecules (MSCRAMMs), including the fibronectin-binding protein (FnBP), these factors are mostly down-regulated as the sessile bacteria encapsulate themselves in an extracellular polysaccharide matrix, or biofilm (44, 55). Hence, vaccines designed to target a



MSCRAMM will be ineffective at clearance after the bacteria transition into the biofilm phenotype. Evaluation of the MSCRAMM FnBP vaccine demonstrated it provided partial protection against *S. aureus* in a murine model of sepsis, but the study failed to enumerate bacteria in the blood and/or kidneys to verify bacterial clearance. It is feasible that *S. aureus* can subvert the humoral response to FnBP, form a sessile biofilm and down-regulate FnBP, and become completely recalcitrant the host response.

A vaccine strategy that circumvents the incomplete protection of monovalent vaccines caused by protein redundancy, differential protein expression, or isolate-specific genetic divergence is the generation of a multifactorial assault using a multivalent subunit vaccine. Stranger-Jones et al. demonstrated a quadrivalent vaccine comprised of surface-exposed proteins: iron-regulated surface determinant A (IsdA), IsdB, and serine aspartate repeat protein D (SdrD), and SdrE increased survival rates against *S. aureus*-mediated lethal challenge compared to protection afforded by each monovalent variant (61). Although the authors stressed the survival rates after lethal challenge, they omitted enumeration of *S. aureus* in the kidneys and survival rates beyond 7 days post-infection from the data analysis. These omissions preclude a conclusion to be reached on the vaccine's ability to promote complete bacterial clearance and prevent future complications due to *S. aureus* persistence via biofilm formation. Overall, the multivalent vaccine had limited efficacy, providing complete protection against only two of five clinical *S. aureus* isolates tested (61). In addition, comparative analysis of multiple *S. aureus* genomes found a lack of conservation amongst some surface proteins, including SdrD and SdrE (39), which indicates the limited efficacy of the IsdA/IsdB/SdrD/SdrE vaccine formulation may extend beyond the clinical isolates tested by Stranger-Jones.

Vaccine studies have predominately focused on protection against planktonic-mediated infection by examining sepsis (20, 27, 33, 38, 41, 61, 65) or pneumonia (9), while few studies have incidentally evaluated protection, mediated by popular vaccine candidates, against biofilm infection with experimental endocarditis (2), skin (8, 22, 29), or abscess models (20, 61). As a departure from previous *S. aureus* vaccine strategies, Brady et al. focused on identifying biofilm upregulated proteins that are immunogenic (4) and established that a multivalent biofilm-based vaccine when coupled with vancomycin treatment could eradicate a biofilm infection, which is traditionally recalcitrant to clearance by either antibiotic treatment or immune response (5). Previous attempts to target the biofilm phenotype, most notably against the staphylococcal intercellular adhesion (PIA) composed of poly-N-acetyl- $\beta$ -1,6-glucosamine (PNAG) (38, 40, 41), were directed towards the biofilm matrix encapsulating the bacteria versus cell wall-associated proteins. The polysaccharide PNAG vaccine elicited a response that reduced bacterial counts (40), but polysaccharides tend to be weak immunogens and induce antibodies with low opsonic killing activity. In addition, PNAG molecules tend to be loosely associated with the bacterial surface and the acetylated PNAG form is released into suspension (11). Efforts to improve efficacy of the PNAG vaccine have evaluated the deacetylated form of PNAG (dPNAG), which may be retained on the cell surface, conjugated to diphtheria toxoid or a synthetic 9-mer of  $\beta$ -(1 $\rightarrow$ 6)-D-glucosamine (GlcNH<sub>2</sub>) conjugated to tetanus toxoid, but partial protection against multiple *S. aureus* strains was observed despite improved immunogenicity (22, 38). PIA is generated by enzymes encoded on the icaABDC

locus (28), but the presence of the icaABDC locus does not directly correlate to biofilm formation in vitro (32) and the icaABDC locus in *S. aureus* was dispensable in a subset of in vivo orthopedic prosthesis-associated and catheter-associated infections, which are identified as biofilm-mediated infections (53). While the efficacy of the PNAG vaccine against *S. aureus* biofilms requires further evaluation, the dispensability of the icaABDC locus in some *S. aureus* strains isolated from clinical infections suggests that the PNAG vaccine would provide limited protection against *S. aureus* biofilm infections.

Another consideration for vaccine development is the type of response elicited by the host immune system and the ability of the pathogen to subvert immune mediators using immunoavoidance factors, which may have varied outcomes depending on the host environment. The immune response elicited in vitro against *S. aureus* or its virulence factors, specifically staphylococcal enterotoxin A or B and the alpha toxin, is a pro-inflammatory Th1-response (3, 7, 15, 42). Indeed, comparison of *S. aureus* bacteremia outcomes in mice with different genetic backgrounds found that Th1-biased C57BL/6J mice were resistant and Th2-biased BALB/c mice were susceptible to this acute form of *S. aureus* infection (63). In contrast, a robust Th-1 response was elicited against a *S. aureus* implant infection in C57BL/6J mice, but the mice were susceptible and developed a chronic infection with 10<sup>7</sup> CFU/tibia at 49 days post-infection (45). The *S. aureus* biofilm appears to be recalcitrant to the pro-inflammatory response, which damages host tissue at the infection site generating devitalized sites for *S. aureus* to colonize. Subsequent evaluation found that Th-2 biased BALB/c mice were resistant to the *S. aureus* implant infection, and ablation of interleukin-4 or the depletion of Treg cells abrogated the protection against *S. aureus* in BALB/c mice (46). Th2-mediated resistance to bacterial infection was also revealed for subcutaneous infections with *S. aureus*, where higher bacterial loads were observed in C57BL/6J mice versus BALB/c mice (45). Increased CXCL-2 expression in the C57BL/6J mice correlated with the susceptibility to subcutaneous infection (45), and may halt the killing activity of polymorphonuclear neutrophils (PMNs) after influx and internalization of *S. aureus* (23). This differential immune response against *S. aureus*, which was observed with chronic infections (implant or subcutaneous) versus acute (sepsis), indicates that the choice of mouse strain may impact the outcome of vaccine studies. Most vaccine studies have examined protection against *S. aureus* using experimental models developed in BALB/c mice (2, 8, 33, 61, 65), while few studies have evaluated vaccine efficacy in C57BL/6J mice (9, 29). Emphasis on BALB/c experimental models to evaluate *S. aureus* vaccines may yield insight about efficacy against acute or planktonic infections, but these models will be poor evaluators of chronic, biofilm infections and do not represent the immune response bias in humans.

Additional vaccine formulations would add to the arsenal of means used to treat and/or prevent *S. aureus* infections.

#### SUMMARY

*Staphylococcus aureus* has re-emerged as a major human pathogen and there are presently no vaccines that afford consistent, long-term protection against *S. aureus* infections. While infections, particularly those with MRSA, are often nosocomial in origin, community acquired infections associated with this microbial species have reached epidemic levels. One of the ways in which *S. aureus* is able to persist



in the host and remain recalcitrant to clearance by the immune system or antimicrobial agents is through a biofilm mode of growth. Therefore, an effective vaccine and/or treatment modality that could prevent the establishment of biofilm-mediated chronic infections by *S. aureus* is needed.

The present invention demonstrates protection against biofilm-associated *S. aureus* infection through the use of a multi-component vaccine, alone or in combination with subsequent antimicrobial agent therapy. Complete protection was demonstrated in a murine tibial implant model using a biofilm- and planktonic-specific pentavalent vaccine, with 100% clearance of *S. aureus*.

The vaccine formulations of the present invention hold significant promise for those with identified risk factors for *S. aureus* biofilm infection. Even in patients that acquire a *S. aureus* infection, an anti-biofilm vaccine could allow these previously untreatable infections to be halted or cured without the need for surgical intervention. The present invention thus provides new means to limit and eradicate *S. aureus* biofilm infections that could help to prevent the onset of chronic disease, saving patients from significant morbidity and mortality.

The present invention is directed to the following embodiments of vaccine formulations.

In a first embodiment the present invention is directed to a vaccine formulation comprising five different polypeptides of a strain of *S. aureus* (a first, second, third, fourth and fifth polypeptide of a strain of *S. aureus*), or portions thereof, or variants thereof, or combinations thereof, and a pharmaceutically acceptable carrier or diluent. The strain of *S. aureus* may be a methicillin-resistant or a methicillin-sensitive strain of *S. aureus*.

In one aspect, at least one of the *S. aureus* polypeptides is a polypeptide expressed by a planktonic form of the bacteria and at least one of the *S. aureus* polypeptides is a polypeptide expressed by a biofilm form of the bacteria. In a related aspect, one of the *S. aureus* polypeptides is a polypeptide expressed by a planktonic form of the bacteria and four of the *S. aureus* polypeptides are polypeptides expressed by a biofilm form of the bacteria.

In another aspect, the first, second, third, fourth and fifth polypeptides are *S. aureus* polypeptide SA0037 set forth in SEQ ID NO:13, *S. aureus* polypeptide SA0119 set forth in SEQ ID NO:14, *S. aureus* polypeptide SA0486 set forth in SEQ ID NO:15, *S. aureus* polypeptide SA0688 set forth in SEQ ID NO:16, and *S. aureus* glucosaminidase set forth in SEQ ID NO:17.

In further aspects, the vaccine formulations comprise one or more portions of one or more of the *S. aureus* polypeptides, wherein the portions individually encompass at least about 20 contiguous amino acids of the full length polypeptide. In the same or aspects, the vaccine formulations comprise one or more variants of one or more of the *S. aureus* polypeptides or portions thereof, wherein the variants individually have at least about 95% identity to a *S. aureus* polypeptide or portion thereof.

In a particular aspect, the present invention is directed to a vaccine formulation comprising five different, full-length polypeptides of a strain of *S. aureus*. In one example, the five polypeptides are *S. aureus* polypeptide SA0037 set forth in SEQ ID NO:13, *S. aureus* polypeptide SA0119 set forth in SEQ ID NO:14, *S. aureus* polypeptide SA0486 set forth in SEQ ID NO:15, *S. aureus* polypeptide SA0688 set forth in SEQ ID NO:16, and *S. aureus* glucosaminidase set forth in SEQ ID NO:17.

The present invention is also directed to the following embodiments of methods of using the vaccine formulations

of the invention. Thus, in a second embodiment, the present invention is directed to methods of generating an immune response in a subject comprising administering an immunologically effective amount of a vaccine formulation of the present invention to a subject, thereby generating an immune response in a subject. In one aspect, the immune response is a protective immune response.

In a third embodiment the present invention is directed to methods for treating a *S. aureus* infection in a subject, comprising administering a therapeutically effective amount of a vaccine formulation of the present invention to a subject having a *S. aureus* infection, thereby treating a *S. aureus* infection in a subject.

In a fourth embodiment the present invention is directed to methods of inhibiting a *S. aureus* infection in a subject, comprising administering a therapeutically effective amount of a vaccine formulation of the present invention to a subject at risk of developing a *S. aureus* infection, thereby inhibiting a *S. aureus* infection in a subject.

In related embodiments, the methods for treating or inhibiting a *S. aureus* infection may further comprise administering one or more antimicrobial agents to a subject having a *S. aureus* infection or at risk of developing a *S. aureus* infection, wherein the antimicrobial agent is administered prior to, concurrent with or after the vaccine formulation. In these embodiments the antimicrobial agent(s) may be selected from the group that includes, but is not limited to, an Aminoglycoside, such as Amikacin, Gentamicin, Kanamycin, Neomycin, Netilmicin, Streptomycin, Tobramycin or Paromomycin; a Carbacephem, such as Loracarbef; a Carbapenem, such as Ertapenem, Doripenem, Imipenem/Cilastatin or Meropenem; a Cephalosporin, such as Cefadroxil, Cefazolin, Cefalotin, Cefalexin, Cefaclor, Cefamandole, Cefoxitin, Cefprozil, Cefuroxime, Cefixime, Cefdinir, Cefditoren, Cefoperazone, Cefotaxime, Cefpodoxime, Ceftazidime, Ceftibuten, Ceftizoxime, Ceftriaxone, Cefepime or Ceftobiprole; a Glycopeptide, such as Teicoplanin or Vancomycin; a Macrolide, such as Azithromycin, Clarithromycin, Dirithromycin, Erythromycin, Erythroped, Roxithromycin, Troleandomycin, Telithromycin or Spectinomycin; a Monobactam, such as Aztreonam; a Penicillin, such as Amoxicillin, Ampicillin, Azlocillin, Carbenicillin, Cloxacillin, Dicloxacillin, Flucloxacillin, Mezlocillin, Metcillin, Nafcillin, Oxacillin, Penicillin, Piperacillin or Ticarcillin; a Polypeptide, such as Bacitracin, Colistin or Polymyxin B; a Quinolone, such as Ciprofloxacin, Enoxacin, Gatifloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Norfloxacin, Ofloxacin or Trovafloxacin; a Sulfonamide, such as Mafenide, Prontosil (archaic), Sulfacetamide, Sulfamethizole, Sulfanilamide (archaic), Sulfasalazine, Sulfisoxazole, Trimethoprim or Trimethoprim-Sulfamethoxazole (Cotrimoxazole) (TMP-SMX); a Tetracycline, such as Demeclocycline, Doxycycline, Minocycline, Oxytetracycline or Tetracycline; as well as Chloramphenicol, Clindamycin, Lincomycin, Fusidic acid, Furazolidone, Linezolid, Metronidazole, Mupirocin, Nitrofurantoin, Macrobid, Platensimycin, Quinupristin/Dalfopristin, Rifampin or Rifampicin.

In the embodiments directed to methods of treatment and inhibition, the *S. aureus* infection may be any *S. aureus* infection of a subject, including, for example, one or more of a *S. aureus* biofilm infection, a planktonic *S. aureus* infection, a *S. aureus* osteomyelitis infection, a biofilm-associated *S. aureus* osteomyelitis infection, a *S. aureus* indwelling medical device infection, a *S. aureus* endocarditis infection, a *S. aureus* diabetic wound or ulcer infection, a *S. aureus* chronic rhinosinusitis infection, a *S. aureus* ventilator



associated pneumonia infection, a *S. aureus* intravenous catheter associated infection, a *S. aureus* skin infection, a *S. aureus* nectrotizing fasciitis, a *S. aureus* keratitis, a *S. aureus* endophthalmitis, a *S. aureus* pyopneumothorax, a *S. aureus* empyema, and a *S. aureus* septicemia.

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: (A) Development of chronic, biofilm-mediated infection that is recalcitrant to antimicrobial therapy. CFU/g bone over time, indicating the development of a chronic infection. Tibiae from infected and uninfected mice were removed at days 4, 7, 14, 21, 28, and 49 days post-infection. No CFUs were found in uninfected mice. Serial dilutions of bone homogenates were plated on blood agar plates. CFU/g bone were calculated and plotted over time (n=5-8 mice per group, experiments performed in triplicate, \* denotes p<0.05 compared to controls by Fishers exact test). Bars represent SD. (B-D) Confocal scanning laser microscopic images of (B) uninfected pins removed 21 days post-implantation, and *S. aureus* infected pins removed at (C) 7 and (D) 21 days post-implantation. Pins were labeled using a FITC-labeled PNA-FISH probe. Biofilm formation is evident on the pin removed from the infected mouse.

FIG. 2: Vaccination with quadrivalent vaccine and adjunctive vancomycin treatment in a rabbit model of an *S. aureus* osteomyelitis biofilm infection. (A) Animals vaccinated with PBS only (1), PBS and subsequent treatment with vancomycin (2), the quadrivalent vaccine only (3), or the vaccine plus vancomycin (4). The mean+/-SEM for CFU/grams bone is shown for each group. \*=significant difference from group 1, PBS control (P<0.05, Student's t test). (B) Animals in each group that were completely cleared of infection. \*=significant difference from group 1, PBS control (P<0.05, Fisher's Exact Test).

FIG. 3: Vaccination with quadrivalent biofilm vaccine, planktonic vaccine, or pentavalent dual phenotype vaccine in a murine model of a *S. aureus* implant infection. Control mice received no treatment (column 1) or unvaccinated with Alum alone (column 2). Experimental mice received a biofilm-directed quadrivalent vaccine (column 3), a planktonic-specific monovalent vaccine (SA0119; column 4), or a combination of the antigens in a pentavalent vaccine (column 5).

#### DETAILED DESCRIPTION

Biofilm-embedded bacteria have remarkably different phenotypic and antigenic properties compared to their free-floating, planktonic counterparts. These differences have presented a struggle when designing vaccine formulations for use in treating and preventing both types of bacterial infections. Even individual stages of biofilm growth (from early attached to maturing and fully mature stages) have been shown to be more antigenically distinct from one another than even biofilm versus planktonic bacteria (66).

Through extensive research into acceptable vaccine candidates, the inventors have identified genes expressed/produced uniquely in biofilm and in planktonic modes of growth via proteomics and transcriptomics techniques. In particular, the inventors found that one must compare multiple stages of biofilm growth (from early attached to maturing and fully mature stages) to multiple stages of planktonic growth (early log, late log, stationary, and post stationary) in order to find those cell wall antigens with up-regulated and sustained expression in all biofilm stages and those with up-regulated and sustained expression in all planktonic

growth stages. By combining biofilm and planktonic antigens that are expressed on the membrane or cell wall into a multivalent vaccine, protection of the host against microbial challenge by the specific microbial species can be elicited.

5 This protection can be promoted since bacteria in the host exist in antigenically distinct forms of the planktonic and biofilm modes of growth during an infection and, as a result, a dual immune response against both phenotypes must be produced in the host.

10 The vaccine formulations of the present invention include antigens effective at priming the host immune response to clear both detached, free-floating populations of bacteria as well as bacteria forming a biofilm type of infection. This work is the first to acknowledge, and overcome, the differences of protein expression within different types of infection caused by the same microorganism, and demonstrate (as shown in the Examples) complete clearance in an *S. aureus* animal model of infection instead of only a significant reduction in bacterial populations.

20 As discussed above and herein, the present invention relates to vaccine formulations effective against *S. aureus*, including methicillin-resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA), and to methods of using the vaccines in the treatment and prevention of *S. aureus* infections in a subject.

#### I. Vaccine Components—Proteins

The vaccine formulations of the present invention comprise at least a portion of each of five different polypeptides of a strain of *S. aureus* and a pharmaceutically acceptable carrier or diluent. The vaccine formulations are characterized in that they comprise at least one *S. aureus* polypeptide expressed by a planktonic form of the bacteria and at least one *S. aureus* polypeptide expressed by a biofilm form of the bacteria. The vaccine formulations of the present invention may thus comprise one, two, three, or four *S. aureus* polypeptides expressed by a planktonic form of the bacteria, and one, two, three, or four *S. aureus* polypeptides expressed by a biofilm form of the bacteria. In one aspect, the vaccine formulations comprise one *S. aureus* polypeptide expressed by a planktonic form of the bacteria and four *S. aureus* polypeptides expressed by a biofilm form of the bacteria.

The skilled artisan will understand that the identity, number and size of the different *S. aureus* proteins that can be included in the vaccine formulations of the present invention may vary. For example, the formulations may comprise only full-length versions of the polypeptides. Or the formulations may comprise only portions of the full-length polypeptides. Or the formulations may comprise a combination of portions and full-length polypeptides. Furthermore, combinations include formulations having one, two, three, four, five, six or more different portions of the same *S. aureus* polypeptide in combination with one or more portions of other polypeptides and/or full-length polypeptides and/or both portions and full-length versions of the same polypeptide. However, each of the formulations comprises at least one portion of each of five different polypeptides of a strain of *S. aureus*.

The identity of the planktonic- and biofilm-expressed polypeptides included in the vaccine formulations of the present invention is not particularly limited but each is a polypeptide from a strain of *S. aureus*. However, because the primary purpose of the vaccine formulations is to prime and activate the immune system of the subject receiving the vaccine formulation, the use of polypeptides exposed on the surface of the bacteria is particularly preferred. For example, the polypeptides may be cell wall and cell wall-associated polypeptides of *S. aureus*. Examples of such polypeptides include the *S. aureus* polypeptides SA0037 (SEQ ID



NO:13), SA0119 (SEQ ID NO:14), SA0486 (SEQ ID NO:15), SA0688 (SEQ ID NO:16), and glucosaminidase (SEQ ID NO:17).

Additional *S. aureus* polypeptides that may be used in the vaccine formulations of the present invention include the polypeptides of Table 1.

TABLE 1

Biofilm Expressed Polypeptides	
SACOL0405	MATE efflux family protein (SEQ ID NO: 18)
SACOL0379	bacteriophage L54a, M23/M37 peptidase domain protein (SEQ ID NO: 19)
SACOL2658	arginine repressor (SEQ ID NO: 20)
SACOL1041	hypothetical protein (SEQ ID NO: 21)
SACOL0048	conserved hypothetical protein (SEQ ID NO: 22)
SACOL2292	Na <sup>+</sup> /H <sup>+</sup> antiporter (SEQ ID NO: 23)
SACOL0204	formate acetyltransferase (SEQ ID NO: 24)
SACOL2729	integrase/recombinase, core domain family (SEQ ID NO: 25)
SACOL2424	6-carboxyhexanoate--CoA ligase (SEQ ID NO: 26)
SACOL1183	membrane protein, putative (SEQ ID NO: 27)
SACOL2446	epimerase/dehydratase, putative (SEQ ID NO: 28)
SACOL0386	bacteriophage L54a, hypothetical protein (SEQ ID NO: 29)
Planktonic Expressed Polypeptides	
SACOL0633	conserved hypothetical protein (SEQ ID NO: 30)
SACOL1664	conserved hypothetical protein TIGR00370 (SEQ ID NO: 31)
SACOL0541	stage V sporulation protein G spoVG (SEQ ID NO: 32)
SACOL1138	29-kDa cell surface protein, putative sasJ (SEQ ID NO: 33)
SACOL0117	polysaccharide extrusion protein (SEQ ID NO: 34)
SACOL1659	conserved hypothetical protein (SEQ ID NO: 35)
SACOL2150	mrp protein sasB (SEQ ID NO: 36)

When only a portion(s) of a polypeptide is used in a vaccine formulation, the size of the peptide is only limited by its ability to be recognized by the immune system of the subject to which the vaccine is administered. In general, the peptides included in the formulations should be about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 or more contiguous amino acids of the full-length protein. The preferred size of the peptides is between about 20 amino acids and 3000 amino acids in length, more preferably between about 40 amino acids and 1500 amino acids in length, even more preferably between about 150 amino acids and 1300 amino acids in length. In other aspects, the peptides may 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% of the size of the full-length protein.

As indicated above, the polypeptides and portions thereof used in the formulations of the present invention are from strains of *S. aureus*. There is no limitation on the different strains of *S. aureus* that might be used. As an example only, polypeptides from medically important strains of *S. aureus*, such methicillin-resistant *S. aureus* (either community-associated or hospital-acquired strains) and methicillin-sensitive *S. aureus*, may be used to constitute the vaccine formulations of the present invention. Therefore, the vaccine formulations of the present invention include the use of variants of the *S. aureus* polypeptides and portions thereof defined herein and having at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity over their entire length to *S. aureus* polypeptides and portions thereof. Sequence identity is determined by aligning the amino acid sequence of two peptides or proteins and calculating the number of amino

acid differences over the entire length of the alignment. The skilled artisan will understand that there are a number of commercially available sequence manipulation programs for use in making such calculations, including the website of the National Center for Biotechnology Information.

The polypeptides, portions, and variants thereof (collectively, termed "proteins") used in the vaccine formulations may be obtained through any of the many well-established means known in the art. The skilled artisan will understand that the proteins can possess the native glycosylation of polypeptide as it is produced by the corresponding strain of *S. aureus*, or they can lack such glycosylation, or they can have altered glycosylation.

## II. Vaccine Components—Carriers and Excipients

The pharmaceutically acceptable carrier, diluent or excipient included in the vaccine formulations will vary based on the identity of the proteins in the formulation, the means used to administer the formulation, the site of administration and the dosing schedule used. Suitable examples of carriers and diluents are well known to those skilled in the art and include water-for-injection, saline, buffered saline, dextrose, water, glycerol, ethanol, propylene glycol, polysorbate 80 (Tween-80™), poly(ethylene)glycol 300 and 400 (PEG 300 and 400), PEGylated castor oil (e.g. Cremophor EL), poloxamer 407 and 188, hydrophilic and hydrophobic carriers, and combinations thereof. Hydrophobic carriers include, for example, fat emulsions, lipids, PEGylated phospholipids, polymer matrices, biocompatible polymers, lipospheres, vesicles, particles, and liposomes. The terms specifically exclude cell culture medium. Additional carriers include cornstarch, gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride, alginic acid, croscarmellose sodium, and sodium starch glycolate.

Excipients included in a formulation have different purposes depending, for example on the nature of the vaccine formulation and the mode of administration. Examples of generally used excipients include, without limitation: stabilizing agents, solubilizing agents and surfactants, buffers, antioxidants and preservatives, tonicity agents, bulking agents, lubricating agents, emulsifiers, suspending or viscosity agents, inert diluents, fillers, disintegrating agents, binding agents, wetting agents, lubricating agents, antibacterials, chelating agents, sweeteners, perfuming agents, flavouring agents, coloring agents, administration aids, and combinations thereof.

As a specific example, intramuscular preparations can be prepared and administered in a pharmaceutically acceptable diluent such as Water-for-Injection, 0.9% saline, or 5% glucose solution.

In one embodiment of the present invention, the vaccine formulations exist as atomized dispersions for delivery by inhalation. The atomized dispersion of the vaccine formulation typically contains carriers common for atomized or aerosolized dispersions, such as buffered saline and/or other compounds well known to those of skill in the art. The delivery of the vaccine formulations via inhalation has the effect of rapidly dispersing the vaccine formulation to a large area of mucosal tissues as well as quick absorption by the blood for circulation. One example of a method of preparing an atomized dispersion is described in U.S. Pat. No. 6,187,344, entitled, "Powdered Pharmaceutical Formulations Having Improved Dispersibility," which is hereby incorporated by reference in its entirety.

Additionally, the vaccines and vaccine formulations may also be administered in a liquid form. The liquid can be for oral dosage, for ophthalmic or nasal dosage as drops, or for



use as an enema or douche. When the vaccine formulation is formulated as a liquid, the liquid can be either a solution or a suspension of the vaccine formulation. There are a variety of suitable formulations for the solution or suspension of the vaccine formulation that are well known to those of skill in the art, depending on the intended use thereof. Liquid formulations for oral administration prepared in water or other aqueous vehicles may contain various suspending agents such as methylcellulose, alginates, tragacanth, pectin, kelgin, carrageenan, acacia, polyvinylpyrrolidone, and polyvinyl alcohol. The liquid formulations may also include solutions, emulsions, syrups and elixirs containing, together with the active compound(s), wetting agents, sweeteners, and coloring and flavoring agents. Various liquid and powder formulations can be prepared by conventional methods for inhalation into the lungs of the mammal to be treated.

The vaccine formulations of the present invention may also include an adjuvant. Suitable adjuvants include Freund's Complete and Incomplete Adjuvant, Titermax, Oil in Water Adjuvants, as well as Aluminum compounds where antigens, normally proteins, are physically precipitated with hydrated insoluble salts of aluminum hydroxide or aluminum phosphate. Other adjuvants include liposome-type adjuvants comprising spheres having phospholipid bilayers that form an aqueous compartment containing the vaccine candidate and protecting it from rapid degradation, and that provide a depot effect for sustained release. Surface active agents may also be used as adjuvants and include lipoteichoic acid of gram-positive organisms, lipid A, and TDM. Quil A and QS-21 (saponin-type adjuvants), monophosphoryl lipid A, and lipophilic MDP derivatives are suitable adjuvants that have hydrophilic and hydrophobic domains from which their surface-active properties arise. Compounds normally found in the body such as vitamin A and E, and lysolecithin may also be used as surface-active agents. Other classes of adjuvants include glycan analog, coenzyme Q, amphotericin B, dimethyldioctadecylammonium bromide (DDA), levamisole, and benzimidazole compounds. The immunostimulation provided by a surface active agent may also be accomplished by either developing a fusion protein with non-active portions of the cholera toxin, exotoxin A, or the heat labile toxin from *E. coli* Immunomodulation through the use of anti-IL-17, anti IFN- $\gamma$ , anti-IL-12, IL-2, IL-10, or IL-4 may also be used to promote a strong Th2 or antibody mediated response to the vaccine formulation.

### III. Methods of Generating an Immune Response

The present invention is also directed to methods of generating an immune response in a subject to a vaccine formulation of the present invention. In one embodiment, the present invention is directed to methods of generating an immune response in a subject, comprising administering an immunologically effective amount of a vaccine formulation of the present invention to a subject, thereby generating an immune response in a subject. In each of the methods of generating an immune response of the present invention, the immune response is preferably a protective immune response.

An "immunologically effective amount" of a vaccine formulation is one that is sufficient to induce an immune response to vaccine components in the subject to which the vaccine formulation is administered. A "protective immune response" is one that confers on the subject to which the vaccine formulation is administered protective immunity against *S. aureus*. The protective immunity may be partial or complete immunity.

### IV. Methods of Treatment and Prevention

The present invention is also directed to methods of treating a *S. aureus* infection in a subject using the vaccine formulations of the present invention. In one embodiment, the present invention is directed to methods of treating a *S. aureus* infection in a subject, comprising administering a therapeutically effective amount of a vaccine formulation of the present invention to a subject having a *S. aureus* infection, thereby treating a *S. aureus* infection in a subject. In certain aspects, the method further comprises administering an antimicrobial agent to the subject having a *S. aureus* infection in conjunction with the administration of the vaccine formulation.

The vaccine formulations of the present invention may also be used in methods of inhibiting a *S. aureus* infection in a subject. Such methods comprise administering a therapeutically effective amount of a vaccine formulation of the present invention to a subject at risk of developing a *S. aureus* infection, thereby inhibiting a *S. aureus* infection in a subject. In certain aspects, the method further comprises administering an antimicrobial agent to the subject at risk of developing a *S. aureus* infection in conjunction with the administration of the vaccine formulation.

A "therapeutically effective amount" of a vaccine formulation is one that is sufficient to provide at least some reduction in the symptoms of a *S. aureus* infection in a subject to which the vaccine formulation is administered, or one that is sufficient to achieve the goal of the method.

As used herein, the terms "treating" and "treatment" have their ordinary and customary meanings, and include one or more of, ameliorating a symptom of a *S. aureus* infection in a subject, blocking or ameliorating a recurrence of a symptom of a *S. aureus* infection in a subject, decreasing in severity and/or frequency a symptom of a *S. aureus* infection in a subject, as stasis, decreasing, or inhibiting growth of *S. aureus* in a subject. Treatment means ameliorating, blocking, reducing, decreasing or inhibiting by about 1% to about 100% versus a subject to which the vaccine formulation of the present invention has not been administered (with or without the additional administration of the antimicrobial agent). Preferably, the ameliorating, blocking, reducing, decreasing or inhibiting is 100%, 99%, 98%, 97%, 96%, 95%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5% or 1%. The treatment may begin prior to, concurrent with, or after the onset of clinical symptoms of the infection. The results of the treatment may be permanent, such as where the *S. aureus* infection is completely cleared from the subject, or may be for a period of days (such as 1, 2, 3, 4, 5, 6 or 7 days), weeks (such as 1, 2, 3 or 4 weeks) or months (such as 1, 2, 3, 4, 5, 6 or more months).

As used herein, the terms "inhibit", "inhibiting" and "inhibition" have their ordinary and customary meanings, and include one or more of inhibiting colonization of *S. aureus*, inhibiting growth of *S. aureus* (all forms, including planktonic and biofilm) and inhibiting propagation of *S. aureus*. Such inhibition is an inhibition of about 1% to about 100% versus a subject to which the vaccine formulation of the present invention has not been administered (with or without the additional administration of the antimicrobial agent). Preferably, the inhibition is an inhibition of 100%, 99%, 98%, 97%, 96%, 95%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5% or 1%. As used herein, the inhibition lasts at least a period of days, weeks, months or years upon completing of the dosing schedule. Preferably the inhibition is for the lifespan of the subject.

The methods for treating or inhibiting a *S. aureus* infection may further comprise administering one or more antimicrobial agents to a subject having a *S. aureus* infection or



at risk of developing a *S. aureus* infection. When an antimicrobial agent is included in the methods of the present invention, the antimicrobial agent may be administered prior to, concurrent with or after the vaccine formulation is administered to the subject. Where the antimicrobial agent is administered prior to or after the vaccine formulation, the period of time between when the antimicrobial agent and the vaccine formulation are administered may be a period of hours (such as 6, 12, 18 or 24 hours), days (such as 1, 2, 3, 4, 5, 6 or 7 days), weeks (such as 1, 2, 3 or 4 weeks) or months (such as 1, 2, 3, 4, 5, 6 or more months). The antimicrobial agent may be any that is effective in the treatment of a *S. aureus* infection and may include, but is not limited to, an Aminoglycoside, such as Amikacin, Gentamicin, Kanamycin, Neomycin, Netilmicin, Streptomycin, Tobramycin or Paromomycin; a Carbacephem, such as Loracarbef; a Carbapenem, such as Ertapenem, Doripenem, Imipenem/Cilastatin or Meropenem; a Cephalosporin, such as Cefadroxil, Cefazolin, Cefalotin, Cefalexin, Cefaclor, Cefamandole, Cefoxitin, Cefprozil, Cefuroxime, Cefixime, Cefdinir, Cefditoren, Cefoperazone, Cefotaxime, Cefpodoxime, Ceftazidime, Ceftibuten, Ceftizoxime, Ceftriaxone, Cefepime or Ceftobiprole; a Glycopeptide, such as Teicoplanin or Vancomycin; a Macrolide, such as Azithromycin, Clarithromycin, Dirithromycin, Erythromycin, Erythroped, Roxithromycin, Troleandomycin, Telithromycin or Spectinomycin; a Monobactam, such as Aztreonam; a Penicillin, such as Amoxicillin, Ampicillin, Azlocillin, Carbenicillin, Cloxacillin, Dicloxacillin, Flucloxacillin, Mezlocillin, Meticcillin, Nafcillin, Oxacillin, Penicillin, Piperacillin or Ticarcillin; a Polypeptide, such as Bacitracin, Colistin or Polymyxin B; a Quinolone, such as Ciprofloxacin, Enoxacin, Gatifloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Norfloxacin, Ofloxacin or Trovafloxacin; a Sulfonamide, such as Mafenide, Prontosil (archaic), Sulfacetamide, Sulfamethizole, Sulfanilamide (archaic), Sulfasalazine, Sulfisoxazole, Trimethoprim or Trimethoprim-Sulfamethoxazole (Cotrimoxazole) (TMP-SMX); a Tetracycline, such as Demeclocycline, Doxycycline, Minocycline, Oxytetracycline or Tetracycline; as well as Chloramphenicol, Clindamycin, Lincomycin, Fusidic acid, Furazolidone, Linezolid, Metronidazole, Mupirocin, Nitrofurantoin, Macrobid, Platensimycin, Quinupristin/Dalfopristin, Rifampin or Rifampicin.

In each of the methods of the present invention the vaccine formulations are administered in a pharmaceutically acceptable form and in substantially non-toxic quantities. The vaccine formulations may be administered to a subject using different dosing schedules, depending on the particular use to which the formulations are put (e.g., administration to the subject pre- or post-exposure to *S. aureus*), the age and size of the subject, and the general health of the subject, to name only a few factors to be considered. In general, the vaccine formulations may be administered once, or twice, three times, four times, five times, six times or more, over a dosing schedule. The timing between each dose in a dosing schedule may range between a few hours, six, 12, or 18 hours, or 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 or more days. The same quantity of protein in the formulation may be administered in each dose of the dosing schedule, or the amounts in each dose may vary. The identity of the particular

peptides and polypeptides in the formulation may also vary or remain the same in each dose in a dosing schedule.

The amount of protein administered to a subject in a dose when the methods of the present invention are practiced will vary based on the particular methods being practiced (e.g., prevention versus treatment of a *S. aureus* infection), the means and formulation of administration, the age and size of the subject, and the general health of the subject, to name only a few factors to be considered. In general, however, the amount of *S. aureus* protein administered to a subject in a dose will be sufficient to induce or boost an immune response in a subject to the components of the vaccine. For example, the vaccines formulations may contain between about 1 to about 1000 ug of total *S. aureus* protein per kg of body weight of the subject to which the dose of the vaccine formulation will be administered, more preferably between about 10 to about 200 ug, even more preferably between about 15 to about 100 ug.

Appropriate doses and dosing schedules can readily be determined by techniques well known to those of ordinary skill in the art without undue experimentation. Such a determination will be based, in part, on the tolerability and efficacy of a particular dose.

Administration of the vaccine formulations may be via any of the means commonly known in the art of vaccine delivery. Such routes include intravenous, intraperitoneal, intramuscular, subcutaneous and intradermal routes of administration, as well as nasal application, by inhalation, ophthalmically, orally, rectally, vaginally, or by any other mode that results in the vaccine formulation contacting mucosal tissues.

As used herein, the *S. aureus* infection may be any *S. aureus* infection of a subject, including, for example, one or more of a *S. aureus* biofilm infection, a planktonic *S. aureus* infection, a *S. aureus* osteomyelitis infection, a biofilm-associated *S. aureus* osteomyelitis infection, a *S. aureus* indwelling medical device infection, a *S. aureus* endocarditis infection, a *S. aureus* diabetic wound or ulcer infection, a *S. aureus* chronic rhinosinusitis infection, a *S. aureus* ventilator associated pneumonia infection, a *S. aureus* intravenous catheter associated infection, a *S. aureus* skin infection, a *S. aureus* necrotizing fasciitis, a *S. aureus* keratitis, a *S. aureus* endophthalmitis, a *S. aureus* pyopneumothorax, a *S. aureus* empyema, and a *S. aureus* septicemia.

The term "subject" is intended to mean an animal, such birds or mammals, including humans and animals of veterinary or agricultural importance, such as dogs, cats, horses, sheep, goats, and cattle.

A kit comprising the necessary components of a vaccine formulation that elicits an immune response to a strain of *S. aureus* and instructions for its use is also within the purview of the present invention.

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims.

## EXAMPLES

### Materials and Methods

Unless stated otherwise, the following experimental details pertain to each of the examples provided in the specific Examples set forth and discussed below.



## 15

Mice. Inbred C57BL/6 (6-8 weeks old) were purchased from Jackson Laboratories (Bar Harbor, Me.). Mice were maintained under micro-isolator conditions in the animal facility at the University of Maryland Dental School (Baltimore, Md.), in accordance with protocols reviewed and approved by the Institutional Animal Care and Use Committee (IACUC).

Bacterial strain and preparation of infectious inocula. The strain of *S. aureus* used in these experiments, MRSA-M2, is a clinical isolate obtained from an osteomyelitis patient undergoing treatment at the University of Texas Medical Branch (Galveston, Tex.) and has been used in previous biofilm molecular analyses and animal infection models (5, 34, 37, 60) (6, 47, 49, 50). An overnight *S. aureus* Tryptic Soy Broth (TSB) culture grown at 37° C. with 250 rpm shaking was diluted 1:100 in fresh, prewarmed TSB and incubated for 2 h at 37° C. with 250 rpm shaking. Cells were centrifuged, rinsed with PBS, counted via a Petroff Hausser counter, and diluted to 1×10<sup>6</sup> CFU/ml.

Cloning, expression, and purification of proteins. Candidate antigens selected from Brady et al. (5) were amplified using the primers listed in Table 2.

TABLE 2

Primers utilized in this study (all products amplified from <i>S. aureus</i> M2 MRSA strain).		
Primer name	Sequence (5'-3'); SEQ ID NO:	Product, size
5' SA0037 SEQ ID NO: 1	ATGAATACAATCAAACTACGAAA	Conserved hypothetical protein, 519 bp
3' SA0037 SEQ ID NO: 2	CTTCTCATCGTCATCTGATTTCAAATCCATTTT TGA	
5' Lipase SEQ ID NO: 3	ACTCTAGGTCTCACTCCCATCTGAAACAACATT ATGACCAAAT	Lipase, 966 bp
3' Lipase SEQ ID NO: 4	ATGGTAGGTCTCATATCATAAAGGATTTAACGG TAATTCATTACT	
5' SA0688 SEQ ID NO: 5	ATGGTAGGTCTCACTCCGATAAGTCAAATGGCA AACTAAAAGT	ABC trans. lipoprotein, 860 bp (SEQ ID NO: 38)
3' SA0688 SEQ ID NO: 6	ATGGTAGGTCTCATATCATTTTCATGCTTCCGTGT ACAGTT	
5' Glucosaminidase SEQ ID NO: 7	ATGGTAGGTCTCACTCCGCTTATACTGTTACTA AACCACAAAC	Glucosaminidase, 1443 bp (SEQ ID NO: 39)
3' Glucosaminidase SEQ ID NO: 8	ATGGTAGGTCTCATATCATTTATATTGTGGGAT GTCGAAGTATT	
5' SA0486 SEQ ID NO: 9	ACTCTAGGTCTCACTCCAAAGAAGATTCAAAG AAGAACAAT	Hypothetical lipoprotein, 683 bp (SEQ ID NO: 37)
3' SA0486 SEQ ID NO: 10	ATGGTAGGTCTCATATCAGCTATCTTCATCAGA CGGCCCA	
5' SA0119 SEQ ID NO: 11	CATGCCATGGACACGACTTCAATGAATG	Putative uncharacterized protein, 726 bp
3' SA0119 SEQ ID NO: 12	AGCTTTGTTTTAACTCAATGATGATGATGATGA TGAACTTTTTTGTTACTTTGGTTC	

Bsal sites are underlined in primers.

The PCR products were cloned into pBAD-Thio/TOPO (SACOL0037 and SACOL0119) or pASK-IBA14 (SACOL0486, SACOL0688, and glucosaminidase), transformed into TOP10 *E. coli*, and sequenced. Details regarding the plasmids are provided in Table 3.

## 16

TABLE 3

Plasmids utilized in this study.		
Plasmid	Genotype or Characteristics	Source
pBAD-Thio/TOPO	4454 bp pUC ori, Amp <sup>R</sup> , pBAD promoter, for arabinose-inducible expression of PCR product	Invitrogen Life Technologies
pASK-IBA14	3001 bp pUC ori, Amp <sup>R</sup> , tetA promoter, for tetracycline-inducible expression of PCR product	IBA, Gottingen, Germany

The clones were then expressed using either arabinose induction (SACOL0037 and SACOL0119) or anhydrotetracycline induction (all others). SACOL0037 and SACOL0119 were purified via ProBond cobalt affinity chromatography (Invitrogen, Life technologies, Carlsbad, Calif.), while all other antigens were purified using Strep-Tactin Superflow Columns (IBA, Gottingen, Germany). Purity was confirmed by resolving each protein on 10-20% SDS-PAGE and quantities were determined by BCA (Pierce, Rockford Ill.). Desalting and buffer exchange to phosphate-buffered saline (PBS) was performed for SACOL0486,

SACOL0688, and glucosaminidase using 30 kDa molecular weight cut-off (MWCO) Amicon filtration units (Millipore, Billerica, Mass.) per the manufacturer's instructions. Desalting and buffer exchange to PBS was performed for SACOL0119 using 10 kDa MWCO Amicon filtration units



(Millipore, Billerica, Mass.). Desalting of SACOL0037 into Nano-pure water was achieved using desalting PD-10 columns (GE Healthcare, Waukesha, Wis.) following the manufacturer's procedure. Subsequently, SACOL0037 was lyophilized using a Virtis freezer dryer (SP Scientific, Warm-

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Bone Cultures. In order to demonstrate animal model efficacy, At 4, 7, 14, 21, 28, and 49 days post-implantation, infected and uninfected mice were euthanized, left tibiae were removed, and all soft tissue was dissected from the bone. Using sterile scissors, tibiae were cut into small pieces and placed in 300  $\mu$ l of sterile 0.85% saline per 100  $\mu$ g of bone. Bones were homogenized using a Polytron PT 1200 handheld homogenizer (Kinematica, Bohemia, N.Y.) and serial 10-fold dilutions of bone homogenates were plated on tryptic soy blood agar plates to enumerate viable *S. aureus* per g bone and CHROMagar MRSA plates (CHROMagar, Paris, France) to verify a monomicrobial *S. aureus* infection. In addition, non-vaccinated mice (alum alone) and mice vaccinated with the quadrivalent vaccine, the single additional antigen SA0119, or all antigens combined were euthanized at 21 days post infection and tibial colony-forming units (CFUs) were determined as described above. Dissemination of the *S. aureus* infection was monitored by homogenizing kidneys and plating the homogenates as described above.

PNA-FISH Biofilm Detection on Explanted Pins. In order to demonstrate biofilms on infected pins in the tibia of mice, the pins from infected and uninfected mice were carefully removed from the tibiae to prevent perturbation of biofilm mass at 7 and 21 days post-implantation. Pins were fixed in 2% paraformaldehyde in PBS before PNA-FISH hybridization with a FITC-labeled *S. aureus* probe and a rhodamine-labeled universal eukaryotic cell probe, as per manufactur-

er's instructions (Advandx, Woburn, Mass.). Each pin was then examined with a Zeiss LSM 510 confocal scanning laser microscope (Carl Zeiss, Thornwood, N.Y.) for both green and red fluorescence using a FITC/Texas Red dual-band filter and a 63 $\times$  objective.

Statistical Analysis. Mean and SD were calculated and analyzed using Student's t-test with a P value of <0.05 to determine statistical significance. Experiments determining the percentage of mice still infected after vancomycin or PBS treatment were analyzed using Fishers Exact test with a p value of <0.05 for statistical significance.

#### Results

*S. aureus* implant infection results in chronic infection. Tibiae from mice with pins infected with *S. aureus* and control tibiae with non-infected pins were harvested and processed at 4, 7, 14, 21, 28, and 49 days post-implantation. CFUs were enumerated from homogenized bone to determine the development of chronic infection and bacterial loads in the tibia. Results demonstrate that viable *S. aureus* were cultured from the *S. aureus* infected pin and surrounding bone at all time points tested, as far out as 49 days post-infection (FIG. 1). Bacterial loads initially increased to over 3 logs of the infecting dose to >10<sup>8</sup> CFU/tibia but then decreased between 4 and 7 days post-infection. However, at day 7 and beyond, bacterial loads were consistent. Biofilm formation was evident on implanted pins from infected (see FIG. 1B) but not uninfected mice (see FIG. 1C,D) by confocal scanning laser microscopy.

Vaccination with biofilm-upregulated antigens coupled with antibiotic therapy promotes clearance of a *S. aureus* osteomyelitis infection. In previous work, Brady et al. identified candidate proteins that were upregulated during the biofilm mode of growth and highly immunogenic in rabbits to formulate a multivalent vaccine against *S. aureus* biofilm-mediated infections (4). In an initial vaccination trial, a quadrivalent vaccine composed of SACOL0486, SACOL0688, SACOL0037, and glucosaminidase (10  $\mu$ g per recombinant protein) was injected into rabbits at 20 and 10 days prior to challenge using a *S. aureus* tibial osteomyelitis infection. Vaccinated rabbits had a slight reduction in bacterial load at 14 days post-infection compared to control animals, but bacterial clearance was not achieved (data not shown/Brady 2011). While the quadrivalent vaccine targets the *S. aureus* biofilm, its components do not activate an effective humoral response against *S. aureus* planktonic cells and these bacteria persist at day 14 post-infection due to the expression of immunoavoidance factors. Hence, the vaccination strategy was adapted by adding a 10 day vancomycin treatment course starting 14 days post-challenge to eradicate the antibiotic-sensitive, planktonic bacteria dispersed from the biofilm. To evaluate the efficacy of the dual therapy, *S. aureus* enumeration (FIG. 2A) and clearance rates (FIG. 2B) in rabbits of the dual therapy group were compared with those in unvaccinated and untreated, unvaccinated but treated, and vaccinated but untreated groups. Significant reductions in both bacterial counts and infection rate were observed with the dual therapy (column 4), which establishes that targeting the planktonic phenotype of *S. aureus* is critical to eradicate a biofilm-mediated infection. Overall, a 99.9% reduction in the bacterial population was observed in vaccinated animals compared to control animals.

Vaccination with a pentavalent vaccine composed of biofilm-upregulated and planktonic-specific antigens promotes clearance of a *S. aureus* tibial implant infection. As an extension of the vaccine study in the rabbit tibial osteomyelitis model, we targeted the planktonic phenotype of a *S. aureus* infection with the addition of a planktonic-specific



antigen, SACOL0119, to the biofilm-directed quadrivalent vaccine (SACOL0486, SACOL0688, SACOL0037, and glucosaminidase). The efficacy of this pentavalent vaccine against *S. aureus* infection was evaluated using a murine tibial implant model, which is a critical evaluation of the vaccine against another biofilm-mediated infection besides osteomyelitis. The pentavalent vaccine, which was composed of 12.5 µg of each recombinant antigen, was administered at 28 and 14 days prior to *S. aureus* challenge using the tibial implant model. At 21 days post-challenge, CFUs in the tibiae from mice vaccinated with the pentavalent vaccine were enumerated and compared to counts from mice vaccinated with either the quadrivalent vaccine or monovalent SACOL0119 vaccine and unvaccinated mice. Kidney homogenates were also examined for bacterial counts. We did not observe *S. aureus* in the kidneys of any control or experimental animals, which confirms that the infections were localized and did not disseminate from the tibia. In the unvaccinated mice, we observed a 100% infection rate (FIG. 3) and the development of an involucrum around the implant insertion site (data not shown). The quadrivalent vaccine and the SACOL0119 vaccine provided partial protection against *S. aureus* infection with bacterial clearance observed in 50% and 40% of the animals, respectively (FIG. 3). In the quadrivalent and SACOL0119 vaccinated mice, the presence of an involucrum on the tibia corresponded with the presence of *S. aureus* at the implant site. Since vaccination with either the biofilm-upregulated antigens or the planktonic-specific antigen alone provide approximately equivalent protection, we surmised that a combination of the antigens would have a synergistic effect and provide complete clearance of *S. aureus* in the tibial implant model. The addition of this planktonic antigen would substitute for the use of an adjunctive antibiotic therapy to eradicate persisting *S. aureus* as previously demonstrated by our lab. Indeed, the pentavalent vaccine provided complete protection against *S. aureus* with 100% clearance in all mice within this vaccine subgroup (FIG. 3). Additionally, tibiae from the pentavalent vaccinated mice resembled uninfected tibiae with no signs of infection. Therefore, the incorporation of the single planktonic antigen to the multivalent biofilm-directed vaccine enhanced the vaccine efficacy from 50% to 100% prevention of a biofilm-mediated, implant infection in C57BL/6J mice. Here, we achieved complete bacterial clearance of *S. aureus*, which is an accomplishment that has never been attained with other vaccine formulations including those that advanced into clinical trials, using a vaccination strategy that targeted both the planktonic and biofilm phenotypes of the pathogen.

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<220> FEATURE:



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<223> OTHER INFORMATION: 3' Glucosaminidase PCR primer

<400> SEQUENCE: 8

atggtaggtc tcatatcatt tatattgtgg gatgtcgaag tatt 44

<210> SEQ ID NO 9  
 <211> LENGTH: 43  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: 5' SA0486 PCR primer

<400> SEQUENCE: 9

actctaggtc tcaactccaaa gaagattcaa aagaagaaca aat 43

<210> SEQ ID NO 10  
 <211> LENGTH: 40  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: 3' SA0486 PCR primer

<400> SEQUENCE: 10

atggtaggtc tcatatcagc tatcttcac agacggccca 40

<210> SEQ ID NO 11  
 <211> LENGTH: 28  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: 5' SA0119 PCR primer

<400> SEQUENCE: 11

catgccatgg acacgacttc aatgaatg 28

<210> SEQ ID NO 12  
 <211> LENGTH: 57  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: 3' SA0119 PCR primer

<400> SEQUENCE: 12

agctttgttt aaactcaatg atgatgatga tgatgaactt ttttgttact ttggttc 57

<210> SEQ ID NO 13  
 <211> LENGTH: 168  
 <212> TYPE: PRT  
 <213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 13

Met Asn Thr Ile Lys Asn Thr Ile Tyr Thr Glu Ala Ile Phe Ser Lys  
 1 5 10 15

Asp Glu Lys His Arg Tyr Leu Leu Lys Lys Thr Trp Asp Glu Lys Lys  
 20 25 30

Pro Ala Cys Thr Val Ile Thr Met Tyr Pro His Leu Asp Gly Val Leu  
 35 40 45

Ser Leu Asp Leu Thr Thr Val Leu Ile Leu Asn Gln Leu Ala Asn Ser  
 50 55 60

Glu Arg Tyr Gly Ala Val Tyr Leu Val Asn Leu Phe Ser Asn Ile Lys  
 65 70 75 80

Thr Pro Glu Asn Leu Lys His Ile Lys Glu Pro Tyr Asp Lys His Thr  
 85 90 95



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Asp Ile His Leu Met Lys Ala Ile Ser Glu Ser Asp Thr Val Ile Leu  
 100 105 110

Ala Tyr Gly Ala Tyr Ala Lys Arg Pro Val Val Val Glu Arg Val Glu  
 115 120 125

Gln Val Met Glu Met Leu Lys Pro His Lys Lys Lys Val Lys Lys Leu  
 130 135 140

Ile Asn Pro Ala Thr Asn Glu Ile Met His Pro Leu Asn Pro Lys Ala  
 145 150 155 160

Arg Gln Lys Trp Thr Leu Lys Ala  
 165

<210> SEQ ID NO 14  
 <211> LENGTH: 241  
 <212> TYPE: PRT  
 <213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 14

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

Val Phe Ser Ser Met Pro Phe Gln Asn Ala His Ala Asp Thr Thr Ser  
 20 25 30

Met Asn Val Pro Asn Lys Gln Ser Gln Asn Val Gln Asn His Arg Pro  
 35 40 45

Tyr Gly Gly Val Val Pro Gln Gly Met Thr Gln Ala Gln Tyr Thr Glu  
 50 55 60

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

Tyr Asn Met Lys Leu Tyr Asp Ala Thr Gln Asn Ile Ala Asp Lys Tyr  
 85 90 95

Asn Val Ile Ile Thr Thr Asn Val Gly Val Phe Lys Pro His Ala Val  
 100 105 110

Arg Asp Met Asn Gly His Ala Leu Pro Leu Thr Lys Asp Gly Asn Phe  
 115 120 125

Tyr Gln Thr Asn Val Asp Ala Asn Gly Val Asn His Gly Gly Ser Glu  
 130 135 140

Met Val Gln Asn Lys Thr Gly His Met Ser Gln Gln Asp His Met Asn  
 145 150 155 160

Gln Asn Thr His Met Asn Gln Gln Pro Gln Ile Gln Gln Gly His Met  
 165 170 175

Gln Ser Ser Asn His Gln Met Met Ser Pro Lys Ala Asn Met His Ser  
 180 185 190

Ser Asn His Gln Met Asn Gln Ser Asn Lys Lys Val Leu Pro Ala Ala  
 195 200 205

Gly Glu Ser Met Thr Ser Ser Ile Leu Thr Ala Ser Ile Ala Ala Leu  
 210 215 220

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

Lys

<210> SEQ ID NO 15  
 <211> LENGTH: 270  
 <212> TYPE: PRT  
 <213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 15



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

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&lt;210&gt; SEQ ID NO 16

&lt;211&gt; LENGTH: 309

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Staphylococcus aureus

&lt;400&gt; SEQUENCE: 16

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

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Lys Lys Val Ile Ala Val Ser Lys Asp Val Lys Pro Ile Tyr Leu Asn  
 115 120 125  
 Gly Glu Glu Gly Asn Lys Asp Lys Gln Asp Pro His Ala Trp Leu Ser  
 130 135 140  
 Leu Asp Asn Gly Ile Lys Tyr Val Lys Thr Ile Gln Gln Thr Phe Ile  
 145 150 155 160  
 Asp Asn Asp Lys Lys His Lys Ala Asp Tyr Glu Lys Gln Gly Asn Lys  
 165 170 175  
 Tyr Ile Ala Gln Leu Glu Lys Leu Asn Asn Asp Ser Lys Asp Lys Phe  
 180 185 190  
 Asn Asp Ile Pro Lys Glu Gln Arg Ala Met Ile Thr Ser Glu Gly Ala  
 195 200 205  
 Phe Lys Tyr Phe Ser Lys Gln Tyr Gly Ile Thr Pro Gly Tyr Ile Trp  
 210 215 220  
 Glu Ile Asn Thr Glu Lys Gln Gly Thr Pro Glu Gln Met Arg Gln Ala  
 225 230 235 240  
 Ile Glu Phe Val Lys Lys His Lys Leu Lys His Leu Leu Val Glu Thr  
 245 250 255  
 Ser Val Asp Lys Lys Ala Met Glu Ser Leu Ser Glu Glu Thr Lys Lys  
 260 265 270  
 Asp Ile Phe Gly Glu Val Tyr Thr Asp Ser Ile Gly Lys Glu Gly Thr  
 275 280 285  
 Lys Gly Asp Ser Tyr Tyr Lys Met Met Lys Ser Asn Ile Glu Thr Val  
 290 295 300  
 His Gly Ser Met Lys  
 305

<210> SEQ ID NO 17  
 <211> LENGTH: 1257  
 <212> TYPE: PRT  
 <213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 17

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



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165				170				175							
Ala	Thr	Pro	Val	Ala	Pro	Lys	Ala	Lys	Thr	Glu	Ala	Thr	Pro	Lys	Val
			180												190
Thr	Thr	Phe	Ser	Ala	Ser	Ala	Gln	Pro	Arg	Ser	Ala	Ala	Ala	Ala	Pro
			195				200								205
Lys	Thr	Ser	Leu	Pro	Lys	Tyr	Lys	Pro	Gln	Val	Asn	Ser	Ser	Ile	Asn
			210				215								220
Asp	Tyr	Ile	Arg	Lys	Asn	Asn	Leu	Lys	Ala	Pro	Lys	Ile	Glu	Glu	Asp
			225				230				235				240
Tyr	Thr	Ser	Tyr	Phe	Pro	Lys	Tyr	Ala	Tyr	Arg	Asn	Gly	Val	Gly	Arg
			245												255
Pro	Glu	Gly	Ile	Val	Val	His	Asp	Thr	Ala	Asn	Asp	Arg	Ser	Thr	Ile
			260												270
Asn	Gly	Glu	Ile	Ser	Tyr	Met	Lys	Asn	Asn	Tyr	Gln	Asn	Ala	Phe	Val
			275				280								285
His	Ala	Phe	Val	Asp	Gly	Asp	Arg	Ile	Ile	Glu	Thr	Ala	Pro	Thr	Asp
			290				295								300
Tyr	Leu	Ser	Trp	Gly	Val	Gly	Ala	Val	Gly	Asn	Pro	Arg	Phe	Ile	Asn
			305				310								320
Val	Glu	Ile	Val	His	Thr	His	Asp	Tyr	Ala	Ser	Phe	Ala	Arg	Ser	Met
			325												335
Asn	Asn	Tyr	Ala	Asp	Tyr	Ala	Ala	Thr	Gln	Leu	Gln	Tyr	Tyr	Gly	Leu
			340												350
Lys	Pro	Asp	Ser	Ala	Glu	Tyr	Asp	Gly	Asn	Gly	Thr	Val	Trp	Thr	His
			355				360								365
Tyr	Ala	Val	Ser	Lys	Tyr	Leu	Gly	Gly	Thr	Asp	His	Ala	Asp	Pro	His
			370				375								380
Gly	Tyr	Leu	Arg	Ser	His	Asn	Tyr	Ser	Tyr	Asp	Gln	Leu	Tyr	Asp	Leu
			385				390								400
Ile	Asn	Glu	Lys	Tyr	Leu	Ile	Lys	Met	Gly	Lys	Val	Ala	Pro	Trp	Gly
			405												415
Thr	Gln	Ser	Thr	Thr	Thr	Pro	Thr	Thr	Pro	Ser	Lys	Pro	Ser	Thr	Pro
			420												430
Ser	Lys	Pro	Ser	Thr	Pro	Ser	Thr	Gly	Lys	Leu	Thr	Val	Ala	Ala	Asn
			435				440								445
Asn	Gly	Val	Ala	Gln	Ile	Lys	Pro	Thr	Asn	Ser	Gly	Leu	Tyr	Thr	Thr
			450				455								460
Val	Tyr	Asp	Lys	Thr	Gly	Lys	Ala	Thr	Asn	Glu	Val	Gln	Lys	Thr	Phe
			465				470								480
Ala	Val	Ser	Lys	Thr	Ala	Thr	Leu	Gly	Asn	Gln	Lys	Phe	Tyr	Leu	Val
			485												495
Gln	Asp	Tyr	Asn	Ser	Gly	Asn	Lys	Phe	Gly	Trp	Val	Lys	Glu	Gly	Asp
			500												510
Val	Val	Tyr	Asn	Thr	Ala	Lys	Ser	Pro	Val	Asn	Val	Asn	Gln	Ser	Tyr
			515				520								525
Ser	Ile	Lys	Pro	Gly	Thr	Lys	Leu	Tyr	Thr	Val	Pro	Trp	Gly	Thr	Ser
			530				535								540
Lys	Gln	Val	Ala	Gly	Ser	Val	Ser	Gly	Ser	Gly	Asn	Gln	Thr	Phe	Lys
			545				550								560
Ala	Ser	Lys	Gln	Gln	Gln	Ile	Asp	Lys	Ser	Ile	Tyr	Leu	Tyr	Gly	Ser
			565												575
Val	Asn	Gly	Lys	Ser	Gly	Trp	Val	Ser	Lys	Ala	Tyr	Leu	Val	Asp	Thr
			580												590



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Ala Lys Pro Thr Pro Thr Pro Thr Pro Lys Pro Ser Thr Pro Thr Thr  
595 600 605

Asn Asn Lys Leu Thr Val Ser Ser Leu Asn Gly Val Ala Gln Ile Asn  
610 615 620

Ala Lys Asn Asn Gly Leu Phe Thr Thr Val Tyr Asp Lys Thr Gly Lys  
625 630 635 640

Pro Thr Lys Glu Val Gln Lys Thr Phe Ala Val Thr Lys Glu Ala Ser  
645 650 655

Leu Gly Gly Asn Lys Phe Tyr Leu Val Lys Asp Tyr Asn Ser Pro Thr  
660 665 670

Leu Ile Gly Trp Val Lys Gln Gly Asp Val Ile Tyr Asn Asn Ala Lys  
675 680 685

Ser Pro Val Asn Val Met Gln Thr Tyr Thr Val Lys Pro Gly Thr Lys  
690 695 700

Leu Tyr Ser Val Pro Trp Gly Thr Tyr Lys Gln Glu Ala Gly Ala Val  
705 710 715 720

Ser Gly Thr Gly Asn Gln Thr Phe Lys Ala Thr Lys Gln Gln Gln Ile  
725 730 735

Asp Lys Ser Ile Tyr Leu Tyr Gly Thr Val Asn Gly Lys Ser Gly Trp  
740 745 750

Ile Ser Lys Ala Tyr Leu Ala Val Pro Ala Ala Pro Lys Lys Ala Val  
755 760 765

Ala Gln Pro Lys Thr Ala Val Lys Ala Tyr Ala Val Thr Lys Pro Gln  
770 775 780

Thr Thr Gln Thr Val Ser Lys Ile Ala Gln Val Lys Pro Asn Asn Thr  
785 790 795 800

Gly Ile Arg Ala Ser Val Tyr Glu Lys Thr Ala Lys Asn Gly Ala Lys  
805 810 815

Tyr Ala Asp Arg Thr Phe Tyr Val Thr Lys Glu Arg Ala His Gly Asn  
820 825 830

Glu Thr Tyr Val Leu Leu Asn Asn Thr Ser His Asn Ile Pro Leu Gly  
835 840 845

Trp Phe Asn Val Lys Asp Leu Asn Val Gln Asn Leu Gly Lys Glu Val  
850 855 860

Lys Thr Thr Gln Lys Tyr Thr Val Asn Arg Ser Asn Asn Gly Leu Ser  
865 870 875 880

Met Val Pro Trp Gly Thr Lys Asn Gln Val Ile Leu Thr Gly Asn Asn  
885 890 895

Ile Ala Gln Gly Thr Phe Asn Ala Thr Lys Gln Val Ser Val Gly Lys  
900 905 910

Asp Val Tyr Leu Tyr Gly Thr Ile Asn Asn Arg Thr Gly Trp Val Asn  
915 920 925

Ser Lys Asp Leu Thr Ala Pro Thr Ala Val Lys Pro Thr Thr Ser Ala  
930 935 940

Ala Lys Asp Tyr Asn Tyr Thr Tyr Val Ile Lys Asn Gly Asn Gly Tyr  
945 950 955 960

Tyr Tyr Val Thr Pro Asn Ser Asp Thr Ala Lys Tyr Ser Leu Lys Ala  
965 970 975

Phe Asn Glu Gln Pro Phe Ala Val Val Lys Glu Gln Val Ile Asn Gly  
980 985 990

Gln Thr Trp Tyr Tyr Gly Lys Leu Ser Asn Gly Lys Leu Ala Trp Ile  
995 1000 1005



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Lys Ser Thr Asp Leu Ala Lys Glu Leu Ile Lys Tyr Asn Gln Ile  
 1010 1015 1020  
 Gly Met Thr Leu Asn Gln Val Ala Gln Ile Gln Ala Gly Leu Gln  
 1025 1030 1035  
 Tyr Lys Pro Gln Val Gln Arg Val Pro Gly Lys Trp Thr Asp Ala  
 1040 1045 1050  
 Asn Phe Asn Asp Val Lys His Ala Met Asp Thr Lys Arg Leu Ala  
 1055 1060 1065  
 Gln Asp Pro Ala Leu Lys Tyr Gln Phe Leu Arg Leu Asp Gln Pro  
 1070 1075 1080  
 Gln Asn Ile Ser Ile Asp Lys Ile Asn Gln Phe Leu Lys Gly Lys  
 1085 1090 1095  
 Gly Val Leu Glu Asn Gln Gly Ala Ala Phe Asn Lys Ala Ala Gln  
 1100 1105 1110  
 Met Tyr Gly Ile Asn Glu Val Tyr Leu Ile Ser His Ala Leu Leu  
 1115 1120 1125  
 Glu Thr Gly Asn Gly Thr Ser Gln Leu Ala Lys Gly Ala Asp Val  
 1130 1135 1140  
 Val Asn Asn Lys Val Val Thr Asn Ser Asn Thr Lys Tyr His Asn  
 1145 1150 1155  
 Val Phe Gly Ile Ala Ala Tyr Asp Asn Asp Pro Leu Arg Glu Gly  
 1160 1165 1170  
 Ile Lys Tyr Ala Lys Gln Ala Gly Trp Asp Thr Val Ser Lys Ala  
 1175 1180 1185  
 Ile Val Gly Gly Ala Lys Phe Ile Gly Asn Ser Tyr Val Lys Ala  
 1190 1195 1200  
 Gly Gln Asn Thr Leu Tyr Lys Met Arg Trp Asn Pro Ala His Pro  
 1205 1210 1215  
 Gly Thr His Gln Tyr Ala Thr Asp Val Asp Trp Ala Asn Ile Asn  
 1220 1225 1230  
 Ala Lys Ile Ile Lys Gly Tyr Tyr Asp Lys Ile Gly Glu Val Gly  
 1235 1240 1245  
 Lys Tyr Phe Asp Ile Pro Gln Tyr Lys  
 1250 1255

&lt;210&gt; SEQ ID NO 18

&lt;211&gt; LENGTH: 451

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Staphylococcus aureus

&lt;400&gt; SEQUENCE: 18

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



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

&lt;210&gt; SEQ ID NO 19

&lt;211&gt; LENGTH: 2066

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Staphylococcus aureus

&lt;400&gt; SEQUENCE: 19

Met Asn Glu Lys Val Glu Gly Met Thr Leu Glu Leu Lys Leu Asp His  
 1 5 10 15

Leu Gly Val Gln Glu Gly Met Lys Gly Leu Lys Arg Gln Leu Gly Val



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20					25					30					
Val	Asn	Ser	Glu	Met	Lys	Ala	Asn	Leu	Ser	Ala	Phe	Asp	Lys	Ser	Glu
	35						40					45			
Lys	Ser	Met	Glu	Lys	Tyr	Gln	Ala	Arg	Ile	Lys	Gly	Leu	Asn	Asp	Arg
	50					55					60				
Leu	Lys	Val	Gln	Lys	Lys	Met	Tyr	Ser	Gln	Val	Glu	Asp	Glu	Leu	Lys
	65					70					75				80
Gln	Val	Asn	Ala	Asn	Tyr	Gln	Lys	Ala	Lys	Ser	Ser	Val	Lys	Asp	Val
				85					90					95	
Glu	Lys	Ala	Tyr	Leu	Lys	Leu	Val	Glu	Ala	Asn	Lys	Lys	Glu	Lys	Leu
			100					105					110		
Ala	Leu	Asp	Lys	Ser	Lys	Glu	Ala	Leu	Lys	Ser	Ser	Asn	Thr	Glu	Leu
		115					120					125			
Lys	Lys	Ala	Glu	Asn	Gln	Tyr	Lys	Arg	Thr	Asn	Gln	Arg	Lys	Gln	Asp
	130					135					140				
Ala	Tyr	Gln	Lys	Leu	Lys	Gln	Leu	Arg	Asp	Ala	Glu	Gln	Lys	Leu	Lys
	145					150					155				160
Asn	Ser	Asn	Gln	Ala	Thr	Thr	Ala	Gln	Leu	Lys	Arg	Ala	Ser	Asp	Ala
				165					170					175	
Val	Gln	Lys	Gln	Ser	Ala	Lys	His	Lys	Ala	Leu	Val	Glu	Gln	Tyr	Lys
			180					185					190		
Gln	Glu	Gly	Asn	Gln	Val	Gln	Lys	Leu	Lys	Val	Gln	Asn	Asp	Asn	Leu
		195					200					205			
Ser	Lys	Ser	Asn	Asp	Lys	Ile	Glu	Ser	Ser	Tyr	Ala	Lys	Thr	Asn	Thr
	210					215					220				
Lys	Leu	Lys	Gln	Thr	Glu	Lys	Glu	Phe	Asn	Asp	Leu	Asn	Asn	Thr	Ile
	225					230					235				240
Lys	Asn	His	Ser	Ala	Asn	Val	Ala	Lys	Ala	Glu	Thr	Ala	Val	Asn	Lys
				245					250					255	
Glu	Lys	Ala	Ala	Leu	Asn	Asn	Leu	Glu	Arg	Ser	Ile	Asp	Lys	Ala	Ser
			260					265					270		
Ser	Glu	Met	Lys	Thr	Phe	Asn	Lys	Glu	Gln	Met	Ile	Ala	Gln	Ser	His
		275					280					285			
Phe	Gly	Lys	Leu	Ala	Ser	Gln	Ala	Asp	Val	Met	Ser	Lys	Lys	Phe	Ser
	290					295					300				
Ser	Ile	Gly	Asp	Lys	Met	Thr	Ser	Leu	Gly	Arg	Thr	Met	Thr	Met	Gly
	305					310					315				320
Val	Ser	Thr	Pro	Ile	Thr	Leu	Gly	Leu	Gly	Ala	Ala	Leu	Lys	Thr	Ser
				325					330					335	
Ala	Asp	Phe	Glu	Gly	Gln	Met	Ser	Arg	Val	Gly	Ala	Ile	Ala	Gln	Ala
			340					345					350		
Ser	Ser	Lys	Asp	Leu	Lys	Ser	Met	Ser	Asn	Gln	Ala	Val	Asp	Leu	Gly
		355					360					365			
Ala	Lys	Thr	Ser	Lys	Ser	Ala	Asn	Glu	Val	Ala	Lys	Gly	Met	Glu	Glu
	370						375					380			
Leu	Ala	Ala	Leu	Gly	Phe	Asn	Ala	Lys	Gln	Thr	Met	Glu	Ala	Met	Pro
	385					390					395				400
Gly	Val	Ile	Ser	Ala	Ala	Glu	Ala	Ser	Gly	Ala	Glu	Met	Ala	Thr	Thr
				405					410					415	
Ala	Thr	Val	Met	Ala	Ser	Ala	Ile	Asn	Ser	Phe	Gly	Leu	Lys	Ala	Ser
			420					425					430		
Asp	Ala	Asn	His	Val	Ala	Asp	Leu	Leu	Ala	Arg	Ser	Ala	Asn	Asp	Ser
		435					440					445			



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Ala Ala Asp Ile Gln Tyr Met Gly Asp Ala Leu Lys Tyr Ala Gly Thr  
450 455 460

Pro Ala Lys Ala Leu Gly Val Ser Ile Glu Asp Thr Ser Ala Ala Ile  
465 470 475 480

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

Leu Arg Ala Ser Phe Ile Arg Leu Ala Asn Pro Ser Lys Asn Thr Ala  
500 505 510

Lys Glu Met Lys Lys Leu Gly Ile His Leu Ser Asp Ala Lys Gly Gln  
515 520 525

Phe Val Gly Met Gly Glu Leu Ile Arg Gln Phe Gln Asp Asn Met Lys  
530 535 540

Gly Met Thr Arg Glu Gln Lys Leu Ala Thr Val Ala Thr Ile Val Gly  
545 550 555 560

Thr Glu Ala Ala Ser Gly Phe Leu Ala Leu Ile Glu Ala Gly Pro Asp  
565 570 575

Lys Ile Asn Ser Tyr Ser Lys Ser Leu Lys Asn Ser Asn Gly Glu Ser  
580 585 590

Lys Lys Ala Ala Asp Leu Met Lys Asp Asn Leu Lys Gly Ala Leu Glu  
595 600 605

Gln Leu Gly Gly Ala Phe Glu Ser Leu Ala Ile Glu Val Gly Lys Asp  
610 615 620

Leu Thr Pro Met Ile Arg Ala Gly Ala Glu Gly Leu Thr Lys Leu Val  
625 630 635 640

Asp Gly Phe Thr His Leu Pro Gly Trp Val Arg Lys Ala Ser Val Gly  
645 650 655

Leu Ala Leu Phe Gly Ala Ala Ile Gly Pro Ala Val Leu Ala Gly Gly  
660 665 670

Leu Leu Ile Arg Thr Val Gly Ser Ala Ala Lys Gly Tyr Ala Ser Leu  
675 680 685

Asn Arg Arg Ile Ala Glu Asn Thr Ile Leu Ser Asn Thr Asn Ser Lys  
690 695 700

Ala Met Lys Ser Leu Gly Leu Gln Thr Leu Phe Leu Gly Ser Thr Thr  
705 710 715 720

Gly Lys Thr Ser Lys Gly Phe Lys Gly Leu Ala Gly Ala Met Met Phe  
725 730 735

Asn Leu Lys Pro Ile Asn Val Leu Lys Asn Ser Ala Lys Leu Ala Ile  
740 745 750

Leu Pro Phe Lys Leu Leu Lys Asn Gly Leu Gly Leu Ala Ala Lys Ser  
755 760 765

Leu Phe Ala Val Ser Gly Gly Ala Arg Phe Ala Gly Val Ala Leu Arg  
770 775 780

Phe Leu Thr Gly Pro Ile Gly Ala Thr Ile Thr Ala Ile Thr Ile Ala  
785 790 795 800

Tyr Lys Val Phe Lys Thr Ala Tyr Asp Arg Val Glu Trp Phe Arg Asn  
805 810 815

Gly Ile Asn Gly Leu Gly Glu Thr Ile Lys Phe Phe Gly Gly Lys Ile  
820 825 830

Ile Gly Gly Ala Val Arg Lys Leu Gly Glu Phe Lys Asn Tyr Leu Gly  
835 840 845

Ser Ile Gly Lys Ser Phe Lys Glu Lys Phe Ser Lys Asp Met Lys Asp  
850 855 860

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Gly	Tyr	Lys	Ser	Leu	Ser	Asp	Asp	Asp	Leu	Leu	Lys	Val	Gly	Val	Asn	865	870	875	880
Lys	Phe	Lys	Gly	Phe	Met	Gln	Thr	Met	Gly	Thr	Ala	Ser	Lys	Lys	Ala	885	890	895	
Ser	Asp	Thr	Val	Lys	Val	Leu	Gly	Lys	Gly	Val	Ser	Lys	Glu	Thr	Glu	900	905	910	
Lys	Ala	Leu	Glu	Lys	Tyr	Val	His	Tyr	Ser	Glu	Glu	Asn	Ser	Arg	Ile	915	920	925	
Met	Glu	Lys	Val	Arg	Leu	Asn	Ser	Gly	Gln	Ile	Ser	Glu	Asp	Lys	Ala	930	935	940	
Lys	Lys	Leu	Leu	Lys	Ile	Glu	Thr	Asp	Leu	Ser	Asn	Asn	Leu	Ile	Ala	945	950	955	960
Glu	Ile	Glu	Lys	Arg	Asn	Lys	Lys	Glu	Leu	Glu	Lys	Thr	Gln	Glu	Leu	965	970	975	
Ile	Asp	Lys	Tyr	Ser	Ala	Phe	Asp	Glu	Gln	Glu	Lys	Gln	Asn	Ile	Leu	980	985	990	
Thr	Arg	Thr	Lys	Glu	Lys	Asn	Asp	Leu	Arg	Ile	Lys	Lys	Glu	Gln	Glu	995	1000	1005	
Leu	Asn	Gln	Lys	Ile	Lys	Glu	Leu	Lys	Glu	Lys	Ala	Leu	Ser	Asp	1010	1015	1020		
Gly	Gln	Ile	Ser	Glu	Asn	Glu	Arg	Lys	Glu	Ile	Glu	Lys	Leu	Glu	1025	1030	1035		
Asn	Gln	Arg	Arg	Asp	Ile	Thr	Val	Lys	Glu	Leu	Ser	Lys	Thr	Glu	1040	1045	1050		
Lys	Glu	Gln	Glu	Arg	Ile	Leu	Val	Arg	Met	Gln	Arg	Asn	Arg	Asn	1055	1060	1065		
Ala	Tyr	Ser	Ile	Asp	Glu	Ala	Ser	Lys	Ala	Ile	Lys	Glu	Ala	Glu	1070	1075	1080		
Lys	Ala	Arg	Lys	Ala	Arg	Lys	Lys	Glu	Val	Asp	Lys	Gln	Tyr	Glu	1085	1090	1095		
Asp	Asp	Val	Ile	Ala	Ile	Lys	Asn	Asn	Val	Asn	Leu	Ser	Lys	Ser	1100	1105	1110		
Glu	Lys	Asp	Lys	Leu	Leu	Ala	Ile	Ala	Asp	Gln	Arg	His	Lys	Asp	1115	1120	1125		
Glu	Val	Arg	Lys	Ala	Lys	Ser	Lys	Lys	Asp	Ala	Val	Val	Asp	Val	1130	1135	1140		
Val	Lys	Lys	Gln	Asn	Lys	Asp	Ile	Asp	Lys	Glu	Met	Asp	Leu	Ser	1145	1150	1155		
Ser	Gly	Arg	Val	Tyr	Lys	Asn	Thr	Glu	Lys	Trp	Trp	Asn	Gly	Leu	1160	1165	1170		
Lys	Ser	Trp	Trp	Ser	Asn	Phe	Arg	Glu	Asp	Gln	Lys	Lys	Lys	Ser	1175	1180	1185		
Asp	Lys	Tyr	Ala	Lys	Glu	Gln	Glu	Glu	Thr	Ala	Arg	Arg	Asn	Arg	1190	1195	1200		
Glu	Asn	Ile	Lys	Lys	Trp	Phe	Gly	Asn	Ala	Trp	Asp	Gly	Val	Lys	1205	1210	1215		
Thr	Lys	Thr	Gly	Glu	Ala	Phe	Ser	Lys	Met	Gly	Arg	Asn	Ala	Asn	1220	1225	1230		
His	Phe	Gly	Gly	Glu	Met	Lys	Lys	Met	Trp	Ser	Gly	Ile	Lys	Gly	1235	1240	1245		
Ile	Pro	Ser	Lys	Leu	Ser	Ser	Ser	Trp	Ser	Ser	Ala	Lys	Ser	Ser	1250	1255	1260		
Val	Gly	Tyr	His	Thr	Lys	Ala	Ile	Ala	Asn	Ser	Thr	Gly	Lys	Trp					



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1265	1270	1275
Phe Gly Lys Ala Trp Gln Ser Val Lys Ser Thr Thr Gly Ser Ile 1280 1285 1290		
Tyr Asn Gln Thr Lys Gln Lys Tyr Ser Asp Ala Ser Asp Lys Ala 1295 1300 1305		
Trp Ala His Ser Lys Ser Ile Trp Lys Gly Thr Ser Lys Trp Phe 1310 1315 1320		
Ser Asn Ala Tyr Lys Ser Ala Lys Gly Trp Leu Thr Asp Met Ala 1325 1330 1335		
Asn Lys Ser Arg Ser Lys Trp Asp Asn Ile Ser Ser Thr Ala Trp 1340 1345 1350		
Ser Asn Ala Lys Ser Val Trp Lys Gly Thr Ser Lys Trp Phe Gly 1355 1360 1365		
Asn Ser Tyr Lys Ser Leu Lys Gly Trp Thr Gly Asp Met Tyr Ser 1370 1375 1380		
Arg Ala His Asp Arg Phe Asp Ala Ile Ser Ser Ser Ala Trp Ser 1385 1390 1395		
Asn Ala Lys Ser Val Phe Asn Gly Phe Arg Lys Trp Leu Ser Lys 1400 1405 1410		
Thr Tyr Asp Trp Ile Arg Asp Ile Gly Lys Asp Met Gly Arg Ala 1415 1420 1425		
Ala Ala Asp Leu Gly Lys Asn Val Ala Asn Lys Ala Ile Gly Gly 1430 1435 1440		
Leu Asn Ser Met Ile Gly Gly Ile Asn Lys Ile Ser Lys Ala Ile 1445 1450 1455		
Thr Asp Lys Asn Leu Ile Lys Pro Ile Pro Thr Leu Ser Thr Gly 1460 1465 1470		
Thr Leu Ala Gly Lys Gly Val Ala Thr Asp Asn Ser Gly Ala Leu 1475 1480 1485		
Thr Gln Pro Thr Phe Ala Val Leu Asn Asp Arg Gly Ser Gly Asn 1490 1495 1500		
Ala Pro Gly Gly Gly Val Gln Glu Val Ile His Arg Ala Asp Gly 1505 1510 1515		
Thr Phe His Ala Pro Gln Gly Arg Asp Val Val Val Pro Leu Gly 1520 1525 1530		
Val Gly Asp Ser Val Ile Asn Ala Asn Asp Thr Leu Lys Leu Gln 1535 1540 1545		
Arg Met Gly Val Leu Pro Lys Phe His Gly Gly Thr Lys Lys Lys 1550 1555 1560		
Lys Trp Met Glu Gln Val Thr Glu Asn Leu Gly Lys Lys Ala Gly 1565 1570 1575		
Asp Phe Gly Ser Lys Ala Lys Asn Thr Ala His Asn Ile Lys Lys 1580 1585 1590		
Gly Ala Glu Glu Met Val Glu Ala Ala Gly Asp Lys Ile Lys Asp 1595 1600 1605		
Gly Ala Ser Trp Leu Gly Asp Lys Ile Gly Asp Val Trp Asp Tyr 1610 1615 1620		
Val Gln His Pro Gly Lys Leu Val Asn Lys Val Met Ser Gly Leu 1625 1630 1635		
Asn Ile Asn Phe Gly Gly Gly Ala Asn Ala Thr Val Lys Ile Ala 1640 1645 1650		
Lys Gly Ala Tyr Ser Leu Leu Lys Lys Lys Leu Val Asp Lys Val 1655 1660 1665		

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Lys	Ser	Trp	Phe	Glu	Asp	Phe	Gly	Gly	Gly	Gly	Asp	Gly	Ser	Tyr
1670						1675					1680			
Leu	Phe	Asp	His	Pro	Ile	Trp	Gln	Arg	Phe	Gly	Ser	Tyr	Thr	Gly
1685						1690					1695			
Gly	Leu	Asn	Phe	Asn	Gly	Gly	Arg	His	Tyr	Gly	Ile	Asp	Phe	Gly
1700						1705					1710			
Met	Pro	Thr	Gly	Thr	Asn	Ile	Tyr	Ala	Val	Lys	Gly	Gly	Ile	Ala
1715						1720					1725			
Asp	Lys	Val	Trp	Thr	Asp	Tyr	Gly	Gly	Gly	Asn	Ser	Ile	Gln	Ile
1730						1735					1740			
Lys	Thr	Gly	Ala	Asn	Glu	Trp	Asn	Trp	Tyr	Met	His	Leu	Ser	Lys
1745						1750					1755			
Gln	Leu	Ala	Arg	Gln	Gly	Gln	Arg	Ile	Lys	Ala	Gly	Gln	Leu	Ile
1760						1765					1770			
Gly	Lys	Ser	Gly	Ala	Thr	Gly	Asn	Phe	Val	Arg	Gly	Ala	His	Leu
1775						1780					1785			
His	Phe	Gln	Leu	Met	Gln	Gly	Ser	His	Pro	Gly	Asn	Asp	Thr	Ala
1790						1795					1800			
Lys	Asp	Pro	Glu	Lys	Trp	Leu	Lys	Ser	Leu	Lys	Gly	Ser	Gly	Val
1805						1810					1815			
Arg	Ser	Gly	Ser	Gly	Val	Asn	Lys	Ala	Ala	Ser	Ala	Trp	Ala	Gly
1820						1825					1830			
Asp	Ile	Arg	Arg	Ala	Ala	Lys	Arg	Met	Gly	Val	Asn	Val	Thr	Ser
1835						1840					1845			
Gly	Asp	Val	Gly	Asn	Ile	Ile	Ser	Leu	Ile	Gln	His	Glu	Ser	Gly
1850						1855					1860			
Gly	Asn	Ala	Gly	Ile	Thr	Gln	Ser	Ser	Ser	Leu	Arg	Asp	Ile	Asn
1865						1870					1875			
Val	Leu	Gln	Gly	Asn	Pro	Ala	Lys	Gly	Leu	Leu	Gln	Tyr	Ile	Pro
1880						1885					1890			
Gln	Thr	Phe	Arg	His	Tyr	Ala	Val	Arg	Gly	His	Asn	Asn	Ile	Tyr
1895						1900					1905			
Ser	Gly	Tyr	Asp	Gln	Leu	Leu	Ala	Phe	Phe	Asn	Asn	Arg	Tyr	Trp
1910						1915					1920			
Arg	Ser	Gln	Phe	Asn	Pro	Arg	Gly	Gly	Trp	Ser	Pro	Ser	Gly	Pro
1925						1930					1935			
Arg	Arg	Tyr	Ala	Asn	Gly	Gly	Leu	Ile	Thr	Lys	His	Gln	Leu	Ala
1940						1945					1950			
Glu	Val	Gly	Glu	Gly	Asp	Lys	Gln	Glu	Met	Val	Ile	Pro	Leu	Thr
1955						1960					1965			
Arg	Arg	Lys	Arg	Ala	Ile	Gln	Leu	Thr	Glu	Gln	Val	Met	Arg	Ile
1970						1975					1980			
Ile	Gly	Met	Asp	Gly	Lys	Pro	Asn	Asn	Ile	Thr	Val	Asn	Asn	Asp
1985						1990					1995			
Thr	Ser	Thr	Val	Glu	Lys	Leu	Leu	Lys	Gln	Ile	Val	Met	Leu	Ser
2000						2005					2010			
Asp	Lys	Gly	Asn	Lys	Leu	Thr	Asp	Ala	Leu	Ile	Gln	Thr	Val	Ser
2015						2020					2025			
Ser	Gln	Asp	Asn	Asn	Leu	Gly	Ser	Asn	Asp	Ala	Ile	Arg	Gly	Leu
2030						2035					2040			
Glu	Lys	Ile	Leu	Ser	Lys	Gln	Ser	Gly	His	Arg	Ala	Asn	Ala	Asn
2045						2050					2055			



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Asn Tyr Met Gly Gly Leu Thr Asn  
2060 2065

<210> SEQ ID NO 20  
<211> LENGTH: 149  
<212> TYPE: PRT  
<213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 20

Met Lys Lys Ser Lys Arg Leu Glu Ile Val Ser Thr Ile Val Lys Lys  
1 5 10 15  
His Lys Ile Tyr Lys Lys Glu Gln Ile Ile Ser Tyr Ile Glu Glu Tyr  
20 25 30  
Phe Gly Val Arg Tyr Ser Ala Thr Thr Ile Ala Lys Asp Leu Lys Glu  
35 40 45  
Leu Asn Ile Tyr Arg Val Pro Ile Asp Cys Glu Thr Trp Ile Tyr Lys  
50 55 60  
Ala Ile Asn Asn Gln Thr Glu Gln Glu Met Arg Glu Lys Phe Arg His  
65 70 75 80  
Tyr Cys Glu His Glu Val Leu Ser Ser Ile Ile Asn Gly Ser Tyr Ile  
85 90 95  
Ile Val Lys Thr Ser Pro Gly Phe Ala Gln Gly Ile Asn Tyr Phe Ile  
100 105 110  
Asp Gln Leu Asn Ile Glu Glu Ile Leu Gly Thr Val Ser Gly Asn Asp  
115 120 125  
Thr Thr Leu Ile Leu Thr Ala Ser Asn Asp Met Ala Glu Tyr Val Tyr  
130 135 140  
Ala Lys Leu Phe Lys  
145

<210> SEQ ID NO 21  
<211> LENGTH: 96  
<212> TYPE: PRT  
<213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 21

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

<210> SEQ ID NO 22  
<211> LENGTH: 86  
<212> TYPE: PRT  
<213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 22

Leu Glu Tyr Asn Lys Lys Met Ile Asn Arg Ile His Arg Ile Gln Gly  
1 5 10 15  
Gln Leu Asn Gly Val Ile Lys Met Met Glu Glu Glu Lys Asn Cys Lys

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	20		25		30	
Asp	Val	Ile	Ser	Gln	Leu	Ser
	35					Ala
						Ser
						Lys
						Ser
						Ser
						Ile
						Gln
						Arg
						Leu

<210> SEQ ID NO 23  
 <211> LENGTH: 466  
 <212> TYPE: PRT  
 <213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 23

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



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Ser Leu Leu Glu Gln Gly Gly Met Met Ser Met Thr Gln Ile Leu Val  
 305 310 315 320

Thr Ile Phe Cys Gly Tyr Ala Phe Ala Gly Ile Val Glu Lys Ala Gly  
 325 330 335

Cys Leu Glu Val Leu Leu Thr Thr Ile Ser Lys Gly Ile His Ser Val  
 340 345 350

Gly Ser Leu Ile Cys Ile Thr Val Ile Cys Cys Ile Ala Leu Val Phe  
 355 360 365

Ala Ala Gly Val Ala Ser Ile Val Ile Ile Met Val Gly Val Leu Met  
 370 375 380

Lys Asp Leu Phe Glu Lys Tyr Gln Val Ser Arg Ser Val Leu Ser Arg  
 385 390 395 400

Thr Leu Glu Asp Ser Ser Thr Met Val Leu Pro Leu Ile Pro Trp Gly  
 405 410 415

Thr Ser Gly Ile Tyr Tyr Thr Asn Gln Leu His Val Ser Val Glu Glu  
 420 425 430

Phe Phe Ile Trp Thr Val Pro Cys Tyr Leu Cys Ala Ile Ile Ala Ile  
 435 440 445

Ile Tyr Gly Phe Thr Gly Ile Gly Ile Lys Lys Ser Ser Asn Ser Arg  
 450 455 460

Leu Thr  
 465

<210> SEQ ID NO 24  
 <211> LENGTH: 749  
 <212> TYPE: PRT  
 <213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 24

Met Leu Glu Thr Asn Lys Asn His Ala Thr Ala Trp Gln Gly Phe Lys  
 1 5 10 15

Asn Gly Arg Trp Asn Arg His Val Asp Val Arg Glu Phe Ile Gln Leu  
 20 25 30

Asn Tyr Thr Leu Tyr Glu Gly Asn Asp Ser Phe Leu Ala Gly Pro Thr  
 35 40 45

Glu Ala Thr Ser Lys Leu Trp Glu Gln Val Met Gln Leu Ser Lys Glu  
 50 55 60

Glu Arg Glu Arg Gly Gly Met Trp Asp Met Asp Thr Lys Val Ala Ser  
 65 70 75 80

Thr Ile Thr Ser His Asp Ala Gly Tyr Leu Asp Lys Asp Leu Glu Thr  
 85 90 95

Ile Val Gly Val Gln Thr Glu Lys Pro Phe Lys Arg Ser Met Gln Pro  
 100 105 110

Phe Gly Gly Ile Arg Met Ala Lys Ala Ala Cys Glu Ala Tyr Gly Tyr  
 115 120 125

Glu Leu Asp Glu Glu Thr Glu Lys Ile Phe Thr Asp Tyr Arg Lys Thr  
 130 135 140

His Asn Gln Gly Val Phe Asp Ala Tyr Ser Arg Glu Met Leu Asn Cys  
 145 150 155 160

Arg Lys Ala Gly Val Ile Thr Gly Leu Pro Asp Ala Tyr Gly Arg Gly  
 165 170 175

Arg Ile Ile Gly Asp Tyr Arg Arg Val Ala Leu Tyr Gly Val Asp Phe  
 180 185 190

Leu Met Glu Glu Lys Met His Asp Phe Asn Thr Met Ser Thr Glu Met  
 195 200 205

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Ser Glu Asp Val Ile Arg Leu Arg Glu Glu Leu Ser Glu Gln Tyr Arg  
 210 215 220  
 Ala Leu Lys Glu Leu Lys Glu Leu Gly Gln Lys Tyr Gly Phe Asp Leu  
 225 230 235 240  
 Ser Arg Pro Ala Glu Asn Phe Lys Glu Ala Val Gln Trp Leu Tyr Leu  
 245 250 255  
 Ala Tyr Leu Ala Ala Ile Lys Glu Gln Asn Gly Ala Ala Met Ser Leu  
 260 265 270  
 Gly Arg Thr Ser Thr Phe Leu Asp Ile Tyr Ala Glu Arg Asp Leu Lys  
 275 280 285  
 Ala Gly Val Ile Thr Glu Ser Glu Val Gln Glu Ile Ile Asp His Phe  
 290 295 300  
 Ile Met Lys Leu Arg Ile Val Lys Phe Ala Arg Thr Pro Asp Tyr Asn  
 305 310 315 320  
 Glu Leu Phe Ser Gly Asp Pro Thr Trp Val Thr Glu Ser Ile Gly Gly  
 325 330 335  
 Val Gly Ile Asp Gly Arg Pro Leu Val Thr Lys Asn Ser Phe Arg Phe  
 340 345 350  
 Leu His Ser Leu Asp Asn Leu Gly Pro Ala Pro Glu Pro Asn Leu Thr  
 355 360 365  
 Val Leu Trp Ser Val Arg Leu Pro Asp Asn Phe Lys Thr Tyr Cys Ala  
 370 375 380  
 Lys Met Ser Ile Lys Thr Ser Ser Ile Gln Tyr Glu Asn Asp Asp Ile  
 385 390 395 400  
 Met Arg Glu Ser Tyr Gly Asp Asp Tyr Gly Ile Ala Cys Cys Val Ser  
 405 410 415  
 Ala Met Thr Ile Gly Lys Gln Met Gln Phe Phe Gly Ala Arg Ala Asn  
 420 425 430  
 Leu Ala Lys Thr Leu Leu Tyr Ala Ile Asn Gly Gly Lys Asp Glu Lys  
 435 440 445  
 Ser Gly Ala Gln Val Gly Pro Asn Phe Glu Gly Ile Asn Ser Glu Val  
 450 455 460  
 Leu Glu Tyr Asp Glu Val Phe Lys Lys Phe Asp Gln Met Met Asp Trp  
 465 470 475 480  
 Leu Ala Gly Val Tyr Ile Asn Ser Leu Asn Val Ile His Tyr Met His  
 485 490 495  
 Asp Lys Tyr Ser Tyr Glu Arg Ile Glu Met Ala Leu His Asp Thr Glu  
 500 505 510  
 Ile Val Arg Thr Met Ala Thr Gly Ile Ala Gly Leu Ser Val Ala Ala  
 515 520 525  
 Asp Ser Leu Ser Ala Ile Lys Tyr Ala Gln Val Lys Pro Ile Arg Asn  
 530 535 540  
 Glu Glu Gly Leu Val Val Asp Phe Glu Ile Glu Gly Asp Phe Pro Lys  
 545 550 555 560  
 Tyr Gly Asn Asn Asp Asp Arg Val Asp Asp Ile Ala Val Asp Leu Val  
 565 570 575  
 Glu Arg Phe Met Thr Lys Leu Arg Ser His Lys Thr Tyr Arg Asp Ser  
 580 585 590  
 Glu His Thr Met Ser Val Leu Thr Ile Thr Ser Asn Val Val Tyr Gly  
 595 600 605  
 Lys Lys Thr Gly Asn Thr Pro Asp Gly Arg Lys Ala Gly Glu Pro Phe  
 610 615 620



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Ala Pro Gly Ala Asn Pro Met His Gly Arg Asp Gln Lys Gly Ala Leu  
625 630 635 640

Ser Ser Leu Ser Ser Val Ala Lys Ile Pro Tyr Asp Cys Cys Lys Asp  
645 650 655

Gly Ile Ser Asn Thr Phe Ser Ile Val Pro Lys Ser Leu Gly Lys Glu  
660 665 670

Pro Glu Asp Gln Asn Arg Asn Leu Thr Ser Met Leu Asp Gly Tyr Ala  
675 680 685

Met Gln Cys Gly His His Leu Asn Ile Asn Val Phe Asn Arg Glu Thr  
690 695 700

Leu Ile Asp Ala Met Glu His Pro Glu Glu Tyr Pro Gln Leu Thr Ile  
705 710 715 720

Arg Val Ser Gly Tyr Ala Val Asn Phe Ile Lys Leu Thr Arg Glu Gln  
725 730 735

Gln Leu Asp Val Ile Ser Arg Thr Phe His Glu Ser Met  
740 745

<210> SEQ ID NO 25  
<211> LENGTH: 116  
<212> TYPE: PRT  
<213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 25

Leu His Leu Phe Ile Leu Ser Ser His Ile Phe Lys Ser Ile Thr Phe  
1 5 10 15

Asp Cys Gly Lys Glu Phe Ser Asn Trp Lys Thr Ile Cys Asn Cys His  
20 25 30

Asp Ile Ser Ile Phe Phe Ala Asp Pro Gly Thr Pro Ser Gln Arg Gly  
35 40 45

Leu Asn Glu His Ser Asn Gly Ile Ile Arg Arg Ser Gly Leu Asp Lys  
50 55 60

Glu Leu Asp Phe Asn Leu Val Thr Asp Asp His Ile Ile Ser Val Ala  
65 70 75 80

Gln Lys Ile Asn His His Pro Arg Lys Ser Leu Gly Tyr Arg Thr Pro  
85 90 95

Leu Glu Val Phe Met Ser Phe Ile Glu Asp Asp Lys Leu Val Gln Leu  
100 105 110

Asn Leu Thr Ile  
115

<210> SEQ ID NO 26  
<211> LENGTH: 230  
<212> TYPE: PRT  
<213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 26

Met Tyr Ser Ile Lys Met Arg Ser Ser Asn Gln Asp Val His Ile Ser  
1 5 10 15

Gly Ala Glu Thr Ile Cys Glu Phe Asp Lys Ile Glu Gln Thr Val Gln  
20 25 30

Arg Phe Tyr Asn Lys Gly Phe Phe His Glu Asn Gly Gln Pro Asp Phe  
35 40 45

Leu Asn Ile Lys Ile Gln Lys Ile Met Glu Pro Ile Gln Gln Ile Lys  
50 55 60

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

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Gln Glu Cys Gly Val Thr Glu Gln Ala Leu Asn Gln Gly Met Thr Tyr  
85 90 95

Ile Lys Asn Glu Thr Val Tyr Thr Gly Ala Ile Ile Leu Ser Ala Ile  
100 105 110

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

His Phe Ser Phe Glu Asp Ile Asn Asn Lys Gly Asp Leu Asn Glu Arg  
130 135 140

Val Thr Asp Ala Leu Ala Ile Ala Ser Cys Ile Asn Ala His Pro Tyr  
145 150 155 160

Val Lys Gly Glu Leu Cys Val Ser Asp Asp Leu Thr Tyr Thr Thr Gly  
165 170 175

Tyr Phe Ala Ala Ala Lys Ile Gly Tyr His Arg Leu Phe Asp Ile Lys  
180 185 190

Pro Val Asn Thr Arg Tyr Gly Gly Arg Ile Ile Phe Val Asp Asp Cys  
195 200 205

Ile Asp Leu Asn His Tyr Ile Ser Phe Leu Glu Ser Thr Pro Lys Gln  
210 215 220

Val Val Tyr Glu Thr Val  
225 230

&lt;210&gt; SEQ ID NO 27

&lt;211&gt; LENGTH: 518

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Staphylococcus aureus

&lt;400&gt; SEQUENCE: 27

Val Glu Asn Thr Ile Asn Glu Ser Glu Lys Lys Lys Arg Phe Lys Leu  
1 5 10 15

Lys Met Pro Gly Ala Phe Met Ile Leu Phe Ile Leu Thr Val Val Ala  
20 25 30

Val Ile Ala Thr Trp Val Ile Pro Ala Gly Ala Tyr Ser Lys Leu Ser  
35 40 45

Tyr Glu Pro Ser Ser Gln Glu Leu Lys Ile Val Asn Pro His Asn Gln  
50 55 60

Val Lys Lys Val Pro Gly Thr Gln Gln Glu Leu Asp Lys Met Gly Val  
65 70 75 80

Lys Ile Lys Ile Glu Gln Phe Lys Ser Gly Ala Ile Asn Lys Pro Val  
85 90 95

Ser Ile Pro Asn Thr Tyr Glu Arg Leu Lys Gln His Pro Ala Gly Pro  
100 105 110

Glu Gln Ile Thr Ser Ser Met Val Glu Gly Thr Ile Glu Ala Val Asp  
115 120 125

Ile Met Val Phe Ile Leu Val Leu Gly Gly Leu Ile Gly Val Val Gln  
130 135 140

Ala Ser Gly Ser Phe Glu Ser Gly Leu Leu Ala Leu Thr Lys Lys Thr  
145 150 155 160

Lys Gly His Glu Phe Met Leu Ile Val Phe Val Ser Ile Leu Met Ile  
165 170 175

Ile Gly Gly Thr Leu Cys Gly Ile Glu Glu Glu Ala Val Ala Phe Tyr  
180 185 190

Pro Ile Leu Val Pro Ile Phe Ile Ala Leu Gly Tyr Asp Ser Ile Val  
195 200 205

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



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

&lt;210&gt; SEQ ID NO 28

&lt;211&gt; LENGTH: 283

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Staphylococcus aureus

&lt;400&gt; SEQUENCE: 28

Met Ser Lys Ile Phe Val Thr Gly Ala Thr Gly Leu Ile Gly Ile Lys  
 1 5 10 15  
 Leu Val Gln Arg Leu Lys Glu Glu Gly His Glu Val Ala Gly Phe Thr  
 20 25 30  
 Thr Ser Glu Asn Gly Gln Gln Lys Leu Ala Ala Val Asn Val Lys Ala  
 35 40 45  
 Tyr Ile Gly Asp Ile Leu Lys Ala Asp Thr Ile Asp Gln Ala Leu Ala  
 50 55 60  
 Asp Phe Lys Pro Glu Ile Ile Ile Asn Gln Ile Thr Asp Leu Lys Asn

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65	70	75	80
Val Asp Met Ala Ala Asn Thr Lys Val Arg Ile Glu Gly Ser Lys Asn 85 90 95			
Leu Ile Asp Ala Ala Lys Lys His Asp Val Lys Lys Val Ile Ala Gln 100 105 110			
Ser Ile Ala Phe Met Tyr Glu Pro Gly Glu Gly Leu Ala Asn Glu Glu 115 120 125			
Thr Ser Leu Asp Phe Asn Ser Thr Gly Asp Arg Lys Val Thr Val Asp 130 135 140			
Gly Val Val Gly Leu Glu Glu Glu Thr Ala Arg Met Asp Glu Tyr Val 145 150 155 160			
Val Leu Arg Phe Gly Trp Leu Tyr Gly Pro Gly Thr Trp Tyr Gly Lys 165 170 175			
Asp Gly Met Ile Tyr Asn Gln Phe Met Asp Gly Gln Val Thr Leu Ser 180 185 190			
Asp Gly Val Thr Ser Phe Val His Leu Asp Asp Ala Val Glu Thr Ser 195 200 205			
Ile Gln Ala Ile His Phe Glu Asn Gly Ile Tyr Asn Val Ala Asp Asp 210 215 220			
Ala Pro Val Lys Gly Ser Glu Phe Ala Glu Trp Tyr Lys Glu Gln Leu 225 230 235 240			
Gly Val Glu Pro Asn Ile Asp Ile Gln Pro Ala Gln Pro Phe Glu Arg 245 250 255			
Gly Val Ser Asn Glu Lys Phe Lys Ala Gln Gly Gly Thr Leu Ile Tyr 260 265 270			
Gln Thr Trp Lys Asp Gly Met Asn Pro Ile Lys 275 280			

<210> SEQ ID NO 29  
 <211> LENGTH: 54  
 <212> TYPE: PRT  
 <213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 29

Met Pro Lys Leu Ile Ser Pro Thr Phe Glu Asp Ile Lys Thr Trp Tyr 1 5 10 15
Gln Leu Lys Glu Tyr Ser Lys Glu Asp Ile Ala Trp Tyr Val Asp Met 20 25 30
Glu Val Ile Asp Lys Glu Glu Tyr Ala Ile Ile Thr Gly Glu Lys Tyr 35 40 45
Pro Glu Asn Leu Glu Ser 50

<210> SEQ ID NO 30  
 <211> LENGTH: 250  
 <212> TYPE: PRT  
 <213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 30

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



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

&lt;210&gt; SEQ ID NO 31

&lt;211&gt; LENGTH: 244

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Staphylococcus aureus

&lt;400&gt; SEQUENCE: 31

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

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Ser Asp Ser Pro Gly Gly Trp Gln Ile Ile Gly Arg Thr Pro Leu Lys  
 180 185 190

Val Phe Ser Ser Glu Arg Glu Pro Met Ser Met Tyr Glu Ala Gly Glu  
 195 200 205

Trp Ile Gln Phe Tyr Ala Ile Asp Glu Gln Lys Phe Ile Gln Ile Glu  
 210 215 220

Arg Asp Ile Ser Asp Gly Asn Phe Asn Val Asp Asp Trp Val Val Ile  
 225 230 235 240

Glu Asn Val Asn

<210> SEQ ID NO 32  
 <211> LENGTH: 108  
 <212> TYPE: PRT  
 <213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 32

Ile Tyr Tyr Arg Gly Ala His Tyr Met Lys Val Thr Asp Val Arg Leu  
 1 5 10 15

Arg Lys Ile Gln Thr Asp Gly Arg Met Lys Ala Leu Val Ser Ile Thr  
 20 25 30

Leu Asp Glu Ala Phe Val Ile His Asp Leu Arg Val Ile Glu Gly Asn  
 35 40 45

Ser Gly Leu Phe Val Ala Met Pro Ser Lys Arg Thr Pro Asp Gly Glu  
 50 55 60

Phe Arg Asp Ile Ala His Pro Ile Asn Ser Asp Met Arg Gln Glu Ile  
 65 70 75 80

Gln Asp Ala Val Met Lys Val Tyr Asp Glu Thr Asp Glu Val Val Pro  
 85 90 95

Asp Lys Asn Ala Thr Ser Glu Asp Ser Glu Glu Ala  
 100 105

<210> SEQ ID NO 33  
 <211> LENGTH: 645  
 <212> TYPE: PRT  
 <213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 33

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 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



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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
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
Lys Leu Lys Ala Glu Tyr Lys Lys Lys Leu Glu Asp Thr Lys Lys Ala	305	310	315
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
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
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
Thr Thr Lys Asp Val Val Gln Thr Ser Ala Gly Ser Ser Glu Ala Lys	565	570	575

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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 34  
<211> LENGTH: 476  
<212> TYPE: PRT  
<213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 34

Met Lys Ser Asp Ser Leu Lys Glu Asn Ile Ile Tyr Gln Gly Leu Tyr  
1 5 10 15

Gln Leu Ile Arg Thr Met Thr Pro Leu Ile Thr Ile Pro Ile Ile Ser  
20 25 30

Arg Ala Phe Gly Pro Ser Gly Val Gly Ile Val Ser Phe Ser Phe Asn  
35 40 45

Ile Val Gln Tyr Phe Leu Met Ile Ala Ser Val Gly Val Gln Leu Tyr  
50 55 60

Phe Asn Arg Val Ile Ala Lys Ser Val Asn Asp Lys Arg Gln Leu Ser  
65 70 75 80

Gln Gln Phe Trp Asp Ile Phe Val Ser Lys Leu Phe Leu Ala Leu Thr  
85 90 95

Val Phe Ala Met Tyr Met Val Val Ile Thr Ile Phe Ile Asp Asp Tyr  
100 105 110

Tyr Leu Ile Phe Leu Leu Gln Gly Ile Tyr Ile Ile Gly Ala Ala Leu  
115 120 125

Asp Ile Ser Trp Phe Tyr Ala Gly Thr Glu Lys Phe Lys Ile Pro Ser  
130 135 140

Leu Ser Asn Ile Val Ala Ser Gly Ile Val Leu Ser Val Val Val Ile  
145 150 155 160

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

Ile Val Thr Val Leu Asn Gln Leu Pro Leu Phe Ile Tyr Leu Lys Arg  
180 185 190

Tyr Ile Ser Phe Val Ser Val Asn Trp Ile His Val Trp Gln Leu Phe  
195 200 205

Arg Ser Ser Leu Ala Tyr Leu Leu Pro Asn Gly Gln Leu Asn Leu Tyr  
210 215 220

Thr Ser Ile Ser Cys Val Val Leu Gly Leu Val Gly Thr Tyr Gln Gln  
225 230 235 240

Val Gly Ile Phe Ser Asn Ala Phe Asn Ile Leu Thr Val Ala Ile Ile  
245 250 255

Met Ile Asn Thr Phe Asp Leu Val Met Ile Pro Arg Ile Thr Lys Met  
260 265 270

Ser Ile Gln Gln Ser His Ser Leu Thr Lys Thr Leu Ala Asn Asn Met  
275 280 285

Asn Ile Gln Leu Ile Leu Thr Ile Pro Met Val Phe Gly Leu Ile Ala



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290	295	300
Ile Met Pro Ser Phe Tyr Leu Trp Phe Phe Gly Glu Glu Phe Ala Ser 305 310 315 320		
Thr Val Pro Leu Met Thr Ile Leu Ala Ile Leu Val Leu Ile Ile Pro 325 330 335		
Leu Asn Met Leu Ile Ser Arg Gln Tyr Leu Leu Ile Val Asn Lys Ile 340 345 350		
Arg Leu Tyr Asn Ala Ser Ile Thr Ile Gly Ala Val Met Asn Leu Val 355 360 365		
Leu Cys Leu Val Leu Ile Tyr Phe Tyr Gly Ile Tyr Gly Ala Ala Ile 370 375 380		
Ala Arg Leu Ile Thr Glu Phe Ile Leu Leu Ile Trp Arg Phe Val Asp 385 390 395 400		
Ile Thr Lys Ile Asn Val Lys Leu Asn Ile Val Ser Thr Ile Gln Cys 405 410 415		
Val Ile Ala Ala Val Met Met Phe Ile Val Leu Gly Val Val Asn His 420 425 430		
Tyr Leu Pro Pro Thr Met Tyr Ala Thr Leu Leu Leu Ile Ala Ile Gly 435 440 445		
Ile Val Val Tyr Leu Leu Leu Met Met Thr Met Lys Asn Gln Tyr Val 450 455 460		
Trp Gln Ile Leu Arg His Leu Arg His Lys Thr Ile 465 470 475		

&lt;210&gt; SEQ ID NO 35

&lt;211&gt; LENGTH: 409

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Staphylococcus aureus

&lt;400&gt; SEQUENCE: 35

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

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Met Lys Leu Val Leu Pro Ile Ile Thr Leu Val Gly Gly Thr Val Gly  
 195 200 205

Gly Tyr Ile Thr Phe Ala Gly Ala His Arg Ile Leu Asp Ser Gly Ile  
 210 215 220

Lys Gly Lys Gln Tyr Leu Pro Phe Val Asn Gln Ser Ala Ile Ala Gly  
 225 230 235 240

Ile Leu Thr Thr Gly Ile Met Arg Thr Leu Leu Phe Leu Ala Val Leu  
 245 250 255

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

Ser Val Phe Glu His Ala Ile Gly Pro Ile Gly Lys Asn Ile Phe Gly  
 275 280 285

Ile Val Leu Phe Ala Ala Ala Met Ser Ser Val Ile Gly Ser Ala Tyr  
 290 295 300

Thr Ser Ala Thr Phe Leu Lys Thr Leu His Lys Ser Leu Asn Glu Arg  
 305 310 315 320

Ser Asn Leu Ile Val Ile Val Phe Ile Val Ile Ser Thr Met Ile Phe  
 325 330 335

Leu Phe Ile Gly Lys Pro Ile Ser Leu Leu Ile Ile Ala Gly Ala Ile  
 340 345 350

Asn Gly Trp Ile Leu Pro Ile Thr Leu Gly Ala Ile Leu Ile Ala Ser  
 355 360 365

Lys Lys Lys Ser Ile Val Gly Asp Tyr Lys His Pro Asn Trp Met Phe  
 370 375 380

Ile Phe Gly Ile Val Ala Val Leu Val Thr Ile Leu Thr Gly Ile Phe  
 385 390 395 400

Ser Phe Lys Glu Val Leu Gln Leu Phe  
 405

&lt;210&gt; SEQ ID NO 36

&lt;211&gt; LENGTH: 2481

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Staphylococcus aureus

&lt;400&gt; SEQUENCE: 36

Met Asn Leu Phe Arg Gln Gln Lys Phe Ser Ile Arg Lys Phe Asn Val  
 1 5 10 15

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

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

Pro Ala Gln Pro Ala Asp Ala Asn Thr Gln Pro Asn Ala Asn Ala Gly  
 50 55 60

Ala Gln Ala Asn Pro Ala Ala Gln Pro Ala Asn Gln Gly Gly Gln Ala  
 65 70 75 80

Asn Pro Ala Gly Gly Ala Ala Gln Pro Ala Gly Gln Gly Asn Gln Ala  
 85 90 95

Asp Pro Asn Asn Ala Ala Gln Ala Gln Pro Gly Asn Gln Ala Ala Pro  
 100 105 110

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

Ala Thr Pro Ala Asn Gln Thr Gln Pro Ala Asn Ala Pro Ala Ala Ala  
 130 135 140

Gln Pro Ala Ala Pro Val Ala Ala Asn Ala Gln Thr Gln Asp Pro Asn  
 145 150 155 160



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Ala Ser Asn Thr Gly Glu Gly Ser Ile Asn Thr Thr Leu Thr Phe Asp  
165 170 175

Asp Pro Ala Ile Ser Thr Asp Glu Asn Arg Gln Asp Pro Thr Val Thr  
180 185 190

Val Thr Asp Lys Val Asn Gly Tyr Ser Leu Ile Asn Asn Gly Lys Ile  
195 200 205

Gly Phe Val Asn Ser Glu Leu Arg Arg Ser Asp Met Phe Asp Lys Asn  
210 215 220

Asn Pro Gln Asn Tyr Gln Ala Lys Gly Asn Val Ala Ala Leu Gly Arg  
225 230 235 240

Val Asn Ala Asn Asp Ser Thr Asp His Gly Asn Phe Asn Gly Ile Thr  
245 250 255

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

Thr Met Gln Thr Asn Ser Lys Gln Gly Ala Thr Asn Leu Val Ile Lys  
275 280 285

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

Gly Thr Ala His Leu Phe Lys Val Pro Thr Asp Ala Asp Arg Leu Asp  
305 310 315 320

Leu Gln Phe Ile Pro Asp Asn Thr Ala Val Ala Asp Ala Ser Arg Ile  
325 330 335

Thr Thr Asn Lys Asp Gly Tyr Lys Tyr Tyr Ser Phe Ile Asp Asn Val  
340 345 350

Gly Leu Phe Ser Gly Ser His Leu Tyr Val Lys Asn Arg Asp Leu Ala  
355 360 365

Pro Lys Ala Thr Asn Asn Lys Glu Tyr Thr Ile Asn Thr Glu Ile Gly  
370 375 380

Asn Asn Gly Asn Phe Gly Ala Ser Leu Lys Ala Asp Gln Phe Lys Tyr  
385 390 395 400

Glu Val Thr Leu Pro Gln Gly Val Thr Tyr Val Asn Asp Ser Leu Thr  
405 410 415

Thr Thr Phe Pro Asn Gly Asn Glu Asp Ser Thr Val Leu Lys Asn Met  
420 425 430

Thr Val Asn Tyr Asp Gln Thr Ala Asn Lys Val Thr Phe Thr Ser Gln  
435 440 445

Gly Val Thr Thr Ala Arg Gly Thr His Thr Lys Glu Val Leu Phe Pro  
450 455 460

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

Thr Pro Lys Asn Ile Asp Phe Asn Glu Lys Leu Thr Tyr Arg Thr Ala  
485 490 495

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

Asp Pro Phe Ser Val Ala Val Glu Met Asn Lys Asp Ala Leu Gln Gln  
515 520 525

Gln Val Asn Ser Gln Val Asp Asn Ser His Tyr Thr Thr Ala Ser Ile  
530 535 540

Ala Glu Tyr Asn Lys Leu Lys Gln Gln Ala Asp Thr Ile Leu Asn Glu  
545 550 555 560

Asp Ala Asn His Val Glu Thr Ala Asn Arg Ala Ser Gln Ala Asp Ile  
565 570 575

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Asp Gly Leu Val Thr Lys Leu Gln Ala Ala Leu Ile Asp Asn Gln Ala  
 580 585 590  
 Ala Ile Ala Glu Leu Asp Thr Lys Ala Gln Glu Lys Val Thr Ala Ala  
 595 600 605  
 Gln Gln Ser Lys Lys Val Thr Gln Asp Glu Val Ala Ala Leu Val Thr  
 610 615 620  
 Lys Ile Asn Asn Asp Lys Asn Asn Ala Ile Ala Glu Ile Asn Lys Gln  
 625 630 635 640  
 Thr Thr Ser Gln Gly Val Thr Thr Glu Lys Asp Asn Gly Ile Ala Val  
 645 650 655  
 Leu Glu Gln Asp Val Ile Thr Pro Thr Val Lys Pro Gln Ala Lys Gln  
 660 665 670  
 Asp Ile Ile Gln Ala Val Thr Thr Arg Lys Gln Gln Ile Lys Lys Ser  
 675 680 685  
 Asn Ala Ser Leu Gln Asp Glu Lys Asp Val Ala Asn Asp Lys Ile Gly  
 690 695 700  
 Lys Ile Glu Thr Lys Ala Ile Lys Asp Ile Asp Ala Ala Thr Thr Asn  
 705 710 715 720  
 Ala Gln Val Glu Ala Ile Lys Thr Lys Ala Ile Asn Asp Ile Asn Gln  
 725 730 735  
 Thr Thr Pro Ala Thr Thr Ala Lys Ala Ala Ala Leu Glu Glu Phe Asp  
 740 745 750  
 Glu Val Val Gln Ala Gln Ile Asp Gln Ala Pro Leu Asn Pro Asp Thr  
 755 760 765  
 Thr Asn Glu Glu Val Ala Glu Ala Ile Glu Arg Ile Asn Ala Ala Lys  
 770 775 780  
 Val Ser Gly Val Lys Ala Ile Glu Ala Thr Thr Thr Ala Gln Asp Leu  
 785 790 795 800  
 Glu Arg Val Lys Asn Glu Glu Ile Phe Lys Ile Glu Asn Ile Thr Asp  
 805 810 815  
 Ser Thr Gln Thr Lys Met Asp Ala Tyr Lys Glu Val Arg Gln Ala Ala  
 820 825 830  
 Thr Ala Arg Lys Ala Gln Asn Ala Thr Val Ser Asn Ala Thr Asp Glu  
 835 840 845  
 Glu Val Ala Glu Ala Asn Ala Ala Val Asp Ala Ala Gln Thr Glu Gly  
 850 855 860  
 Leu His Asp Ile Gln Val Val Lys Ser Gln Gln Glu Val Ala Asp Thr  
 865 870 875 880  
 Lys Ala Lys Val Leu Asp Lys Ile Asn Ala Ile Gln Thr Gln Ala Lys  
 885 890 895  
 Val Lys Pro Ala Ala Asp Thr Glu Val Glu Asn Ala Tyr Asn Thr Arg  
 900 905 910  
 Lys Gln Glu Ile Gln Asn Ser Asn Ala Ser Thr Thr Glu Glu Lys Glu  
 915 920 925  
 Ala Ala Tyr Thr Glu Leu Asp Ala Lys Lys Gln Glu Ala Arg Thr Asn  
 930 935 940  
 Leu Asp Ala Ala Asn Thr Asn Ser Asp Val Thr Thr Ala Lys Asp Asn  
 945 950 955 960  
 Gly Ile Ala Ala Ile Asn Gln Val Gln Ala Ala Thr Thr Lys Lys Ser  
 965 970 975  
 Asp Ala Lys Ala Glu Ile Ala Gln Lys Ala Ser Glu Arg Lys Thr Ala  
 980 985 990  
 Ile Glu Ala Met Asn Asp Ser Thr Thr Glu Glu Gln Gln Ala Ala Lys



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995				1000				1005						
Asp	Lys	Val	Asp	Gln	Ala	Val	Val	Thr	Ala	Asn	Ala	Asp	Ile	Asp
1010						1015					1020			
Asn	Ala	Thr	Ala	Asn	Thr	Asp	Val	Asp	Asn	Ala	Lys	Thr	Thr	Asn
1025						1030					1035			
Glu	Ala	Thr	Ile	Ala	Ala	Ile	Thr	Pro	Asp	Ala	Asn	Val	Lys	Pro
1040						1045					1050			
Ala	Ala	Lys	Gln	Ala	Ile	Ala	Asp	Lys	Val	Gln	Ala	Gln	Glu	Thr
1055						1060					1065			
Ala	Ile	Asp	Ala	Asn	Asn	Gly	Ser	Thr	Thr	Glu	Glu	Lys	Glu	Ala
1070						1075					1080			
Ala	Lys	Gln	Gln	Val	Gln	Thr	Glu	Lys	Thr	Ala	Ala	Asp	Ala	Ala
1085						1090					1095			
Ile	Asp	Ala	Ala	His	Ser	Asn	Val	Glu	Val	Glu	Ala	Ala	Lys	Asn
1100						1105					1110			
Ala	Glu	Ile	Ala	Lys	Ile	Glu	Ala	Ile	Gln	Pro	Ala	Thr	Thr	Thr
1115						1120					1125			
Lys	Asp	Asn	Ala	Lys	Gln	Ala	Ile	Ala	Thr	Lys	Ala	Asn	Glu	Arg
1130						1135					1140			
Lys	Thr	Ala	Ile	Ala	Gln	Thr	Gln	Asp	Ile	Thr	Ala	Glu	Glu	Ile
1145						1150					1155			
Ala	Ala	Ala	Asn	Ala	Asp	Val	Asp	Asn	Ala	Val	Thr	Gln	Ala	Asn
1160						1165					1170			
Ser	Asn	Ile	Glu	Ala	Ala	Asn	Ser	Gln	Asn	Asp	Val	Asp	Gln	Ala
1175						1180					1185			
Lys	Thr	Thr	Gly	Glu	Thr	Ser	Ile	Asp	Gln	Val	Thr	Pro	Thr	Val
1190						1195					1200			
Asn	Lys	Lys	Ala	Thr	Ala	Arg	Asn	Glu	Ile	Thr	Ala	Ile	Leu	Asn
1205						1210					1215			
Asn	Lys	Leu	Gln	Glu	Ile	Gln	Ala	Thr	Pro	Asp	Ala	Thr	Asp	Glu
1220						1225					1230			
Glu	Lys	Gln	Ala	Ala	Asp	Ala	Glu	Ala	Asn	Thr	Glu	Asn	Gly	Lys
1235						1240					1245			
Ala	Asn	Gln	Ala	Ile	Ser	Ala	Ala	Thr	Thr	Asn	Ala	Gln	Val	Asp
1250						1255					1260			
Glu	Ala	Lys	Ala	Asn	Ala	Glu	Ala	Ala	Ile	Asn	Ala	Val	Thr	Pro
1265						1270					1275			
Lys	Val	Val	Lys	Lys	Gln	Ala	Ala	Lys	Asp	Glu	Ile	Asp	Gln	Leu
1280						1285					1290			
Gln	Ala	Thr	Gln	Thr	Asn	Val	Ile	Asn	Asn	Asp	Gln	Asn	Ala	Thr
1295						1300					1305			
Asn	Glu	Glu	Lys	Glu	Ala	Ala	Ile	Gln	Gln	Leu	Ala	Thr	Ala	Val
1310						1315					1320			
Thr	Asp	Ala	Lys	Asn	Asn	Ile	Thr	Ala	Ala	Thr	Asp	Asp	Asn	Gly
1325						1330					1335			
Val	Asp	Thr	Ala	Lys	Asp	Ala	Gly	Lys	Asn	Ser	Ile	Gln	Ser	Thr
1340						1345					1350			
Gln	Pro	Ala	Thr	Ala	Val	Lys	Ser	Asn	Ala	Lys	Asn	Glu	Val	Asp
1355						1360					1365			
Gln	Ala	Val	Thr	Thr	Gln	Asn	Gln	Ala	Ile	Asp	Asn	Thr	Thr	Gly
1370						1375					1380			
Ala	Thr	Thr	Glu	Glu	Lys	Asn	Ala	Ala	Lys	Asp	Leu	Val	Leu	Lys
1385						1390					1395			





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Leu	Glu	Asn	Ile	Asn	Asn	Gly	Val	Asp	Asn	Gly	Asp	Val	Asp	Asp
1790						1795					1800			
Ala	Leu	Thr	Gln	Gly	Lys	Ala	Ala	Ile	Asp	Thr	Ile	Gln	Val	Asp
1805						1810					1815			
Ala	Thr	Val	Lys	Pro	Lys	Ala	Asn	Gln	Ala	Ile	Glu	Ala	Lys	Ala
1820						1825					1830			
Glu	Asp	Thr	Lys	Glu	Ser	Ile	Asp	His	Ser	Asp	Gln	Leu	Thr	Ala
1835						1840					1845			
Glu	Glu	Lys	Thr	Glu	Ala	Leu	Ala	Met	Ile	Lys	Gln	Ile	Thr	Asp
1850						1855					1860			
Gln	Ala	Lys	Gln	Gly	Ile	Thr	Asp	Ala	Thr	Thr	Thr	Ala	Glu	Val
1865						1870					1875			
Glu	Lys	Ala	Lys	Ala	Gln	Gly	Leu	Glu	Ala	Phe	Asp	Asn	Ile	Gln
1880						1885					1890			
Ile	Asp	Ser	Thr	Glu	Lys	Gln	Lys	Ala	Ile	Glu	Glu	Leu	Glu	Thr
1895						1900					1905			
Ala	Leu	Asp	Gln	Ile	Glu	Ala	Gly	Val	Asn	Val	Asp	Ala	Asp	Ala
1910						1915					1920			
Thr	Thr	Glu	Glu	Lys	Glu	Ala	Phe	Thr	Asn	Ala	Leu	Glu	Asp	Ile
1925						1930					1935			
Leu	Ser	Lys	Ala	Thr	Glu	Asp	Ile	Ser	Asp	Gln	Thr	Thr	Asn	Ala
1940						1945					1950			
Glu	Ile	Ala	Thr	Val	Lys	Asn	Ser	Ala	Leu	Glu	Gln	Leu	Lys	Ala
1955						1960					1965			
Gln	Arg	Ile	Asn	Pro	Val	Val	Lys	Lys	Asn	Ala	Leu	Glu	Ala	Ile
1970						1975					1980			
Arg	Glu	Val	Val	Asn	Lys	Gln	Ile	Glu	Ile	Ile	Lys	Asn	Ala	Asp
1985						1990					1995			
Ala	Asp	Ala	Ser	Ala	Lys	Glu	Ile	Ala	Arg	Thr	Asp	Leu	Gly	Arg
2000						2005					2010			
Tyr	Phe	Asp	Arg	Phe	Ala	Asp	Lys	Leu	Asp	Lys	Thr	Gln	Thr	Asn
2015						2020					2025			
Thr	Glu	Val	Ala	Glu	Leu	Gln	Asn	Val	Thr	Ile	Pro	Ala	Ile	Glu
2030						2035					2040			
Ala	Ile	Val	Pro	Gln	Asn	Asp	Pro	Asp	Ala	Asn	Asp	Thr	Asn	Asn
2045						2050					2055			
Gly	Thr	Asp	Asn	Asn	Asp	Ala	Thr	Ala	Asn	Ser	Asn	Ala	Asn	Ala
2060						2065					2070			
Thr	Pro	Glu	Asn	Thr	Gly	Gln	Pro	Asn	Val	Ser	Glu	Thr	Thr	Asp
2075						2080					2085			
Asn	Gly	Lys	Ala	Asp	Ala	Ser	Pro	Thr	Thr	Pro	Asn	Asn	Ser	Asp
2090						2095					2100			
Ala	Ala	Thr	Gly	Glu	Thr	Thr	Val	Thr	Ser	Ala	Thr	Asp	Asp	Ala
2105						2110					2115			
Lys	Asp	Lys	Pro	Gln	Ala	Asn	Asn	Asn	Ser	Ser	Ala	Asp	Ala	Ser
2120						2125					2130			
Thr	Asn	Ser	Pro	Thr	Met	Asp	Asn	Asp	Val	Thr	Ser	Lys	Pro	Glu
2135						2140					2145			
Val	Glu	Ser	Thr	Asn	Asn	Gly	Thr	Thr	Asp	Lys	Pro	Val	Thr	Glu
2150						2155					2160			
Thr	Asp	Asn	Ala	Thr	Pro	Ala	Glu	Ser	Thr	Thr	Asn	Asn	Asn	Ser
2165						2170					2175			
Thr	Thr	Thr	Ala	Thr	Asn	Glu	Asn	Ala	Pro	Thr	Gly	Ser	Thr	Ala

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

&lt;210&gt; SEQ ID NO 37

&lt;211&gt; LENGTH: 231

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Staphylococcus aureus

&lt;400&gt; SEQUENCE: 37

Lys Glu Asp Ser Lys Glu Glu Gln Ile Lys Lys Ser Phe Ala Lys Thr  
1 5 10 15

Leu Asp Met Tyr Pro Ile Lys Asn Leu Glu Asp Leu Tyr Asp Lys Glu  
20 25 30

Gly Tyr Arg Asp Gly Glu Phe Lys Lys Gly Asp Lys Gly Thr Trp Thr  
35 40 45



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Leu Leu Thr Ser Phe Ser Lys Ser Asn Lys Pro Asp Glu Ile Asp Asp  
 50 55 60  
 Glu Gly Met Val Leu Tyr Leu Asn Arg Asn Thr Lys Lys Ala Thr Gly  
 65 70 75 80  
 Tyr Tyr Phe Val Asn Lys Ile Tyr Asp Asp Ile Ser Lys Asn Gln Asn  
 85 90 95  
 Glu Lys Lys Tyr Arg Val Glu Leu Lys Asn Asn Lys Ile Val Leu Leu  
 100 105 110  
 Asp Asn Val Glu Asp Glu Lys Leu Lys Gln Lys Ile Glu Asn Phe Lys  
 115 120 125  
 Phe Phe Ser Gln Tyr Ala Asp Phe Lys Asp Leu Lys Asn Tyr Gln Asp  
 130 135 140  
 Gly Ser Ile Thr Thr Asn Glu Asn Ile Pro Ser Tyr Glu Ala Glu Tyr  
 145 150 155 160  
 Lys Leu Asn Asn Ser Asp Glu Asn Val Lys Lys Leu Arg Asp Ile Tyr  
 165 170 175  
 Pro Ile Thr Thr Lys Lys Ala Pro Ile Leu Lys Leu His Ile Asp Gly  
 180 185 190  
 Asp Ile Lys Gly Ser Ser Val Gly Tyr Lys Lys Ile Glu Tyr Lys Phe  
 195 200 205  
 Ser Lys Val Lys Asp Gln Glu Thr Thr Leu Arg Asp Tyr Leu Asn Phe  
 210 215 220  
 Gly Pro Ser Asp Glu Asp Ser  
 225 230

&lt;210&gt; SEQ ID NO 38

&lt;211&gt; LENGTH: 284

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Staphylococcus aureus

&lt;400&gt; SEQUENCE: 38

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

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Ile Thr Pro Gly Tyr Ile Trp Glu Ile Asn Thr Glu Lys Gln Gly Thr  
 195 200 205

Pro Glu Gln Met Arg Gln Ala Ile Glu Phe Val Lys Lys His Lys Leu  
 210 215 220

Lys His Leu Leu Val Glu Thr Ser Val Asp Lys Lys Ala Met Glu Ser  
 225 230 235 240

Leu Ser Glu Glu Thr Lys Lys Asp Ile Phe Gly Glu Val Tyr Thr Asp  
 245 250 255

Ser Ile Gly Lys Glu Gly Thr Lys Gly Asp Ser Tyr Tyr Lys Met Met  
 260 265 270

Lys Ser Asn Ile Glu Thr Val His Gly Ser Met Lys  
 275 280

<210> SEQ ID NO 39  
 <211> LENGTH: 478  
 <212> TYPE: PRT  
 <213> ORGANISM: Staphylococcus aureus

<400> SEQUENCE: 39

Val Thr Lys Pro Gln Thr Thr Gln Thr Val Ser Lys Ile Ala Gln Val  
 1 5 10 15

Lys Pro Asn Asn Thr Gly Ile Arg Ala Ser Val Tyr Glu Lys Thr Ala  
 20 25 30

Lys Asn Gly Ala Lys Tyr Ala Asp Arg Thr Phe Tyr Val Thr Lys Glu  
 35 40 45

Arg Ala His Gly Asn Glu Thr Tyr Val Leu Leu Asn Asn Thr Ser His  
 50 55 60

Asn Ile Pro Leu Gly Trp Phe Asn Val Lys Asp Leu Asn Val Gln Asn  
 65 70 75 80

Leu Gly Lys Glu Val Lys Thr Thr Gln Lys Tyr Thr Val Asn Arg Ser  
 85 90 95

Asn Asn Gly Leu Ser Met Val Pro Trp Gly Thr Lys Asn Gln Val Ile  
 100 105 110

Leu Thr Gly Asn Asn Ile Ala Gln Gly Thr Phe Asn Ala Thr Lys Gln  
 115 120 125

Val Ser Val Gly Lys Asp Val Tyr Leu Tyr Gly Thr Ile Asn Asn Arg  
 130 135 140

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

Pro Thr Thr Ser Ala Ala Lys Asp Tyr Asn Tyr Thr Tyr Val Ile Lys  
 165 170 175

Asn Gly Asn Gly Tyr Tyr Tyr Val Thr Pro Asn Ser Asp Thr Ala Lys  
 180 185 190

Tyr Ser Leu Lys Ala Phe Asn Glu Gln Pro Phe Ala Val Val Lys Glu  
 195 200 205

Gln Val Ile Asn Gly Gln Thr Trp Tyr Tyr Gly Lys Leu Ser Asn Gly  
 210 215 220

Lys Leu Ala Trp Ile Lys Ser Thr Asp Leu Ala Lys Glu Leu Ile Lys  
 225 230 235 240

Tyr Asn Gln Ile Gly Met Thr Leu Asn Gln Val Ala Gln Ile Gln Ala  
 245 250 255

Gly Leu Gln Tyr Lys Pro Gln Val Gln Arg Val Pro Gly Lys Trp Thr  
 260 265 270

Asp Ala Asn Phe Asn Asp Val Lys His Ala Met Asp Thr Lys Arg Leu



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275	280	285
Ala Gln Asp Pro Ala Leu Lys Tyr Gln Phe Leu Arg Leu Asp Gln Pro 290 295 300		
Gln Asn Ile Ser Ile Asp Lys Ile Asn Gln Phe Leu Lys Gly Lys Gly 305 310 315 320		
Val Leu Glu Asn Gln Gly Ala Ala Phe Asn Lys Ala Ala Gln Met Tyr 325 330 335		
Gly Ile Asn Glu Val Tyr Leu Ile Ser His Ala Leu Leu Glu Thr Gly 340 345 350		
Asn Gly Thr Ser Gln Leu Ala Lys Gly Ala Asp Val Val Asn Asn Lys 355 360 365		
Val Val Thr Asn Ser Asn Thr Lys Tyr His Asn Val Phe Gly Ile Ala 370 375 380		
Ala Tyr Asp Asn Asp Pro Leu Arg Glu Gly Ile Lys Tyr Ala Lys Gln 385 390 395 400		
Ala Gly Trp Asp Thr Val Ser Lys Ala Ile Val Gly Gly Ala Lys Phe 405 410 415		
Ile Gly Asn Ser Tyr Val Lys Ala Gly Gln Asn Thr Leu Tyr Lys Met 420 425 430		
Arg Trp Asn Pro Ala His Pro Gly Thr His Gln Tyr Ala Thr Asp Val 435 440 445		
Asp Trp Ala Asn Ile Asn Ala Lys Ile Ile Lys Gly Tyr Tyr Asp Lys 450 455 460		
Ile Gly Glu Val Gly Lys Tyr Phe Asp Ile Pro Gln Tyr Lys 465 470 475		

What is claimed is:

1. An immunogenic composition comprising:

(a) five purified *Staphylococcus aureus* polypeptides, or portions thereof, or variants thereof, or combinations thereof, wherein the *S. aureus* polypeptides are (i) biofilm-specific *S. aureus* polypeptide SA0037 set forth in SEQ ID NO: 13, (ii) planktonic-specific *S. aureus* polypeptide SA0119 set forth in SEQ ID NO: 14, (iii) biofilm-specific *S. aureus* polypeptide SA0486 set forth in SEQ ID NO: 15, (iv) biofilm-specific *S. aureus* polypeptide SA0688 set forth in SEQ ID NO:16, and (v) biofilm-specific *S. aureus* glucosaminidase set forth in SEQ ID NO: 17, wherein each of the portions is at least 95% of the size of the corresponding full-length polypeptide, and wherein each of the variants has at least 95% sequence identity with the corresponding full-length polypeptide,

(b) a pharmaceutically acceptable carrier or diluent and  
(c) an immunostimulatory amount of an adjuvant.

2. The composition of claim 1, wherein the five purified *S. aureus* polypeptides are full-length *S. aureus* polypeptides.

3. A formulation comprising an immunologically effective amount of a vaccine comprising:

(a) five purified *Staphylococcus aureus* polypeptides, wherein the *S. aureus* polypeptides are (i) biofilm-specific *S. aureus* polypeptide SA0037 set forth in SEQ ID NO: 13, (ii) planktonic-specific *S. aureus* polypeptide SA0119 set forth in SEQ ID NO: 14, (iii) biofilm-specific *S. aureus* polypeptide SA0486 set forth in SEQ ID NO: 15, (iv) biofilm-specific *S. aureus* polypeptide SA0688 set forth in SEQ ID NO:16, and (v) biofilm-specific *S. aureus* glucosaminidase set forth in SEQ ID NO: 17,

(b) a pharmaceutically acceptable carrier or diluent and  
(c) an immunostimulatory amount of an adjuvant.

4. A formulation comprising an immunologically effective amount of a vaccine consisting of:

(a) five purified *Staphylococcus aureus* polypeptides, wherein the *S. aureus* polypeptides are (i) biofilm-specific *S. aureus* polypeptide SA0037 set forth in SEQ ID NO: 13, (ii) planktonic-specific *S. aureus* polypeptide SA0119 set forth in SEQ ID NO: 14, (iii) biofilm-specific *S. aureus* polypeptide SA0486 set forth in SEQ ID NO: 15, (iv) biofilm-specific *S. aureus* polypeptide SA0688 set forth in SEQ ID NO:16, and (v) biofilm-specific *S. aureus* glucosaminidase set forth in SEQ ID NO: 17,

(b) a pharmaceutically acceptable carrier or diluent and  
(c) an immunostimulatory amount of an adjuvant.

5. A method of generating an immune response against *S. aureus* in a subject comprising administering to the subject an immunologically effective amount of the formulation of claim 3.

6. A method of generating an immune response against *S. aureus* in a subject comprising administering to the subject an immunologically effective amount of the formulation of claim 4.

7. A formulation comprising an immunologically effective amount of a pentavalent vaccine consisting of:

(a) five purified *Staphylococcus aureus* polypeptides, wherein the *S. aureus* polypeptides are (i) biofilm-specific *S. aureus* polypeptide SA0037 set forth in SEQ ID NO: 13, (ii) planktonic-specific *S. aureus* polypeptide SA0119 set forth in SEQ ID NO: 14, (iii) biofilm-specific *S. aureus* polypeptide SA0486 set forth in SEQ ID NO: 15, (iv) biofilm-specific *S. aureus* polypeptide



SA0688 set forth in SEQ ID NO:16, and (v) biofilm-specific *S. aureus* glucosaminidase set forth in SEQ ID NO: 17, and

(b) a pharmaceutically acceptable carrier or diluent, wherein the vaccine elicits complete protection against a biofilm-associated *S. aureus* implant infection in a mammal with 100% clearance of the infecting *S. aureus*.

8. A method of eliciting a protective immune response against a biofilm-associated *S. aureus* implant infection in a mammal comprising administering to the mammal an immunologically effective amount of the formulation of claim 7.

9. An immunogenic composition comprising:

(a) five purified *Staphylococcus aureus* polypeptides, or variants thereof, or combinations thereof, wherein the *S. aureus* polypeptides are:

(i) a portion of biofilm-specific *S. aureus* polypeptide SA0037 set forth in SEQ ID NO: 13, wherein the portion is at least 90% of the size of the polypeptide set forth in SEQ ID NO: 13,

(ii) a portion of planktonic-specific *S. aureus* polypeptide SA0119 set forth in SEQ ID NO: 14, wherein the portion is at least 65% of the size of the polypeptide set forth in SEQ ID NO: 14,

(iii) a portion of biofilm-specific *S. aureus* polypeptide SA0486 set forth in SEQ ID NO: 37, wherein the portion is at least 85% of the size of the polypeptide set forth in SEQ ID NO: 37,

(iv) a portion of biofilm-specific *S. aureus* polypeptide SA0688 set forth in SEQ ID NO:38, wherein the portion is at least 95% of the size of the polypeptide set forth in SEQ ID NO: 38, and

(v) a portion of biofilm-specific *S. aureus* glucosaminidase set forth in SEQ ID NO: 39, wherein the portion is at least 95% of the size of the polypeptide set forth in SEQ ID NO: 39,

wherein each variant has at least 95% sequence identity with the corresponding *S. aureus* polypeptide;

(b) a pharmaceutically acceptable carrier or diluent; and

(c) an immunostimulatory amount of an adjuvant.

10. A formulation comprising an immunologically effective amount of a vaccine comprising of:

(a) five purified *Staphylococcus aureus* polypeptides, or variants thereof, or combinations thereof, wherein the *S. aureus* polypeptides are:

(i) a portion of biofilm-specific *S. aureus* polypeptide SA0037 set forth in SEQ ID NO: 13, wherein the portion is at least 90% of the size of the polypeptide set forth in SEQ ID NO: 13,

(ii) a portion of planktonic-specific *S. aureus* polypeptide SA0119 set forth in SEQ ID NO: 14, wherein the portion is at least 65% of the size of the polypeptide set forth in SEQ ID NO: 14,

(iii) a portion of biofilm-specific *S. aureus* polypeptide SA0486 set forth in SEQ ID NO: 37, wherein the portion is at least 85% of the size of the polypeptide set forth in SEQ ID NO: 37,

(iv) a portion of biofilm-specific *S. aureus* polypeptide SA0688 set forth in SEQ ID NO:38, wherein the portion is at least 95% of the size of the polypeptide set forth in SEQ ID NO: 38, and

(v) a portion of biofilm-specific *S. aureus* glucosaminidase set forth in SEQ ID NO: 39, wherein the portion is at least 95% of the size of the polypeptide set forth in SEQ ID NO: 39,

wherein each variant has at least 95% sequence identity with the corresponding *S. aureus* polypeptide,

(b) a pharmaceutically acceptable carrier or diluent; and

(c) an immunostimulatory amount of an adjuvant.

11. A method of generating an immune response against *S. aureus* in a subject comprising administering to the subject an immunologically effective amount of the formulation of claim 10.

12. A formulation comprising an immunologically effective amount of a pentavalent vaccine consisting of:

(a) five purified *Staphylococcus aureus* polypeptides, or variants thereof, or combinations thereof, wherein the *S. aureus* polypeptides are:

(i) a portion of biofilm-specific *S. aureus* polypeptide SA0037 set forth in SEQ ID NO: 13, wherein the portion is at least 90% of the size of the polypeptide set forth in SEQ ID NO: 13,

(ii) a portion of planktonic-specific *S. aureus* polypeptide SA0119 set forth in SEQ ID NO: 14, wherein the portion is at least 65% of the size of the polypeptide set forth in SEQ ID NO: 14,

(iii) a portion of biofilm-specific *S. aureus* polypeptide SA0486 set forth in SEQ ID NO: 37, wherein the portion is at least 85% of the size of the polypeptide set forth in SEQ ID NO: 37,

(iv) a portion of biofilm-specific *S. aureus* polypeptide SA0688 set forth in SEQ ID NO:38, wherein the portion is at least 95% of the size of the polypeptide set forth in SEQ ID NO: 38, and

(v) a portion of biofilm-specific *S. aureus* glucosaminidase set forth in SEQ ID NO: 39, wherein the portion is at least 95% of the size of the polypeptide set forth in SEQ ID NO: 39,

wherein each variant has at least 95% sequence identity with the corresponding *S. aureus* polypeptide; and

(b) a pharmaceutically acceptable carrier or diluent;

wherein the vaccine elicits complete protection against a biofilm-associated *S. aureus* implant infection in a mammal with 100% clearance of the infecting *S. aureus*.

13. A method of eliciting a protective immune response against a biofilm-associated *S. aureus* implant infection in a mammal comprising administering to the mammal an immunologically effective amount of the formulation of claim 12.

14. An immunogenic composition comprising:

(a) five purified *Staphylococcus aureus* polypeptides, wherein the *S. aureus* polypeptides are:

(i) a portion of biofilm-specific *S. aureus* polypeptide SA0037 set forth in SEQ ID NO: 13, wherein the portion is at least 90% of the size of the polypeptide set forth in SEQ ID NO: 13,

(ii) a portion of planktonic-specific *S. aureus* polypeptide SA0119 set forth in SEQ ID NO: 14, wherein the portion is at least 65% of the size of the polypeptide set forth in SEQ ID NO: 14,

(iii) a portion of biofilm-specific *S. aureus* polypeptide SA0486 set forth in SEQ ID NO: 37, wherein the portion is at least 85% of the size of the polypeptide set forth in SEQ ID NO: 37,

(iv) a portion of biofilm-specific *S. aureus* polypeptide SA0688 set forth in SEQ ID NO:38, wherein the portion is at least 95% of the size of the polypeptide set forth in SEQ ID NO: 38, and

(v) a portion of biofilm-specific *S. aureus* glucosaminidase set forth in SEQ ID NO: 39, wherein the portion is at least 95% of the size of the polypeptide set forth in SEQ ID NO: 39;

(b) a pharmaceutically acceptable carrier or diluent; and

(c) an immunostimulatory amount of an adjuvant.



15. A formulation comprising an immunologically effective amount of a vaccine comprising of:

(a) five purified *Staphylococcus aureus* polypeptides, wherein the *S. aureus* polypeptides are:

(i) a portion of biofilm-specific *S. aureus* polypeptide SA0037 set forth in SEQ ID NO: 13, wherein the portion is at least 90% of the size of the polypeptide set forth in SEQ ID NO: 13,

(ii) a portion of planktonic-specific *S. aureus* polypeptide SA0119 set forth in SEQ ID NO: 14, wherein the portion is at least 65% of the size of the polypeptide set forth in SEQ ID NO: 14,

(iii) a portion of biofilm-specific *S. aureus* polypeptide SA0486 set forth in SEQ ID NO: 37, wherein the portion is at least 85% of the size of the polypeptide set forth in SEQ ID NO: 37,

(iv) a portion of biofilm-specific *S. aureus* polypeptide SA0688 set forth in SEQ ID NO: 38, wherein the portion is at least 95% of the size of the polypeptide set forth in SEQ ID NO: 38, and

(v) a portion of biofilm-specific *S. aureus* glucosaminidase set forth in SEQ ID NO: 39, wherein the portion is at least 95% of the size of the polypeptide set forth in SEQ ID NO: 39;

(b) a pharmaceutically acceptable carrier or diluent; and

(c) an immunostimulatory amount of an adjuvant.

16. A method of generating an immune response against *S. aureus* in a subject comprising administering to the subject an immunologically effective amount of the formulation of claim 15.

17. A formulation comprising an immunologically effective amount of a pentavalent vaccine consisting of:

(a) five purified *Staphylococcus aureus* polypeptides, wherein the *S. aureus* polypeptides are:

(i) a portion of biofilm-specific *S. aureus* polypeptide SA0037 set forth in SEQ ID NO: 13, wherein the portion is at least 90% of the size of the polypeptide set forth in SEQ ID NO: 13,

(ii) a portion of planktonic-specific *S. aureus* polypeptide SA0119 set forth in SEQ ID NO: 14, wherein the portion is at least 65% of the size of the polypeptide set forth in SEQ ID NO: 14,

(iii) a portion of biofilm-specific *S. aureus* polypeptide SA0486 set forth in SEQ ID NO: 37, wherein the portion is at least 85% of the size of the polypeptide set forth in SEQ ID NO: 37,

(iv) a portion of biofilm-specific *S. aureus* polypeptide SA0688 set forth in SEQ ID NO: 38, wherein the portion is at least 95% of the size of the polypeptide set forth in SEQ ID NO: 38, and

(v) a portion of biofilm-specific *S. aureus* glucosaminidase set forth in SEQ ID NO: 39, wherein the portion is at least 95% of the size of the polypeptide set forth in SEQ ID NO: 39; and

(b) a pharmaceutically acceptable carrier or diluent; wherein the vaccine elicits complete protection against a biofilm-associated *S. aureus* implant infection in a mammal with 100% clearance of the infecting *S. aureus*.

18. A method of eliciting a protective immune response against a biofilm-associated *S. aureus* implant infection in a mammal comprising administering to the mammal an immunologically effective amount of the formulation of claim 17.

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