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(54) Title: ANTIMICROBIAL METHODS AND MATERIALS

(57) Abstract: The present invention provides methods of identifying agents that bind gene products critical for the survival of microbes, preferably *Staphylococcus* microbes, including agents that interfere with the function of such gene products.

ANTIMICROBIAL METHODS AND MATERIALS

5

BACKGROUND

The staphylococci, of which *Staphylococcus aureus* is the most important human pathogen, are hardy, gram-positive bacteria that colonize the skin of most humans. Staphylococcal strains that produce coagulase are designated *S. aureus*; other clinically important coagulase-negative staphylococci are *S. epidermidis* and *S. saprophyticus*. When the skin or mucous membrane barriers are disrupted, staphylococci can cause localized and superficial infections that are commonly harmless and self-limiting. However, when staphylococci invade the lymphatics and the blood, potentially serious complications may result, such as bacteremia, septic shock, and serious metastatic infections, including endocarditis, arthritis, osteomyelitis, pneumonia and abscesses in virtually any organ. Certain strains of *S. aureus* produce toxins that cause skin rashes, food poisoning, or multisystem dysfunction (as in toxic shock syndrome). *S. aureus* and *S. epidermidis* together have become the most common cause of nosocomial non-urinary tract infection in U.S. hospitals. They are the most frequently isolated pathogens in both primary and secondary bacteremias and in cutaneous and surgical wound infections. See generally *Harrison's Principles of Internal Medicine*, 13th ed., Isselbacher et al., eds., McGraw-Hill, New York (1994), particularly pages 611-617.

Transient colonization of the nose by *S. aureus* is seen in 70 to 90 percent of people, of which 20 to 30 percent carry the bacteria for relatively prolonged periods of time. Independent colonization of the perineal area occurs in 5 to 20 percent of people. Higher carriage rates of *S. aureus* have been documented in persons with atopic dermatitis, hospital employees, hospitalized patients, patients whose care requires frequent puncture of the skin, and intravenous drug abusers.

Infection by staphylococci usually results from a combination of bacterial virulence factors and a diminution in host defenses. Important microbial factors include the ability of the staphylococcus to survive under harsh conditions, its cell wall constituents, the production of enzymes and

toxins that promote tissue invasion, its capacity to persist intracellularly in certain phagocytes, and its potential to acquire resistance to antimicrobial agents. Important host factors include an intact mucocutaneous barrier, an adequate number of functional neutrophils, and removal of foreign bodies or
5 dead tissue.

Cell wall components of *S. aureus* include a large peptidoglycan complex that confers rigidity on the organism and enables it to survive under unfavorable osmotic conditions, a unique teichoic acid linked to peptidoglycan, and protein A, which is found both attached to peptidoglycan over the
10 outermost parts of the cell and released in soluble form. Proteins designated femA and femB are involved in the formation of cell wall peptidoglycan pentaglycine cross-bridges and are factors in methicillin resistance (Berger-Bachi *et al.*, *Mol. Gen. Genet.*, 219, 263-269 (1989)). *S. aureus* also has specific receptors for laminin and fibronectin that may mediate the organism's
15 spread through the bloodstream to other tissues. Both peptidoglycan and teichoic acid are capable of activating the complement cascade via the alternative pathway. *S. aureus* also appears to activate tissue factor in the coagulation pathway.

Certain enzymes produced by *S. aureus* may play a role in virulence.
20 Catalase degrades hydrogen peroxide and may protect the organism during phagocytosis. Coagulase is present in both soluble and cell-bound forms and causes plasma to clot by formation of thrombin-like material. The high correlation between coagulase production and virulence suggests that this substance is important in the pathogenesis of staphylococcal infections, but its
25 precise role as a determinant of pathogenicity has not been determined. Many strains also produce hyaluronidase, an enzyme that degrades hyaluronic acid in the connective tissue matrix and that may promote spreading of infection. A trypsin-like protease from some strains enhances influenza virus infection by proteolytic cleavage of the viral precursor hemagglutinin into its active
30 fragments and may contribute to the morbidity of such co-infections. *S. aureus* produces numerous extracellular exotoxins that have been implicated in disease processes. The exfoliatin toxins A and B, the staphylococcal enterotoxins, and

the toxic shock syndrome toxin, TSST-1, belong to the growing family of microbial superantigens that activate T cells and monocytes/macrophages, resulting in the production of cytokines that mediate local or systemic effects depending on the amount of toxin formed, the immune status of the host, and

5 the access of the toxin to the circulation. The exfoliatin toxins mediate the dermatologic manifestations of the staphylococcal scalded-skin syndrome and bullous impetigo. These toxins cause intraepidermal cleavage of the skin at the stratum granulosum, leading to bullae formation and denudation. Seven distinct enterotoxins (A, B, C1, C2, C3, D, and E) have been implicated in food

10 poisoning due to *S. aureus*. These toxins enhance intestinal peristalsis and appear to induce vomiting by a direct effect on the central nervous system. Toxic shock syndrome (TSS) is most commonly mediated by TSST-1, which is present in 5 to 25 percent of clinical isolates of *S. aureus*. TSS is also mediated less frequently by enterotoxin B and, rarely, enterotoxin C1.

15 *S. aureus* produces other toxins whose role in virulence is incompletely understood. Four different red blood cell hemolysins, which are designated alpha, beta, gamma, and delta toxins, have been identified. Alpha toxin also causes necrosis of the skin when injected subcutaneously into animals, while delta toxin also inhibits water absorption in the intestines and may play a role in

20 the acute watery diarrhea seen in some cases of staphylococcal infection. Leukocidin lyses granulocyte and macrophage membranes by producing membrane pores permeable to cations.

The agr, xpr, sae and sar coding sequences have been identified as being involved in the regulation of staphylococcal exotoxins. See U.S. Patent

25 No. 5,587,228 and International Patent Publication Nos. WO 96/10579 and WO 97/11690. Of interest is the report in WO 97/11690 of screening for inhibitors of these regulatory systems.

Staphylococci can invade the skin or mucosa through plugged hair follicles and sebaceous glands or areas traumatized by burns, wounds,

30 abrasions, insect bites, or dermatitis. Staphylococci often colonize prosthetic devices and intravenous catheters; *S. aureus* infection of the vascular access site is a major cause of morbidity and death among patients on hemodialysis.

Colonization and invasion of the lungs may occur with endotracheal intubation, or when the lungs' clearance mechanisms are depressed, e.g., after viral infections, after aspiration, or in patients with cystic fibrosis. Mucosal damage to the gastrointestinal tract following cytotoxic chemotherapy or radiotherapy
5 predisposes to invasion from that site.

Once the skin or mucosa have been breached, local bacterial multiplication is accompanied by inflammation, neutrophil accumulation, tissue necrosis, thrombosis and fibrin deposition at the site of infection. Later, fibroblasts create a relatively avascular wall about the area. When host
10 mechanisms fail to contain the cutaneous or submucosal infection, staphylococci may enter the lymphatics and the bloodstream. Common sites of metastatic spread include the lungs, kidneys, cardiac valves, myocardium, liver, spleen, bones and brain.

Bacteremia due to *S. aureus* may arise from any local infection, at either
15 extravascular (cutaneous infections, burns, cellulitis, osteomyelitis, arthritis) or intravascular foci (intravenous catheters, dialysis access sites, intravenous drug abuse). Commonly, the disease progresses more slowly, with hectic fever and metastatic abscess formation. Rarely, patients with bacteremia die within 12 to 24 hours with high fever, tachycardia, cyanosis, and vascular collapse.
20 Disseminated intravascular coagulation may produce a disease mimicking meningococcemia.

A major complication of *S. aureus* bacteremia is endocarditis. *S. aureus* is the second most common cause of endocarditis and the most common cause among drug addicts. The disease is typically acute, with high fever, progressive
25 anemia, and frequent embolic and extracardiac septic complications. Valve ring and myocardial abscesses are common. The mortality rate is 20 to 30 percent.

Staphylococcal scalded-skin syndrome (SSSS) is a generalized exfoliative dermatitis that is a complication of infection by exfoliatin toxin-producing strains of *S. aureus*. The disease typically occurs in newborns
30 (Ritter's disease) and in children under the age of five. A scarlatiniform rash begins in the perioral area, becomes generalized over the trunk and extremities, and finally desquamates. The disease may consist of rash alone (staphylococcal

scarlet fever), or large, flaccid bullae develop that may be localized (more common in adults) or generalized. The bullae burst, resulting in red, denuded skin resembling a burn. Most adults with SSSS are immunosuppressed or have renal insufficiency. Blood cultures are frequently positive, and mortality is significant.

Toxic shock syndrome (TSS) is a multisystem disease mediated by toxins (generally TSST-1, and less frequently enterotoxins B and C1) produced by certain strains of *S. aureus*. It was first described in children, but in 1980 became epidemic among young women, with onset during menstruation. The diagnosis of TSS is based on clinical criteria that include high fever, a diffuse rash that desquamates on the palms and soles over the subsequent one or two weeks, hypotension that may be orthostatic, and evidence of involvement in three or more organ systems. Such involvement commonly includes gastrointestinal dysfunction (vomiting or diarrhea), renal or hepatic insufficiency, mucous membrane hyperemia, thrombocytopenia, myalgias with elevated creatine phosphokinase (CK) levels, and disorientation with a normal cerebrospinal fluid examination. The mortality rate of TSS is three percent.

S. aureus causes approximately three percent of community-acquired bacterial pneumonias. This disease occurs sporadically except during influenza outbreaks, when staphylococcal pneumonia is relatively more common, although still less frequent than pneumococcal pneumonia. Primary staphylococcal pneumonia in infants and children frequently presents with high fever and cough. Multiple thin-walled abscesses are seen on the chest X-ray, and empyema formation is common. In older children and healthy adults, staphylococcal pneumonia is generally preceded by an influenza-like respiratory infection. Onset of staphylococcal involvement is abrupt, with chills, high fever, progressive dyspnea, cyanosis, cough, pleural pain, and sometimes bloody sputum. Staphylococcal pneumonia is seen more frequently in patients with cystic fibrosis, in intubated patients in intensive care units and in debilitated patients who are prone to aspiration.

S. aureus is responsible for the majority of cases of acute osteomyelitis. Although the disease is most common in people under the age of 20, it is

becoming increasingly prevalent in adults over 50, particularly with involvement of the spine. A primary portal of entry is frequently not identified, although many patients give a history of preceding trauma to the involved area. Once established, infection spreads through the bone to the periosteum or along the marrow cavity. Rarely, the joint capsule is penetrated, producing pyogenic arthritis. Osteomyelitis in children may present as an acute process beginning abruptly with chills, high fever, nausea, vomiting, and progressive pain at the site of bony involvement.

S. aureus causes 1 to 9 percent of cases of bacterial meningitis and 10 to 15 percent of brain abscesses. Most commonly, the bacteria are spread from a focus outside the central nervous system, typically from infective endocarditis, by extension from a paraspinal or parameningeal abscess, or by nosocomial infection following neurosurgical procedures. Over 50 percent of epidural abscesses are due to *S. aureus*; up to half of these cases may be associated with vertebral osteomyelitis. Patients present with either acute or chronic back pain, usually with low-grade fever and malaise. The onset of radicular pain is an ominous sign that the disease may progress to neurologic dysfunction and ultimate paralysis.

Antimicrobial resistance by staphylococci favors their persistence in the hospital environment. Over 90 percent of both hospital and community strains of *S. aureus* causing infection are resistant to penicillin. This resistance is due to the production of β -lactamase enzymes; the nucleotides encoding these enzymes are usually carried by plasmids. Infections due to organisms with such acquired resistance can sometimes be treated with penicillinase-resistant β -lactam antimicrobial agents. However, the true penicillinase-resistant *S. aureus* organisms, called methicillin-resistant *S. aureus* (MRSA), are resistant to all the β -lactam antimicrobial agents as well as the cephalosporins. MRSA resistance is chromosomally mediated and involves production of an altered penicillin-binding protein (PBP 2a or PBP 2') with a low binding affinity for β -lactams. MRSA frequently also have acquired plasmids mediating resistance to erythromycin, tetracycline, chloramphenicol, clindamycin, and aminoglycosides. MRSA have become increasingly common worldwide,

particularly in tertiary-care referral hospitals. In the United States, approximately 5 percent of hospital isolates of *S. aureus* are methicillin-resistant.

Thus, there continues to exist a need for new agents useful for treating
5 bacterial infections, particularly those caused by antibiotic-resistant bacteria, and for methods of identifying such new agents. Such methods ideally would identify agents that are unrelated to existing antimicrobials and that target different aspects of staphylococcal invasion of and replication in the host, compared to existing antimicrobials.

10

SUMMARY OF THE INVENTION

The present invention provides a method for identifying an agent that binds a polypeptide. The method includes contacting a polypeptide and an agent to form a mixture, and determining whether the agent binds the
15 polypeptide. In some aspects, the polypeptide may be encoded by a coding sequence having a nucleotide sequence of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, or 141. In another aspect of the invention, the polypeptide is encoded by an essential coding sequence having a nucleotide sequence with at least about 57 percent structural similarity to a
20 nucleotide sequence of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, or 137. In another aspect, the polypeptide is encoded by a critical coding sequence having a nucleotide sequence with at least about 57 percent structural similarity to the nucleotide sequence SEQ ID NO:141.

Determining whether the agent binds the polypeptide may be
25 accomplished by conducting an enzyme assay, a binding assay, or a ligand binding assay. The method may further include determining whether the agent decreases the growth rate of a microbe. This includes contacting a microbe with the agent, incubating the microbe and the agent under conditions suitable for growth of the microbe that is not contacted with the agent, and determining
30 the growth rate of the microbe contacted with the agent. A decrease in growth rate compared to the microbe that is not contacted with the agent indicates the agent decreases the growth rate of the microbe. The microbe may be *in vitro* or

in vivo, and the microbe may be a *Staphylococcus aureus*. The present invention also provides an agent identified by the method.

The present invention also provides a method for identifying an agent that decreases the growth rate of a microbe. The method includes contacting a
5 microbe with an agent, incubating the microbe and the agent under conditions suitable for growth of the microbe that is not contacted with the agent, and determining the growth rate of the microbe contacted with the agent. A decrease in growth rate compared to the microbe that is not contacted with the agent indicates the agent decreases the growth rate of the microbe. In some
10 aspects, the polypeptide may be encoded by a coding sequence having a nucleotide sequence of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, or 141. In another aspect of the invention, the polypeptide is encoded by an essential coding sequence having a nucleotide sequence with at least about 57 percent structural similarity to a nucleotide
15 sequence of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, or 137. In another aspect, the polypeptide is encoded by a critical coding sequence having a nucleotide sequence with at least about 57 percent structural similarity to the nucleotide sequence SEQ ID NO:141. The microbe may be *in vitro* or *in vivo*, and the microbe may be a *Staphylococcus aureus*.
20 The present invention also provides an agent identified by the method.

Also provided by the present invention is a method for decreasing the growth rate of a microbe. The method includes contacting a microbe with an agent that binds to a polypeptide. In some aspects, the polypeptide may be encoded by a coding sequence having a nucleotide sequence of SEQ ID NO:7,
25 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, or 141. In another aspect of the invention, the polypeptide is encoded by an essential coding sequence having a nucleotide sequence with at least about 57 percent structural similarity to a nucleotide sequence of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, or 137. In another aspect, the
30 polypeptide is encoded by a critical coding sequence having a nucleotide sequence with at least about 57 percent structural similarity to the nucleotide

sequence SEQ ID NO:141. The microbe may be *in vitro* or *in vivo*, and the microbe may be a *Staphylococcus aureus*.

The present invention provides a method for making an *S. aureus* with reduced virulence. The method includes altering a coding sequence in an *S.*
5 *aureus* to include a mutation, and determining if the *S. aureus* having the mutation has reduced virulence compared to an *S. aureus* that does not have the mutation. The coding sequence that is altered to include a mutation may include a nucleotide sequence of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, or 141. In another aspect of the invention,
10 the coding sequence that is altered to include a mutation is an essential coding sequence that may include a nucleotide sequence having at least about 57 percent structural similarity to a nucleotide sequence of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, or 137. In yet another aspect, the coding sequence that is altered to include a mutation is a critical
15 coding sequence that may include a nucleotide sequence having at least about 57 percent structural similarity to a nucleotide sequence of SEQ ID NO:141. The invention also provides the *S. aureus* having reduced virulence, and a vaccine composition that includes the *S. aureus* having reduced virulence.

The present invention further provides isolated polynucleotides. A
20 polynucleotide may include a nucleotide sequence of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, or 141. In another aspect, a polynucleotide may include a nucleotide sequence having at least about 57 percent structural similarity with a nucleotide sequence of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 109, 113, 117, 121, 125, 129, 133, or 137, wherein
25 the isolated polynucleotide includes an essential coding sequence. In yet another aspect, a polynucleotide may include a nucleotide sequence having at least about 57 percent structural similarity with a nucleotide sequence of SEQ ID NO:141, wherein the isolated polynucleotide includes a critical coding sequence. A polynucleotide may also consist essentially of the above described
30 nucleotide sequences, and the polynucleotide may optionally further include from zero to up to about 5,000 nucleotides upstream and/or downstream of the nucleotide sequence.

Also provided by the present invention are isolated polypeptides that include an amino acid sequence of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 110, 114, 118, 122, 126, 130, 134, 138, or 142.

5 Definitions

As used herein, the term "agent" refers to chemical compounds, including, for instance, an organic compound, an inorganic compound, a metal, a polypeptide, a non-ribosomal polypeptide, a polyketide, or a peptidomimetic compound that binds to a particular polypeptide.

10 As used herein, the term "polypeptide" refers to a polymer of amino acids and does not refer to a specific length of a polymer of amino acids. Thus, for example, the terms peptide, oligopeptide, protein, and enzyme are included within the definition of polypeptide. This term also includes post-expression modifications of the polypeptide, for example, glycosylations, acetylations,
15 phosphorylations and the like.

The term "binds to a polypeptide" refers to a condition of proximity between an agent and a polypeptide. The association may be non-covalent, wherein the juxtaposition is energetically favored by hydrogen bonding, van der Waals forces, or electrostatic interactions, or it may be covalent.

20 As used herein, growth of a microbe "*in vitro*" refers to growth, for instance, in a test tube or on an agar plate. Growth of a microbe "*in vivo*" refers to growth, for instance, in a cultured cell or in an animal.

As used herein, the term "microbe" and "bacteria" are used interchangeably and include single celled prokaryotic and lower eukaryotic
25 (e.g., fungi) organisms, preferably prokaryotic organisms.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1a-z. The nucleotide sequence of the coding sequences of 26 *S. aureus* coding sequences (SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23,
30 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, and 141), the predicted sequence of the peptide (SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 110, 114, 118, 122, 126, 130, 134, 138, or 142,

respectively) encoded by each coding sequence, and primer pairs used for preparing fragments for insertion into a temperature sensitive plasmid (SEQ ID NO: 35-68, 111-112, 115-116, 119-120, 123-124, 127-128, 131-132, 135-136, 139-140, and 143-144). The two underlined sequences in each coding
 5 sequence correspond to the primers listed below the coding sequence.

Figure 2a-i. The nucleotide sequence of each of 9 *S. aureus* coding sequences to be cloned for expression in *E. coli* (SEQ ID NO:69, 71, 73, 75, 77, 79, 81, 83, and 85), the predicted sequence of the peptide (SEQ ID NO:70, 72, 74, 76, 78, 80, 82, 84, and 86, respectively) encoded by each coding sequence after insertion into the appropriate expression plasmid, and the sequence of the primer pair (SEQ ID NO:91-108) used to clone the *S. aureus* coding sequences by amplification. The top primer and bottom primer of each primer pair is the forward primer and the reverse primer, respectively. The underlined ATGG in
 10 SEQ ID NO:69, 73, 75, 77, and 79 shows the location of a portion of the *NcoI* restriction site added to the coding sequence by the forward primer for cloning into the expression vector pQE-60. The underlined AGATCT in SEQ ID NOS:69, 71, 73, 75, 79, 81, 83, and 85 shows the location of the *BglII* restriction site added to the coding sequence by the reverse primer. The
 15 underlined GGATCT in SEQ ID NO:77 shows the location of the ligation of the digested *BamHI* restriction site of the amplified fragment with the digested *BglII* restriction site of the vector.

Figure 3. Nucleotide sequence (SEQ ID NO:87) and the predicted
 25 amino acid sequence (SEQ ID NO:88) of the *S. aureus* uridylate kinase.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

The sequence of the *S. aureus* genome has been determined and
 30 includes about 3,500 coding sequences (see, for instance, Kunsch et al., EP 0 786 519 A2). As used herein, the terms "coding sequence," "coding region," and "open reading frame" are used interchangeably herein and refer to a

nucleotide sequence that encodes a polypeptide and, when placed under the control of appropriate regulatory sequences, expresses the encoded polypeptide. The boundaries of a coding region are generally determined by a translation start codon at its 5' end and a translation stop codon at its 3' end. A regulatory
5 sequence is a nucleotide sequence that regulates expression of a coding region to which it is operably linked. Nonlimiting examples of regulatory sequences include promoters, transcription initiation sites, translation start sites, translation stop sites, and terminators. "Operably linked" refers to a juxtaposition wherein the components so described are in a relationship
10 permitting them to function in their intended manner. A regulatory sequence is "operably linked" to a coding region when it is joined in such a way that expression of the coding region is achieved under conditions compatible with the regulatory sequence.

At this time, it is not possible to predict the function of some of the
15 polypeptides that the approximately 3,500 coding sequences of the *S. aureus* genome are predicted to encode. This subset of coding sequences are referred to herein as "unknown coding sequences." Among the large number of unknown coding sequences in the *S. aureus* genome, those that are required for cell growth are potential novel targets for antimicrobial therapy. The function
20 of other coding sequences of the *S. aureus* genome can be hypothesized by comparing an *S. aureus* coding sequence with a second coding sequence from another organism, where the second coding sequence has a known function. This subset of coding sequences are referred to herein as "known coding sequences." However, even though the function of these coding sequences can
25 be hypothesized, for many it is unknown if they are required for bacterial growth. Those known coding sequences that are required for bacterial growth are potential novel targets for antimicrobial therapy.

As used herein, a "critical coding sequence" encodes a polypeptide that is required for a bacterial cell, preferably *S. epidermidis*, *S. saprophyticus*, or *S.*
30 *aureus*, more preferably, an *S. aureus* cell, to grow at a normal growth rate *in vitro* or *in vivo*, preferably *in vitro*. Such polypeptides are referred to herein as "critical polypeptides." A coding sequence is a critical coding sequence when

mutagenesis of the coding sequence in a bacterial cell decreases the growth rate of the bacterial cell to, in increasing levels of preference, less than about 50%, less than about 60%, less than about 80%, most preferably, less than about 90% of the growth rate of the bacterial cell that does not contain the mutated coding
5 sequence. Methods of measuring the growth rate of microbes are well known and routine in the art. A critical coding sequence may encode a polypeptide having an unknown function, or in some aspects of the invention, encode a polypeptide having a known function. Preferably, a critical coding sequence encodes a polypeptide having an unknown function.

10 Preferably, a critical coding sequence is an essential coding sequence. An "essential coding sequence," as used herein, is a coding sequence that encodes a polypeptide that is essential for the bacterial cell, preferably *S. epidermidis*, *S. saprophyticus*, or *S. aureus*, more preferably, an *S. aureus* cell, to grow *in vitro* or *in vivo*, preferably *in vitro*. Such polypeptides are referred
15 to herein as "essential polypeptides." An essential coding sequence may encode a polypeptide having an unknown function, or in some aspects of the invention, encode a polypeptide having a known function. Preferably, an essential coding sequence encodes a polypeptide having an unknown function.

Identification of these critical coding sequences, preferably essential
20 coding sequences, provides a means for discovering new agents with different targets and mechanisms of action compared to existing agents that are used to inhibit bacteria, preferably *S. epidermidis*, *S. saprophyticus*, or *S. aureus*, more preferably *S. aureus*. The identification of essential coding sequences of microbes, preferably *S. epidermidis*, *S. saprophyticus*, or *S. aureus*, more
25 preferably *S. aureus*, that are useful in the present invention can begin by identifying coding sequences encoding a polypeptide, preferably, a polypeptide having no known function. The coding sequences can be identified in databases, including, for instance, the *S. aureus* databases available from the University of Oklahoma, TIGR, NCBI, Sanger, the HGS contig database, and
30 the HGS GSTS database. The identification of such coding sequences can include constructing contigs from data present in such databases.

As described herein, unknown coding sequences were typically identified by analyzing publicly known polynucleotide sequences. The data obtained from the database contained the nucleotide sequence of genomic clones and predicted open reading frames. However, even though the putative
5 coding sequences may have been known, there was no indication that the coding sequences were in fact expressed, or in fact critical coding sequences. For instance, there is limited data known to the art regarding regulatory regions required for the transcription of a nucleotide sequence in *S. aureus*. Moreover, there is generally no evidence that the critical coding sequences and essential
10 coding sequences identified herein are actually expressed. Thus, a person of ordinary skill, having the polynucleotide sequence of a genomic clone, would not be able to predict that an open reading frame would be transcribed, or that a coding sequence was critical, preferably, essential.

Typically, whether a coding sequence is a critical coding sequence,
15 preferably, an essential coding sequence, can be determined by inactivating the coding sequence in a bacterial cell and determining the growth rate of the bacterial cell. Growth can be measured *in vitro* or *in vivo*, preferably *in vitro*. Inactivating a coding sequence is done by mutating a coding sequence present in a bacterial cell. Mutations include, for instance, a deletion mutation (i.e., the
20 deletion of nucleotides from the coding sequence), an insertion mutation (i.e., the insertion of additional nucleotides into the coding sequence), a nonsense mutation (i.e., changing a nucleotide of a codon so the codon encodes a different amino acid), and a missense mutation (i.e., changing a nucleotide of a codon so the codon functions as a stop codon). Some insertion mutations and
25 some deletion mutations result in frame-shift mutations. Preferably, a coding sequence in a bacterial cell is engineered to contain a deletion.

In general, an internal fragment of a selected coding sequence can be isolated or synthesized by methods known in the art, including, for instance, the polymerase chain reaction (PCR). Typically, the internal fragment is about 150
30 base pairs to about 350 base pairs in length, preferably about 300 base pairs. The internal fragment preferably corresponds to the 5' end of the coding sequence. Preferably, the primers used to amplify the internal fragment contain

a restriction site to allow ligation of the amplified internal fragment into a vector. For instance, when the vector is pSPT246 (described hereinbelow), one primer may contain a PstI site and the other primer may contain a SacI site.

The internal fragment is typically ligated into a vector that can be used
5 to inactivate the coding sequence in the bacterial cell and determine if the coding sequence is a critical coding sequence or an essential coding sequence. Useful vectors include those that are unable to replicate under certain conditions in the bacterial cell that contains the coding sequence to be inactivated. Preferably, a vector is a temperature sensitive vector, i.e., it is
10 unable to replicate in *S. aureus* at higher temperatures of, for instance, at least about 42°C, or a vector is a suicide vector, i.e., it is unable to replicate in *S. aureus*. Preferably, a temperature sensitive vector is a shuttle vector, i.e., it is able to replicate in *E. coli* and *S. aureus* under the appropriate conditions. Examples of temperature sensitive plasmids that can be used to inactivate a
15 coding sequence in *S. aureus* include pSPT181 (Janzon and Arvidson, *EMBO J.*, 9, 1391-1399 (1990)), and pSPT246 (described hereinbelow). An example of a suicide plasmid that can be used to inactivate a coding sequence in *S. aureus* includes pKT4 (Tegmark et al., *Mol. Microbiol.*, 37, 398-409 (2000)).

Using these methods, the following essential coding sequences have
20 been identified: SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, and 137. The polypeptides encoded by the coding sequences are SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 110, 114, 118, 122, 126, 130, 134, and 138, respectively. Of these essential coding sequences, one coding sequence (SEQ
25 ID NO:33) encodes uridylate kinase, and is thus a known coding sequence. Prior to this invention the uridylate kinase coding sequence was not known to be essential for the growth of *S. aureus*. Using these methods, a critical coding sequence having the DNA sequence set forth at SEQ ID NO:141 has been identified. The polypeptide encoded by the critical coding sequence is SEQ ID
30 NO:142.

The coding sequences of the present invention include coding sequences that are similar to the coding sequences present in SEQ ID NO:1, 3,

5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, 141, or the complement thereof. The similarity is referred to as structural similarity and is determined by aligning the residues of the two polynucleotides (i.e., the nucleotide sequence of the candidate coding sequence and the nucleotide sequence of the coding region of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, 141, or the complement thereof) to optimize the number of identical nucleotides along the lengths of their sequences; gaps in either or both sequences are permitted in making the alignment in order to optimize the number of shared nucleotides, although the nucleotides in each sequence must nonetheless remain in their proper order. A candidate coding region is the coding region being compared to a coding region present in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, or 141, or the complement thereof. A candidate nucleotide sequence can be isolated from a microbe, preferably *S. aureus*, or can be produced using recombinant techniques, or chemically or enzymatically synthesized. Preferably, two nucleotide sequences are compared using the Blastn program of the BLAST 2 search algorithm, as described by Tatusova, et al. (*FEMS Microbiol Lett* 1999, 174:247-250), and available at www.ncbi.nlm.nih.gov/gorf/bl2.html. Preferably, the default values for all BLAST 2 search parameters are used, including reward for match = 1, penalty for mismatch = -2, open gap penalty = 5, extension gap penalty = 2, gap x_dropoff = 50, expect = 10, wordsize = 11, and filter on. In the comparison of two nucleotide sequences using the BLAST search algorithm, structural similarity is referred to as "identities." Preferably, a polynucleotide includes a nucleotide sequence having a structural similarity with the coding region of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, 141, or the complement thereof, of, in increasing order of preference, at least about 57 %, at least about 60 %, at least about 70 %, at least about 80 %, at least about 90 %, most preferably at least about 95 % identity.

The present invention includes isolated polynucleotides that include a nucleotide sequence SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, 141, or the complement thereof. As used herein, an "isolated" polypeptide or polynucleotide means a

5 polypeptide or polynucleotide that has been either removed from its natural environment, produced using recombinant techniques, or chemically or enzymatically synthesized. Preferably, a polypeptide or polynucleotide of this invention is purified, i.e., essentially free from any other polypeptides or polynucleotides and associated cellular products or other impurities. An

10 isolated polynucleotide of the invention may include a nucleotide sequence having, in increasing order of preference, at least about 57 %, at least about 60 %, at least about 70 %, at least about 80 %, at least about 90 %, most preferably at least about 95 % structural similarity with a nucleotide sequence SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117,

15 121, 125, 129, 133, 137, 141, or the complement thereof, where the isolated polynucleotide includes a critical coding sequence, preferably, an essential coding sequence. The present invention also includes the polypeptides encoded by the coding sequences.

Another aspect of the invention includes isolated polynucleotides

20 consisting essentially of a nucleotide sequence SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, or 141, or the complement thereof. The polynucleotide optionally further includes from zero to up to about 5,000 nucleotides upstream and/or downstream of the nucleotide sequence SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27,

25 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, 141, or the complement thereof. An isolated polynucleotide of the invention may consist essentially of a nucleotide sequence having, in increasing order of preference, at least about 57 %, at least about 60 %, at least about 70 %, at least about 80 %, at least about 90 %, most preferably at least about 95 % structural similarity with a

30 nucleotide sequence SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, 141, or the complement thereof, where the isolated polynucleotide includes an essential coding

sequence. The polynucleotide optionally further includes from zero to up to about 5,000 nucleotides upstream and/or downstream of the nucleotide sequence SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, 141, or the complement thereof. The present invention also includes the polypeptides encoded by the coding sequences.

Insertional inactivation of critical coding sequences, preferably, essential coding sequences, allows different classes of coding sequences to be identified. Examples of different classes include, for instance, coding sequences encoding proteins involved in cell surface metabolism, enzymes involved in cellular biosynthetic pathways including cell wall biosynthesis and assembly, components of the TCA cycle, proteins similar to oligopeptide transport proteins of the ATP-binding cassette (ABC) transporter superfamily, and involved in cellular regulatory and repair processes, and coding sequences affecting morphogenesis and cell division, secretion and sorting of proteins, and signal transduction systems.

The critical coding sequences, preferably, essential coding sequences may be cloned by PCR, using microbial, preferably *S. epidermidis*, *S. saprophyticus*, or *S. aureus*, more preferably *S. aureus*, genomic DNA as the template. For ease of inserting the open reading frame into expression vectors, PCR primers may be chosen so that the PCR-amplified coding sequence has a restriction enzyme site at the 5' end preceding the initiation codon ATG, and a restriction enzyme site at the 3' end after the termination codon TAG, TGA or TAA. If desirable, the codons in the coding sequence may be changed, without changing the amino acids, to optimize expression of a polypeptide encoded by an essential coding sequence. For instance, if an essential coding sequence is to be expressed in *E. coli*, the codons of the coding sequence can be changed to comply with the *E. coli* codon preference (see, for instance, Grosjean and Fiers, *Gene*, 18, 199-209 (1982), and Konigsberg et al., *Proc. Natl. Acad. Sci., USA*, 80, 687-691 (1983)). Optimization of codon usage may lead to an increase in the expression of the encoded polypeptide when produced in a microbe other than the microbe from which the essential coding sequence was isolated. If the

polypeptide is to be produced extracellularly, either in the periplasm of, for instance, *E. coli* or other bacteria, or into the cell culture medium, the coding sequence may be cloned without its initiation codon and placed into an expression vector behind a signal sequence.

5 Proteins may be produced in prokaryotic or eukaryotic expression systems using known promoters, vectors, and hosts. Such expression systems, promoters, vectors, and hosts are known to the art. A suitable host cell may be used for expression of the polypeptide, such as *E. coli*, other bacteria, including *Bacillus* and *S. aureus*, yeast, including *Pichia pastoris* and *Saccharomyces*
10 *cerevisiae*, insect cells, or mammalian cells, including CHO cells, using suitable vectors known in the art. Proteins may be produced directly or fused to a polypeptide, and either intracellularly or extracellularly by secretion into the periplasmic space of a bacterial cell or into the cell culture medium. Secretion of a protein typically requires a signal peptide (also known as pre-
15 sequence); a number of signal sequences from prokaryotes and eukaryotes are known to function for the secretion of recombinant proteins. During the protein secretion process, the signal peptide is removed by signal peptidase to yield the mature protein.

 The polypeptide encoded by a critical coding sequence, preferably, an
20 essential coding sequence, may be isolated. To simplify the isolation process, a purification tag may be added either at the 5' or 3' end of the coding sequence. Commonly used purification tags include a stretch of six histidine residues (U.S. Patent Nos. 5,284,933 and 5,310,663), a streptavidin-affinity tag described by Schmidt and Skerra, *Protein Engineering*, 6, 109-122 (1993), a
25 FLAG peptide (Hopp *et al*, *Biotechnology*, 6, 1205-1210 (1988)), glutathione S-transferase (Smith and Johnson, *Gene*, 67, 31-40 (1988)), and thioredoxin (LaVallie *et al.*, *Bio/Technology*, 11, 187-193 (1993)). To remove these tags, a proteolytic cleavage recognition site may be inserted at the fusion junction. Commonly used proteases are factor Xa, thrombin, and enterokinase.
30 Preferably, a polypeptide encoded by an essential coding sequence is isolated, more preferably, purified.

The identification of critical coding sequences, preferably, essential coding sequences, renders them useful in methods of identifying new agents according to the present invention. Such methods include assaying potential agents for the ability to interfere with expression of a critical coding sequence, preferably, an essential coding sequence, thereby preventing the expression and decreasing the concentration of a polypeptide encoded by the coding sequence. Without intending to be limiting, it is anticipated that agents can act by, for instance, interacting with a critical coding sequence, preferably, an essential coding sequence, interacting with a nucleotide sequence that is adjacent to a critical coding sequence, preferably, an essential coding sequence (e.g., a promoter sequence), or inhibiting expression of a polypeptide involved in regulating expression of a critical coding sequence, preferably, an essential coding region. Agents that can be used to inhibit the expression of a critical coding sequence, preferably, an essential coding region include, for instance, the use of anti-sense polynucleotides that are complementary to the mRNA molecules transcribed from the coding sequence, and double stranded RNA (Fire et al., *Nature*, 391, 806-11 (1998)).

Such methods also include assaying potential agents for the ability to bind to a polypeptide encoded in whole or in part by a DNA sequence set forth in any one of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, 141 or the complementary strand thereof. Optionally, agents that bind to such a polypeptide can be further evaluated to determine if they inhibit the function of the polypeptide to which they bind.

A polypeptide produced by a critical coding sequence, preferably, an essential coding sequence, may be used in assays including, for instance, high throughput assays, to screen for agents that inhibit the function of the polypeptide. The sources for potential agents to be screened include, for instance, chemical compound libraries, fermentation media of *Streptomyces*, other bacteria and fungi, and cell extracts of plants and other vegetations. For proteins with known enzymatic activity, assays may be established based on the activity, and a large number of potential agents can be screened for ability to

inhibit the activity. Such assays are referred to herein as "enzyme assays."
Enzyme assays vary depending on the enzyme, and typically are known to the art.

For proteins that interact with another protein or nucleic acid, assays
5 can be established to measure such interaction directly, and the potential agents screened for the ability to inhibit the binding interaction (referred to herein as "binding assays"). In another aspect of the invention, assays can be established allowing the identification of agents that bind to a polypeptide encoded by an essential coding sequence (referred to herein as "ligand binding assays").

10 For proteins that interact with another protein or nucleic acid, such binding interactions may be evaluated indirectly using the yeast two-hybrid system described in Fields and Song (*Nature*, 340, 245-246 (1989)), and Fields and Sternglanz (*Trends in Genetics*, 10, 286-292 (1994)). The two-hybrid system is a genetic assay for detecting interactions between two polypeptides.
15 It can be used to identify proteins that bind to a known protein of interest, or to delineate domains or residues critical for an interaction. Variations on this methodology have been developed to clone coding sequences that encode DNA-binding proteins, to identify polypeptides that bind to a protein, and to screen for drugs. The two-hybrid system exploits the ability of a pair of
20 interacting proteins to bring a transcription activation domain into close proximity with a DNA-binding domain that binds to an upstream activation sequence (UAS) of a reporter coding sequence, and is generally performed in yeast. The assay requires the construction of two hybrid coding sequences encoding (1) a DNA-binding domain that is fused to a protein X, and (2) an
25 activation domain fused to a protein Y. The DNA-binding domain targets the first hybrid protein to the UAS of the reporter coding sequence; however, because most proteins lack an activation domain, this DNA-binding hybrid protein does not activate transcription of the reporter coding sequence. The second hybrid protein, which contains the activation domain, cannot by itself
30 activate expression of the reporter because it does not bind the UAS. However, when both hybrid proteins are present, the noncovalent interaction of protein X and protein Y tethers the activation domain to the UAS, activating transcription

of the reporter coding sequence. When the polypeptide encoded by, for instance, an essential coding sequence (protein X, for example) is already known to interact with another protein or nucleic acid (protein Y, for example), this binding assay can be used to detect agents that interfere with the interaction of X and Y. Expression of the reporter coding sequence is monitored as different test agents are added to the system; the presence of an inhibitory agent inhibits binding and results in lack of a reporter signal.

When the function of a polypeptide encoded by, for instance, an essential coding sequence is unknown and no ligands are known to bind the polypeptide, the yeast two-hybrid assay can also be used to identify proteins that bind to the polypeptide. In an assay to identify proteins that bind to protein X (the target protein), a large number of hybrid coding sequences, each containing a different protein Y, are produced and screened in the assay. Typically, Y is encoded by a pool of plasmids in which total cDNA or genomic DNA is ligated to the activation domain. This system is applicable to a wide variety of proteins, and it is not even necessary to know the identity or function of protein Y. The system is highly sensitive and can detect interactions not revealed by other methods; even transient interactions may trigger transcription to produce a stable mRNA that can be repeatedly translated to yield the reporter protein. When a protein is identified that binds to an essential polypeptide, the two-hybrid system can be used in a binding assay to identify agents that inhibit binding and result in lack of a reporter signal.

Ligand binding assays known to the art may be used to search for agents that bind to the target protein. Without intending to be limiting, one such screening method to identify direct binding of test ligands to a target protein is described in Bowie et al. (U.S. Patent No. 5,585,277). This method relies on the principle that proteins generally exist as a mixture of folded and unfolded states, and continually alternate between the two states. When a test ligand binds to the folded form of a target protein (i.e., when the test ligand is a ligand of the target protein), the target protein molecule bound by the ligand remains in its folded state. Thus, the folded target protein is present to a greater extent in the presence of a test ligand which binds the target protein, than in the

absence of a ligand. Binding of the ligand to the target protein can be determined by any method which distinguishes between the folded and unfolded state of the target protein. The function of the target protein need not be known in order for this assay to be performed.

5 Another method for identifying ligands for a target protein is described in Wieboldt *et al.*, *Anal. Chem.*, 69, 1683-1691 (1997). This technique screens combinatorial libraries of 20-30 agents at a time in solution phase for binding to the target protein. Agents that bind to the target protein are separated from other library components by centrifugal ultrafiltration. The specifically selected
10 molecules that are retained on the filter are subsequently liberated from the target protein and analyzed by HPLC and pneumatically assisted electrospray (ion spray) ionization mass spectroscopy. This procedure selects library components with the greatest affinity for the target protein, and is particularly useful for small molecule libraries.

15 Another method allows the identification of ligands present in a sample using capillary electrophoresis (Hughes *et al.*, U.S. Patent 5,783,397). The sample and the target protein are combined and resolved. The conditions of electrophoresis results in simultaneously fractionating the components present in the sample and screening for components that bind to the target molecule.
20 This method is particularly useful for complex samples including, for instance, extracts of plants, animals, microbes, or portions thereof and chemical libraries produced by, for instance, combinatorial chemistry.

 The agents identified by the initial screens are evaluated for their effect on survival of microbes, preferably *S. epidermidis*, *S. saprophyticus*, or *S.*
25 *aureus*, more preferably *S. aureus*. Agents that interfere with bacterial survival are expected to be capable of preventing the establishment of an infection or reversing the outcome of an infection once it is established. Agents may be bacteriocidal (i.e., an agent kills the microbe and prevents the replication of the microbe) or bacteriostatic (i.e., an agent reversibly prevents replication of the
30 microbe). Preferably, the agent is bacteriocidal. Such agents will be useful to treat a subject infected with *S. epidermidis*, *S. saprophyticus*, or *S. aureus*,

preferably *S. aureus*, or at risk of being infected by *S. epidermidis*, *S. saprophyticus*, or *S. aureus*, preferably *S. aureus*.

The identification of *S. aureus* critical coding sequences, preferably, essential coding sequences, also provides for microorganisms exhibiting
5 reduced virulence, which are useful in vaccines. The term "vaccine" refers to a composition that, upon administration to a subject, will provide protection against *S. epidermidis*, *S. saprophyticus*, or *S. aureus*, preferably, *S. aureus*. Administration of a vaccine to a subject will produce an immunological response to the *S. aureus* and result in immunity. A vaccine is administered in
10 an amount effective to result in some therapeutic benefit or effect so as to result in an immune response that inhibits or prevents an infection by *S. aureus* in a subject, or so as to result in the production of antibodies to an *S. aureus*.

Such microorganisms that can be used in a vaccine include *S. epidermidis*, *S. saprophyticus*, or *S. aureus*, preferably *S. aureus*, mutants
15 containing a mutation in a coding sequence represented by any one of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, 141, or a coding sequence having structural similarity thereto. Optionally, an *S. epidermidis*, *S. saprophyticus*, or *S. aureus*, preferably an *S. aureus*, includes more than one mutation. The reduced
20 virulence of these organisms and their immunogenicity may be confirmed by administration to a subject. Animal models useful for evaluating *S. aureus* virulence in a variety of conditions, including for example, pneumonia, peritonitis, endophthalmitis, endocarditis, septicemia, and arthritis, are known to the art.

25 While it is possible for an avirulent microorganism of the invention to be administered alone, one or more of such mutant microorganisms are preferably administered in a vaccine composition containing a suitable adjuvant(s) and a pharmaceutically acceptable diluent(s) or carrier(s). The carrier(s) must be "acceptable" in the sense of being compatible with the
30 avirulent microorganism of the invention and not deleterious to the subject to be immunized. Typically, the carriers will be water or saline which will be

sterile and pyrogen free. The subject to be immunized is a subject needing protection from a disease caused by a virulent form of *S. aureus*.

Any adjuvant known in the art may be used in the vaccine composition, including oil-based adjuvants such as Freund's Complete Adjuvant and

5 Freund's Incomplete Adjuvant, mycolate-based adjuvants (*e.g.*, trehalose dimycolate), bacteria lipopolysaccharide (LPS), peptidoglycans (*i.e.*, mumsins, mucopeptides, or glycoproteins such as N-Opaca, muramyl dipeptide (MDP), or MDP analogs), proteoglycans (*e.g.*, extracted from *Klebsiella* spp.), streptococcal preparations (*e.g.*, OK432), the "Iscoms" of EP 109 942, EP 180

10 564 and EP 231 039, aluminum hydroxide, saponin, DEAE-dextran, neutral oils (such as miglyol), vegetable oils (such as arachis oil), liposomes, the Ribi adjuvant system (see, for example GB-A-2 189 141), or adjuvants available under the trade designation BIOSTIM (*e.g.*, 01K2) and PLURONIC polyols. Recently, an alternative adjuvant consisting of extracts of *Amycolata*, a

15 bacterial genus in the order Actinomycetales, has been described in U.S. Patent No. 4,877,612. Additionally, proprietary adjuvant mixtures are commercially available. The adjuvant used will depend, in part, on the recipient organism. The amount of adjuvant to administer will depend on the type and size of animal. Optimal dosages may be readily determined by routine methods.

20 The vaccine compositions optionally may include pharmaceutically acceptable (*i.e.*, sterile and non-toxic) liquid, semisolid, or solid diluents that serve as pharmaceutical vehicles, excipients, or media. Any diluent known in the art may be used. Exemplary diluents include, but are not limited to, polyoxyethylene sorbitan monolaurate, magnesium stearate, methyl-and

25 propylhydroxybenzoate, talc, alginates, starches, lactose, sucrose, dextrose, sorbitol, mannitol, gum acacia, calcium phosphate, mineral oil, cocoa butter, and oil of theobroma.

The vaccine compositions can be packaged in forms convenient for delivery. The compositions can be enclosed within a capsule, sachet, cachet,

30 gelatin, paper or other container. These delivery forms are preferred when compatible with entry of the immunogenic composition into the recipient organism and, particularly, when the immunogenic composition is being

delivered in unit dose form. The dosage units can be packaged, e.g., in tablets, capsules, suppositories or cachets.

The vaccine compositions may be introduced into the subject to be immunized by any conventional method including, e.g., by intravenous, intradermal, intramuscular, intramammary, intraperitoneal, or subcutaneous injection; by oral, sublingual, nasal, anal, vaginal, or transdermal delivery; or by surgical implantation, e.g., embedded under the splenic capsule or in the cornea. The treatment may consist of a single dose or a plurality of doses over a period of time.

It will be appreciated that the vaccine of the invention may be useful in the fields of human medicine and veterinary medicine. Thus, the subject to be immunized may be a human or an animal, for example, cows, sheep, pigs, horses, dogs, cats, and poultry such as chickens, turkeys, ducks and geese.

The present invention is illustrated by the following examples. It is to be understood that the particular examples, materials, amounts, and procedures are to be interpreted broadly in accordance with the scope and spirit of the invention as set forth herein.

Example 1

Identification of critical and essential *S. aureus* coding sequences

Identification of unknown coding sequences

There are about 3500 open reading frames in the HGS database of *S. aureus* nucleotide sequences. A Fast A homology search was conducted on these open reading frames. This homology search of those open reading frames indicated that 662 of the open reading frames were unknown coding sequences. The methods described herein typically require an open reading frame of about 300 base pairs; 492 of the 662 open reading frames were at least 300 base pairs. Of these 492, 60 had homology with unknown open reading frames from other bacterial species, 270 had no homology with any open reading frames, and 160 had homology with eukaryotic coding sequences. A homology search was also

conducted between the predicted coding sequences of the *Mycoplasma genitalium* genome and the coding sequences of *S. aureus*.

The nucleotide sequences of the unknown coding sequences are shown in Table 1. Whether these coding sequences were critical or essential was

5 determined as described herein.

Table 1. Primers used to amplify unknown coding sequences from *S. aureus*

	Nucleotide sequence of unknown coding sequence	Primer pair used to amplify coding sequence	Predicted polypeptide
5	SEQ ID NO:1	SEQ ID NOs:35-36	SEQ ID NO:2
	SEQ ID NO:3	SEQ ID NOs:37-38	SEQ ID NO:4
	SEQ ID NO:5	SEQ ID NOs:39-40	SEQ ID NO:6
	SEQ ID NO:7	SEQ ID NOs:41-42	SEQ ID NO:8
	SEQ ID NO:9	SEQ ID NOs:43-44	SEQ ID NO:10
10	SEQ ID NO:11	SEQ ID NOs:45-46	SEQ ID NO:12
	SEQ ID NO:13	SEQ ID NOs:47-48	SEQ ID NO:14
	SEQ ID NO:15	SEQ ID NOs:49-50	SEQ ID NO:16
	SEQ ID NO:17	SEQ ID NOs:51-52	SEQ ID NO:18
	SEQ ID NO:19	SEQ ID NOs:53-54	SEQ ID NO:20
15	SEQ ID NO:21	SEQ ID NOs:55-56	SEQ ID NO:22
	SEQ ID NO:23	SEQ ID NOs:57-58	SEQ ID NO:24
	SEQ ID NO:25	SEQ ID NOs:59-60	SEQ ID NO:26
	SEQ ID NO:27	SEQ ID NOs:61-62	SEQ ID NO:28
	SEQ ID NO:29	SEQ ID NOs:63-64	SEQ ID NO:30
20	SEQ ID NO:31	SEQ ID NOs:65-66	SEQ ID NO:32
	SEQ ID NO:33	SEQ ID NOs:67-68	SEQ ID NO:34
	SEQ ID NO:109	SEQ ID NOs:111-112	SEQ ID NO:110
	SEQ ID NO:113	SEQ ID NOs:115-116	SEQ ID NO:114
	SEQ ID NO:117	SEQ ID NOs:119-120	SEQ ID NO:118
25	SEQ ID NO:121	SEQ ID NOs:123-124	SEQ ID NO:122
	SEQ ID NO:125	SEQ ID NOs:127-128	SEQ ID NO:126
	SEQ ID NO:129	SEQ ID NOs:131-132	SEQ ID NO:130
	SEQ ID NO:133	SEQ ID NOs:135-136	SEQ ID NO:134
	SEQ ID NO:137	SEQ ID NOs:139-140	SEQ ID NO:138
30	SEQ ID NO:141	SEQ ID NOs:143-144	SEQ ID NO:142

Insertion inactivation of unknown coding sequences

Inactivation was achieved by integration of a plasmid in the 5' half of the target coding sequence by homologous recombination. An internal fragment of the selected coding sequence was synthesized by PCR. The length of the amplified fragment was between about 250 base pairs to about 350 base pairs, and included the 5' end of the coding sequence. The primers used for amplification included additional nucleotides such that a PstI restriction site was added to one end of the amplified fragment and a SacI restriction site was added to the other end of the amplified fragment. The primers are shown in Table 1. The added restriction sites allowed ligation of the amplified fragment to the temperature sensitive shuttle vector pSPT246. pSPT246 was constructed by ligating pRN8103 and pSP64-PolyA. The pRN8103 thermosensitive replication vector contains a unique EcoRI restriction site and the vector cannot replicate in *E. coli*. pRN8103 is described in Novick et al., (*J. Mol. Biol.*, 192, 209-220 (1986)). The pSP64-PolyA vector, obtained from Promega Corp. (Madison, WI), replicates in *E. coli*, but not in *S. aureus*. pSP64-PolyA also contains a unique EcoRI restriction site. An *E. coli*/*S. aureus* shuttle vector was constructed by digesting each vector with EcoRI, ligating the two vectors together, and transforming the DNA into *E. coli*. The resulting shuttle vector was designated pSPT264.

The recombinant plasmid (i.e., pSPT246 containing an amplified fragment) was used to transform *E. coli*, isolated, and then transferred to *S. aureus* RN4220 (described in Kreiswirth et al., *Nature*, 305, 709-712 (1983)) by electroporation. Transformants were selected by incubation on Nutrient agar plates containing tetracycline (10 µg/ml) at the permissive temperature (30°C). The presence of the correct plasmid was verified by PCR.

One clone with the correct plasmid was grown on Nutrient agar with tetracycline (10 µg/ml) at 32°C overnight to allow recombination between the plasmid and the selected chromosomal allele. To select for recombinants the bacteria were then grown at the non-permissive temperature (43°C) for 18 hours in Brain Heart Infusion (BHI) broth without tetracycline, followed by a 1:10 dilution into BHI broth containing 5 µg/ml tetracycline. The cells were

incubated overnight at 43°C. The bacterial culture was then diluted, spread on Nutrient agar plates containing 5 µg/ml tetracycline and incubated at 43°C overnight. As the plasmid cannot replicate at 43°C, only cells with the plasmid integrated into the chromosome are tetracycline resistant and form colonies.

- 5 Micro-colonies that appear at the non-permissive temperature are also considered, as they may represent mutations in coding sequences that are important (e.g., critical), but not essential, for growth.

The plasmid integrates at a low frequency at other sites in the chromosome, thus tetracycline resistant clones appeared even when the target coding sequence was essential. Therefore, ten colonies from each selection at 43°C were tested for specific integration of the plasmid into the selected target coding sequence by PCR. A primer pair consisting of one primer that binds to the vector DNA, and a second primer that binds upstream of the target coding sequence in the chromosome was used for PCR amplification. The primer pair
15 amplifies the intervening chromosomal-vector region, and an amplified DNA fragment is produced only if the vector integrated at the predicted location. The absence of a band suggests the vector cannot integrate, and that the coding sequence is essential. Typically, all or none out of the tested colonies were specific recombinants. In those cases where no recombinants are found the target coding sequence is considered essential. For a number of target coding
20 sequences (both essential and non-essential) the same results have been obtained when the whole selection procedure was repeated.

This protocol has successfully been used to analyze about 300 out of the of 492 unknown complete or partial coding sequences identified. Out of the
25 analyzed coding sequences, 26 appeared to be critical and were further analyzed as described below.

Example 2

Cloning of essential *S. aureus* coding sequences and expression in *E. coli*
30 *Overview of the expression system and cloning procedure*

The overexpression of *S. aureus* proteins is accomplished using the Qiagen Type ATG expression system (Qiagen GmbH, Santa Clara, CA). This

system utilizes *E. coli* strain "M15" whose genotype has been described by Qiagen as *Nal^r*, *Str^r*, *rif^r*, *lac⁻*, *ara⁻*, *gal⁻*, *mtl⁻*, *F⁻*, *recA⁺*, *uvr⁺*. Two replication compatible vectors, pREP4 and pQE-60 (each obtained from Qiagen), are introduced into the M15 strain during the procedure. Alternatively, pQE-70
5 can be used instead of pQE-60. The pREP4 vector is a pACYC-derived vector that contains the *lacI* gene encoding for the Lactose (LacI) repressor protein, and the vector encodes kanamycin drug resistance. The expression vector pQE-60 is a pBR322-derived vector that contains a modified T5 phage promoter, a strong ribosome binding site (RBS), and the coding sequence of the
10 specific *S. aureus* coding sequence to be expressed. The T5 promoter modifications include the placement of operator sites for binding and regulation of the promoter by the LacI repressor. Induction of expression is performed by the addition of IPTG (isopropylthio- β -D-galactoside) to a log phase culture.

The general cloning strategy is to first amplify the specific coding
15 sequence from *S. aureus* genomic DNA using PCR primers to the 5' and 3' ends of the coding sequence. The PCR primers are designed to add an *NcoI* and a *BglII* restriction site at the 5' and 3' ends of the coding sequence respectively. The coding sequence should be free of any *NcoI* or *BglII* restriction sites. If such sites are present, they are eliminated using site-
20 directed PCR mutagenesis procedures known to the art. Alternatively, a different restriction site, for instance a *BamHI* restriction site, is used instead of a *BglII* restriction site. The amplified *S. aureus* coding sequence is ligated into pCR-2.1 (Invitrogen, Carlsbad, CA) and transformed into *E. coli* using techniques known to the art. Colonies are screened for the presence of the
25 coding sequence by PCR amplification or vector restriction analysis. Clones are randomly selected and the nucleotide sequence of the insert DNA, i.e., the *S. aureus* coding sequence, is determined to confirm authenticity of the insert.

The pCR-2.1 vector containing the desired coding sequence is digested with *NcoI/BglII* and the coding sequence is isolated and ligated into the
30 corresponding *NcoI/BglII* restriction sites of pQE-60. The ligation mixture is used to electroporate the vector DNA into the M15 strain that contained the pREP4 vector. The resulting transformants are screened by PCR or restriction

analysis. Candidates are grown in a shake-flask and screened for the over-expression of a protein band having the appropriate size as analyzed by SDS-PAGE or Western analysis. Anti-His antibody (Invitrogen) is used in the Western analysis. A single candidate is selected for the overexpression and
 5 isolation of the protein encoded by each coding sequence.

Culture and Media

The medium for cloning and maintenance of cells containing recombinant plasmids in *E. coli* is LB supplemented with the appropriate
 10 antibiotic (100 µg/ml ampicillin, 25 µg/ml kanamycin). *S. aureus* was grown in Mueller-Hinton medium. Competent INV α cells (Invitrogen, Carlsbad, CA) are used according to the manufacturer's direction. The M15 pREP-4 strain was purchased from Qiagen. SOC medium was used in the electroporation of cells. LB and SOC media are described in Sambrook et al.
 15 (*Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, pp. A1-A4 (1989)). Mueller-Hinton medium is described in Atlas et al., Handbook of Microbiological Media, CRC Press.

Design of the pQE60 expression vector

20 The portion of the pQE-60 DNA sequence containing the T5 promoter, the RBS, the ATG start codon (in bold), the *NcoI* restriction site (underlined), the *BglIII* restriction site (underlined), 6 His tag (double underline), and the TAA stop codon (in bold) is shown (SEQ ID NO:89):

25 CTCGAGAAAT CATAAAAAAT TTATTTGCTT TGTGAGCGGA
 TAACAATTAT AATAGATTCA ATTGTGAGCG GATAACAATT
 TCACACAGAA TTCATTAAAG AGGAGAAATT **AACCATGGGA**
 GGATCCAGAT CTCATCACCA TCACCATCAC **TAAGCTTAAT** TA *NcoI*
 30 *BglIII*

The *S. aureus* coding sequences are modified by PCR to contain compatible in-frame *NcoI* and *BglIII* restriction sites.

Primer design

The general formula for the design of the primer to the 5' portion of the *S. aureus* coding sequence is usually 5'- CCATGGGAN₂₀₋₃₀, and the general formula for the 3' primer is usually 5'- AGATCTN₂₀₋₃₀. These primers add the

5 *NcoI* and *BglII* restriction sequences. The first "N" nucleotide of the 5' sequence correspond to the codon of the second amino acid of the *S. aureus* coding sequence after its ATG start. The first "N" nucleotide of the 3' primer corresponds to the third nucleotide in the codon preceding the stop codon of the *S. aureus* coding sequence. The number of nucleotides to include in the primer

10 varied depending on the specific DNA sequence, but is typically in a range of 20 to 30 bases. The primers are phosphorylated. Examples of primers that can be used to amplify some coding sequences are shown in Table 2.

Table 2. Primers used to amplify essential coding sequences from *S. aureus*

	Essential coding sequence	Primer pair used to clone coding sequence	Resulting sequence in pQE-60 or pQE-70	Predicted polypeptide and predicted molecular weight
5	SEQ ID NO:1	SEQ ID NOs:91-92	SEQ ID NO:69	SEQ ID NO:70, 28.1 kD
	SEQ ID NO:3	SEQ ID NOs:93-94	SEQ ID NO:71	SEQ ID NO:72, 31.6 kD
	SEQ ID NO:5	SEQ ID NOs:95-96	SEQ ID NO:73	SEQ ID NO:74, 28.5 kD
	SEQ ID NO:9	SEQ ID NOs:97-98	SEQ ID NO:75	SEQ ID NO:76, 37.4 kD
	SEQ ID NO:11	SEQ ID NOs:99-100	SEQ ID NO:77	SEQ ID NO:78, 40.9 kD
10	SEQ ID NO:13	SEQ ID NOs:101-102	SEQ ID NO:79	SEQ ID NO:80, 30.4 kD
	SEQ ID NO:15	SEQ ID NOs:103-104	SEQ ID NO:81	SEQ ID NO:82, 78.1 kD
	SEQ ID NO:17	SEQ ID NOs:105-106	SEQ ID NO:83	SEQ ID NO:84, 57.4 kD
	SEQ ID NO:19	SEQ ID NOs:107-108	SEQ ID NO:85	SEQ ID NO:86, 16.1 kD

15 *Preparation of the S. aureus Genomic DNA*

Strain ISP3 (obtained from S. Arvidson, Karolinska Institute) is used to inoculate 10 mls of Mueller-Hinton broth. After overnight growth at 37°C, 1.5 mls of culture are pelleted in an eppendorf tube and then resuspended in 400 µl of TE, pH 8.0 (Sambrook et al. (*Molecular Cloning: A Laboratory Manual*.,

20 Cold Spring Harbor Laboratory Press, p. B.20 (1989)). Following the addition of 50 µl lysostaphin solution (10 mg/ml), the cells are incubated at 37°C for 1 hour. Seventy microliters of 10% SDS and 10 µl of proteinase K (20 mg/ml) are added and the incubation continued at 37°C for another hour. After the

25 addition of 100 µl of 5 M NaCl, the cell suspension is vortexed and 80 µl of a solution containing 10% hexadecyltrimethyl ammonium bromide, 0.7 M NaCl (CTAB/NaCl) is added. The cells are vortexed and then incubated at 65°C for 10 minutes. Following the addition of an equal volume of 25:24:1 phenol:chloroform:isoamyl alcohol, the cells are vortexed and centrifuged for 5

minutes. The aqueous phase is then transferred to a fresh tube, leaving behind the white CTAB/NaCl interface. The extraction is repeated, and the aqueous layer is again transferred to a fresh tube. Following the addition of an equal volume of isopropanol, the tube is gently mixed causing a stringy precipitate to form. A Pasteur pipette fashioned into a small hook is used to gently remove the precipitate and to transfer it into another tube containing 1 ml of 70% ethanol. The tube is centrifuged, and the resulting pellet is washed once with 70% ethanol. After drying, the DNA pellet is resuspended in 100 µl of water and the concentration of the recovered DNA is determined using techniques known in the art.

PCR amplification

PCR reactions are performed using either the Perkin-Elmer Cetus GeneAmp 9600 or 2400 thermal cyclers (Perkin-Elmer, Norwalk, CT). The deoxynucleotide mix and the *Pfu* DNA polymerase are purchased from Stratagene (La Jolla, CA). The AmpliTaq Gold kit is purchased from Perkin Elmer. The PCR synthesis protocol for long template amplification is as follows: 1 µg of *S. aureus* genomic DNA, 10 µl of 10x reaction buffer (with 15 mM MgCl₂), 500 ng of each primer, 16 µl of 1.25 mM dNTP's, 1 µl of AmpliTaq Gold, and water to 100 µl are added per PCR microtube. The DNA is amplified for 35 cycles using Cycle Program of 95°C for 5 minutes followed by 35 cycles of 94°C for 30 seconds, 50°C for 1 minute and 72°C for 3 minutes, an extension at 72°C for 5 minutes, and finally 40°C on hold. A 10 µl aliquot of the synthesis reaction is loaded onto a 1.2% agarose gel to confirm the presence and size of the synthesized fragment. The PCR product is produced by combining multiple PCR reaction, EtOH precipitating the DNA, and cutting the desired fragment out of a 1.2% agarose gel. The DNA is isolated from the agarose using Amicon Ultrafree-DA extraction filters (Millipore Corp., Bedford, MA). The filters are used according to manufacturer's directions.

Ligation and Transformation

The pQE-60 vector and the pCR2.1 vector containing the *S. aureus* coding sequence are digested with *NcoI* and *BglII* restriction enzymes. The pQE-60 vector fragment and the *S. aureus* coding sequence are isolated from an agarose gel. The two DNAs are ligated and transformed into electrocompetent M15 cells containing pREP-4, and plated on LB agar with ampicillin and kanamycin supplementation. Ligase is purchased from BioLab (Beverly, MA), and used in accordance with the manufacturer's instructions. Electroporation of the ligated DNA into M15 pREP-4 cells is performed using a Bio-Rad Gene Pulser (Hercules, CA). Competent cells are prepared from 1 liter of cells with an optical density of 1 at A_{550} . The cells are chilled and washed successively with 1 liter and 0.5 liters of ice cold sterile water. The cells are resuspended in 20 mls of ice cold sterile 10% glycerol, re-centrifuged and placed into a final suspension of 2 to 3 mls of cold sterile 10% glycerol. Fifty microliters of cells are mixed with 5 μ ls or less of ligated DNA. The cell/DNA mixture is transferred to an electroporation cuvette and pulsed with the settings at 25 μ F, 2.5kV, and the Pulse Controller set to 200 Ω . One ml of SOC media is then added. The cells are incubated at 30°C for one hour and plated on selective media.

Several resultant colonies from the transformation are selected at random and vector DNA is isolated using the Miniprep or Maxiprep kits purchased from Qiagen. The vector DNA is isolated according to the manufacturer's instructions. The candidates are screened by restriction enzyme digestions. Restriction enzymes are purchased from New England BioLab (Beverly, MA). Restriction enzymes are used according to the manufacturer's instructions.

Expression conditions

The expression culture is streaked on an LB plate containing ampicillin and kanamycin. A single colony isolate is used to inoculate 50 mls of LB medium supplemented with ampicillin and kanamycin and grown overnight at the desired temperature. Following sub-culture into the suitable volume of the

identical media at 0.50 A₅₅₀/ml, the culture is grown at the same temperature with vigorous aeration until an A₅₅₀ of 3.0 was reached. The culture is induced by the addition of IPTG to a final concentration of 1 mM. Culture aliquots are removed at 0, 2, and 4 hours post-induction for SDS-PAGE or Western
5 analysis. Cells are harvested for protein isolation between 4 and 6 hours. Proteins are isolated using a metal-chelate affinity chromatography purification system (QIAEXPRESS, Qiagen).

Example 3

10 Use of essential coding sequence products in screen for antimicrobial agents

Individual purified proteins (i.e., target proteins) are combined with samples and screened for ligands that would bind the target protein. The method used to screen is described in Hughes et al., U.S. Patent 5,783,397.

15 The screening is conducted by Cetek Corporation, Marlborough, MA.

Example 4

Cloning of *S. aureus* uridylate kinase coding sequence for expression in *E. coli*

20 The *S. aureus pyrH* coding sequence encoding for uridylate kinase was cloned into the expression vector pQE60 for production of recombinant uridylate kinase in the *E. coli* strain M15 containing the plasmid pREP4. Cloning of the *pyrH* coding sequence was by PCR with two oligonucleotide primers 5' CCCGGGCCATGGCTCAAATT (SEQ ID NO:90) and 5'
25 GGGCCCAAGCTTAGTGATGG (SEQ ID NO:145), using *S. aureus* genomic DNA as the template. The PCR product was treated with restriction enzymes *NcoI* and *HindIII*, purified by agarose gel electrophoresis, and ligated into pQE60 digested with *NcoI* and *HindIII*. The ligation mixture was transformed into M15 cells containing pREP4; transformants were selected and the
30 nucleotide sequence of the *pyrH* coding sequence was verified by restriction enzyme analysis and DNA sequencing. The resulting plasmid for production of *S. aureus* uridylate kinase in *E. coli* was designated pQE60-UMK. Procedures

for DNA and plasmid preparation, restriction enzyme treatment, ligation, and transformation were according to those described in Sambrook et al.

(*Molecular Cloning: A Laboratory Manual.*, Cold Spring Harbor Laboratory Press (1989)).

- 5 The nucleotide and amino acid sequences of the recombinant uridylate kinase are shown in Figure 3. Six histidine residues are added to the C-terminus for purification with Ni- chelating chromatography. Due to the use of NcoI site for cloning and vector sequence, a alanine residue is added after the initiation methionine, and arginine and serine residues are added prior to the
- 10 histidine residues.

Example 5

Production of recombinant *S. aureus* uridylate kinase

- 15 The production strain, designated M15(pQE60-UMK), was grown to A_{550} of about 1 at 30°C in NS86 medium. NS86 medium is 2.6 grams (g) K_2HPO_4 , 10.9 g $NaNH_4HPO_4 \cdot 4H_2O$, 2.1 g citric acid, 0.67 g $(NH_4)_2SO_4$, 0.25 g $MgSO_4 \cdot 7H_2O$, 10.4 g yeast extract, and 5 g glycerol in 1 liter of H_2O . The NS86 medium was supplemented with 100 µg/ml ampicillin and 25 µg/ml
- 20 kanamycin. Frozen ampules with 20% glycerol added as a cryoprotectant were prepared and stored in liquid nitrogen.

- Seed culture was prepared by inoculation of 0.1 ml thawed cells from an ampule into 50 ml of NS86 medium, grown overnight at 30°C, and used to inoculate 100 ml MIM medium. MIM medium is 32 g tryptone, 20 g yeast
- 25 extract, 6 g Na_2HPO_4 , 3 g KH_2PO_4 , 0.5 g NaCl, and 1 g NH_4Cl in 1 liter of H_2O containing 100 µg/ml ampicillin and 25 µg/ml kanamycin to A_{550} 0.1. Cells were grown at 30°C overnight to A_{550} 7-8 and used for 10-liter fermentation.

- Seed culture was used to inoculate a 10-liter fermentor (New Brunswick Microgens) with MIM medium to A_{550} 0.1. When cells grew up to a density of
- 30 A_{550} of about 1 at 30°C, isopropyl-β-D-thiogalactoside was added to 1 mM to induce the expression of the recombinant protein. Cells were harvested at 2.5 hours post-induction and stored frozen. The average amount of uridylate

kinase produced from a 10-liter fermentation was estimated at 170 mg/l and corresponded to about 20-25% of total cell protein.

Example 6

5 Purification of recombinant *S. aureus* uridylate kinase

The frozen cells from a 10-liter fermentation were thawed and mixed with 200 ml cold lysis buffer (50 mM Tris, pH 7.8 at 22°C, 500 mM NaCl, 10% glycerol, 25 mM imidazole, 5 mM 2-mercaptoethanol, 0.1 mg/ml DNase).

10 The pellet was homogenized to yield a uniform suspension, and processed two times through a Rainie homogenizer to lyse the cells. The lysed cells were centrifuged at 35,000 x g for 75 minutes and the supernatant liquid was filtered sequentially through Nalgene 0.45 micron and 0.2 micron filters to remove particulates prior to column chromatography.

15 Column chromatography was carried out at 4°C, using a 2.6 cm x 6.7 cm column packed with Qiagen Ni-NTA Superflow resin. The column was washed with 3 bed volumes of water and equilibrated with 3 bed volumes of equilibration buffer (50 mM Tris, pH 7.8 at 22°C, 500 mM NaCl, 10% glycerol, 5 mM 2-mercaptoethanol) containing 25 mM imidazole. The filtered
20 supernatant was applied to the column at a rate of 3 bed volumes per hour. After loading, the column was washed with equilibration buffer with 25 mM imidazole until the absorbance at 280 nanometers (nm) decreased to 50% of baseline, followed by 6-7 bed volumes of equilibration buffer plus 40 mM imidazole and then 6-7 bed volumes of equilibration buffer plus 50 mM
25 imidazole. The bound uridylate kinase was eluted at a rate of 2-3 bed volumes per hour with equilibration buffer plus 300 mM imidazole, and was recovered in four separate fractions which were pooled, diluted 3-fold to reduce the protein concentration, and dialyzed against 50 mM Tris, pH 7.8 at 22°C, 500 mM NaCl, 10% glycerol, 5 mM 2-mercaptoethanol. The dialyzed pool was
30 stored frozen until further use.

This isolation yielded about 700 mg of recombinant uridylate kinase protein at a purity of 95-98%. N-terminal sequencing showed that the N-

terminal methionine was absent, which is expected due to the activity of host methionine aminopeptidase.

Example 7

5 Enzyme assays for uridylate kinase activity

Uridylate kinase catalyzes the transfer of a phosphoryl group from ATP to UMP to form UDP. In the cell, UDP is the substrate/precursor in several metabolic pathways including RNA and synthesis. A spectrophotometry assay
10 was established by coupling the uridylate kinase reaction to NADH oxidation using pyruvate kinase and lactate dehydrogenase, which ultimately convert the products of uridylate kinase reaction to lactate and NAD⁺. NADH oxidation was monitored by following the decrease in absorbance at 340 nm. EDTA at a final concentration of 5 mM can be used to stop the assay. This assay was
15 optimized in high-throughput format in 96-well microtiter plates to screen for agents that inhibit uridylate kinase. A secondary assay for pyruvate kinase and lactate dehydrogenase coupling enzymes was also developed to test the specificity of agents detected in the primary coupled assay.

20 The coupled assay is diagramed below.



25



Abbreviations:

ATP / ADP- Adenosine 5' triphosphate / Adenosine 5'-diphosphate

30 UMP/ UDP- Uridine 5' Monophosphate / Uridine 5' diphosphate

PEP- Phospho(enol)pyruvate

NADH / NAD⁺ - Nicotinamide Adenine Dinucleotide Reduced / Oxidized

The uridylate kinase coupled assay contains the following reagents in a final volume of 200 μ l: assay buffer (50 mM HEPES, pH 7.5, 100 mM KCl, 2 mM $MgCl_2$), 1 mM UMP, 2 mM ATP, 0.22 mM NADH, 2 mM PEP, 3.2 units pyruvate kinase (Sigma, St. Louis, MO), 4 units lactate dehydrogenase, 5 (Sigma) and 10 ng uridylate kinase. The assay was carried out at 25°C with the decrease in absorbance at 340 nm monitored at 15 second intervals in the kinetics mode for 1 or 3 hours.

The complete disclosures of all patents, patent applications, 10 publications, and nucleic acid and protein database entries, including for example GenBank accession numbers and EMBL accession numbers, that are cited herein are hereby incorporated by reference as if individually incorporated. Various modifications and alterations of this invention will become apparent to those skilled in the art without departing from the scope 15 and spirit of this invention, and it should be understood that this invention is not to be unduly limited to the illustrative embodiments set forth herein.

Sequence Listing Free Text

20	SEQ ID NO:35-68, 90-108, 111, 112, 115, 116, 119, 120, 123, 124, 127, 128, 131, 132, 135, 136, 139, 140, 143-145	Oligonucleotide primer
25	SEQ ID NO:69, 71, 73, 75, 77, 79, 81, 83, 85	Nucleotide sequence of <i>S. aureus</i> coding region cloned for expression in <i>E. coli</i>
30	SEQ ID NO: 70, 72, 74, 76, 78, 80, 82, 84, 86	Amino acid sequence encoded by <i>S. aureus</i> coding region cloned for expression in <i>E. coli</i>

SEQ ID NOs:49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93; Cloned coding
sequence

5

SEQ ID NOs:50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94; Polypeptide
encoded by cloned
essential coding
sequence

10

SEQ ID NO:89

DNA sequence of portion
of pQE-60 vector

15

What is claimed is:

1. A method for identifying an agent that binds a polypeptide, the method comprising:
 - contacting a polypeptide and an agent to form a mixture,
 - wherein the polypeptide is encoded by a coding sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, and 141;
 - determining whether the agent binds the polypeptide.
2. The method of claim 1 wherein determining comprises an assay selected from the group consisting of an enzyme assay, a binding assay, and a ligand binding assay.
3. The method of claim 1 further comprising determining whether the agent decreases the growth rate of a microbe, comprising:
 - contacting a microbe with the agent;
 - incubating the microbe and the agent under conditions suitable for growth of the microbe that is not contacted with the agent; and
 - determining the growth rate of the microbe contacted with the agent, wherein a decrease in growth rate compared to the microbe that is not contacted with the agent indicates the agent decreases the growth rate of the microbe.
4. The method of claim 3 wherein the microbe is *in vitro* or *in vivo*.
5. The method of claim 3 wherein the microbe is a *Staphylococcus aureus*.
6. An agent identified by the method of claim 1.
7. A method for identifying an agent that binds a polypeptide, the method comprising:

contacting a polypeptide and an agent to form a mixture,
wherein the polypeptide is encoded by an essential coding sequence comprising
a nucleotide sequence having at least about 57 percent structural similarity with
a nucleotide sequence selected from the group consisting of SEQ ID NO:7, 21,
23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, and 137;
determining whether the agent binds the polypeptide.

8. The method of claim 7 wherein determining comprises an assay
selected from the group consisting of an enzyme assay, a binding assay, and a
ligand binding assay.

9. The method of claim 7 further comprising determining whether the
agent decreases the growth rate of a microbe, comprising:
contacting a microbe with the agent;
incubating the microbe and the agent under conditions suitable
for growth of the microbe that is not contacted with the agent; and
determining the growth rate of the microbe contacted with the
agent, wherein a decrease in growth rate compared to the microbe that is not
contacted with the agent indicates the agent decreases the growth rate of the
microbe.

10. The method of claim 9 wherein the microbe is *in vitro* or *in vivo*.

11. The method of claim 9 wherein the microbe is an *S. aureus*.

12. An agent identified by the method of claim 9.

13. A method for identifying an agent that binds a polypeptide, the method
comprising:

contacting a polypeptide and an agent to form a mixture,
wherein the polypeptide is encoded by a critical coding sequence comprising a

nucleotide sequence having at least about 57 percent structural similarity with a nucleotide sequence comprising SEQ ID NO:141;
determining whether the agent binds the polypeptide.

14. The method of claim 13 wherein determining comprises an assay selected from the group consisting of an enzyme assay, a binding assay, and a ligand binding assay.

15. The method of claim 13 further comprising determining whether the agent decreases the growth rate of a microbe, comprising:
contacting a microbe with the agent;
incubating the microbe and the agent under conditions suitable for growth of the microbe that is not contacted with the agent; and
determining the growth rate of the microbe contacted with the agent, wherein a decrease in growth rate compared to the microbe that is not contacted with the agent indicates the agent decreases the growth rate of the microbe.

16. The method of claim 13 wherein the microbe is *in vitro* or *in vivo*.

17. The method of claim 13 wherein the microbe is an *S. aureus*.

18. An agent identified by the method of claim 13.

19. A method for identifying an agent that decreases the growth rate of a microbe, the method comprising:
contacting a microbe with an agent, wherein the agent binds to a polypeptide encoded by a coding sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, and 141;
incubating the microbe and the agent under conditions suitable for growth of the microbe that is not contacted with the agent; and

determining the growth rate of the microbe contacted with the agent, wherein a decrease in growth rate compared to the microbe that is not contacted with the agent indicates the agent decreases the growth rate of the microbe.

20. The method of claim 19 wherein the microbe is *in vitro* or *in vivo*.

21. The method of claim 19 wherein the microbe is an *S. aureus*.

22. An agent identified by the method of claim 19.

23. A method for identifying an agent that decreases the growth rate of a microbe, the method comprising:

contacting a microbe with an agent, wherein the agent binds to a polypeptide encoded by an essential coding sequence comprising a nucleotide sequence having at least about 57 percent structural similarity with a nucleotide sequence selected from the group consisting of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, and 137;

incubating the microbe and the agent under conditions suitable for growth of the microbe that is not contacted with the agent; and

determining the growth rate of the microbe contacted with the agent, wherein a decrease in growth rate compared to the microbe that is not contacted with the agent indicates the agent decreases the growth rate of the microbe.

24. The method of claim 23 wherein the microbe is *in vitro* or *in vivo*.

25. The method of claim 23 wherein the microbe is an *S. aureus*.

26. An agent identified by the method of claim 23.

27. A method for identifying an agent that decreases the growth rate of a microbe, the method comprising:

contacting a microbe with an agent, wherein the agent binds to a polypeptide encoded by a critical coding sequence comprising a nucleotide sequence having at least about 57 percent structural similarity with a nucleotide sequence comprising SEQ ID NO:141;

incubating the microbe and the agent under conditions suitable for growth of the microbe that is not contacted with the agent; and

determining the growth rate of the microbe contacted with the agent, wherein a decrease in growth rate compared to the microbe that is not contacted with the agent indicates the agent decreases the growth rate of the microbe.

28. The method of claim 27 wherein the microbe is *in vitro* or *in vivo*.

29. The method of claim 27 wherein the microbe is an *S. aureus*.

30. An agent identified by the method of claim 27.

31. A method for decreasing the growth rate of a microbe, the method comprising:

contacting a microbe with an agent that binds to a polypeptide encoded by a coding sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, and 141.

32. The method of claim 31 wherein the microbe is *in vitro* or *in vivo*.

33. The method of claim 31 wherein the microbe is an *S. aureus*.

34. A method for decreasing the growth rate of a microbe, the method comprising:

contacting a microbe with an agent that binds to a polypeptide encoded by an essential coding sequence comprising a nucleotide sequence having at least about 57 percent structural similarity with a nucleotide sequence selected from the group consisting of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, and 137.

35. The method of claim 34 wherein the microbe is *in vitro* or *in vivo*.

36. The method of claim 34 wherein the microbe is an *S. aureus*.

37. A method for decreasing the growth rate of a microbe, the method comprising:

contacting a microbe with an agent that binds to a polypeptide encoded by a critical coding sequence comprising a nucleotide sequence having at least about 57 percent structural similarity with a nucleotide sequence comprising SEQ ID NO:141.

38. The method of claim 37 wherein the microbe is *in vitro* or *in vivo*.

39. The method of claim 38 wherein the microbe is an *S. aureus*.

40. A method for making an *S. aureus* with reduced virulence, the method comprising:

altering a coding sequence in an *S. aureus* to comprise a mutation, the non-mutagenized coding sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, and 141; and

determining if the *S. arueus* comprising the mutation has reduced virulence compared to an *S. arueus* that does not comprise the mutation.

41. An *S. aureus* of claim 40.

42. A vaccine composition comprising the *S. aureus* organism of claim 40.

43. A method for making an *S. aureus* with reduced virulence, the method comprising:

altering an essential coding sequence in an *S. aureus* to comprise a mutation, the non-mutagenized coding sequence comprising a nucleotide sequence having at least about 57 percent structural similarity to a nucleotide sequence selected from the group consisting of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, and 137; and

determining if the *S. aureus* comprising the mutation has reduced virulence compared to an *S. aureus* that does not comprise the mutation

44. An *S. aureus* of claim 43.

45. A vaccine composition comprising the *S. aureus* organism of claim 43.

46. A method for making an *S. aureus* with reduced virulence, the method comprising:

altering a critical coding sequence in an *S. aureus* to comprise a mutation, the non-mutagenized coding sequence comprising a nucleotide sequence having at least about 57 percent structural similarity to a nucleotide sequence comprising SEQ ID NO:141; and

determining if the *S. aureus* comprising the mutation has reduced virulence compared to an *S. aureus* that does not comprise the mutation

47. An *S. aureus* of claim 46.

48. A vaccine composition comprising the *S. aureus* organism of claim 46.

49. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, and 141.

50. An isolated polynucleotide consisting essentially of a nucleotide sequence selected from the group consisting of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, and 141, and wherein the polynucleotide optionally further comprises from zero to up to about 5,000 nucleotides upstream and/or downstream of the nucleotide sequence selected from the group consisting of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 33, 109, 113, 117, 121, 125, 129, 133, 137, and 141.

51. An isolated polynucleotide comprising a nucleotide sequence having at least about 57 percent structural similarity with a nucleotide sequence selected from the group consisting of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 109, 113, 117, 121, 125, 129, 133, and 137, wherein the isolated polynucleotide comprises an essential coding sequence.

52. An isolated polynucleotide consisting essentially of a nucleotide sequence having at least about 57 percent structural similarity with a nucleotide sequence selected from the group consisting of SEQ ID NO:7, 21, 23, 25, 27, 29, 31, 109, 113, 117, 121, 125, 129, 133, and 137, wherein the isolated polynucleotide comprises an essential coding sequence.

53. An isolated polynucleotide comprising a nucleotide sequence having at least about 57 percent structural similarity with a nucleotide sequence comprising SEQ ID NO:141, wherein the isolated polynucleotide comprises a critical coding sequence.

54. An isolated polynucleotide consisting essentially of a nucleotide sequence having at least about 57 percent structural similarity with a nucleotide

sequence comprising SEQ ID NO:141, wherein the isolated polynucleotide comprises a critical coding sequence.

55. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 110, 114, 118, 122, 126, 130, 134, 138, and 142.

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Seq. ID No: 1

1 ATGTATTAC TTACCTCAA TTATAATTGT ACCGGTTCAA TTTGTAACG CCGATACAAT TATAATATTT TGTGCTATAA TAATTACAGA CAAAGTGAAA
 101 ACGAGGACAG AATATTGTTA AGTATGAAC ATATTGCTAA GCAACTTAAT GCGTTTATAC ATCAATCTAA TTTCAAACCC GGTGATAAAT TGCCAGCGT
 201 GACGCAATTA AAGAACGTT ATCAAGTAAG TAAGAGTACT ATCAATTAAAG CATTAGGCTT ATTGGAACAA GATGGTTTGA TCTATCAAGC ACAAGGCAGT
 301 GGTATTTATG TGAGAAATAT TGCTGATGCC AATCGTATCA ACGTCTTAA GACTAATGGT TTCTCTAAAA GTTTAGGTGA ACACCGAATG ACAAGTAAGG
 401 TACTTGT TTTT TAAGGAGATT GCAACGCCAC CTAAATCTGT ACAAGATGAG CTCCAATTAA ATGCAGATGA TACCGTCTAC TATTTAGAGC GATTAGATT
 501 CGTGGACGAT GATGTTTAT GTATCGAATA TTTCTTATTAT CATAAAGAAA TCGTGAATAA TTAAATGAT GATATTGCTA AGGCTCTAT CTTGACTAT
 601 TTAGAATCAA ACATGAACT TCGTATTGGT TTTTCAGATA TTTTCTTTAA TGATAGATCAA CTCACCTCAA GTGAAGCTTC ATTACTACAA TTGTCTACAG
 701 GTGAACCATG TTTACGTTAC CACCAGACTT TTTATACAAT GACTGGCAAA CCCTTTGATT CATCTGACAT CGTATTTTCAT TATCGTCATG CACAGTTTAA
 801 TATTCCTAGT AAAAAGTAA

Seq. ID No: 2

1 MYLLTSNYNC TGSICKRRYN YNLCYNNYR QSENECDRILL KYEHIAKQLN AFHQSNFKP GDKLPSVTQL KERYQVSKST IIKALGLLEQ DGLIYQAQGS
 101 GIYVRNIADA NRINVKTNQ FSKSLGEHRM TSKVLVFKEI ATPPKSVQDE LQLNADDTVY YLERLRFVDD DVLCIEYSY HKEIVKYLND DIAKGSIFDY
 201 LESNMKLRIG FSDIFFNVQD LSTSEASLLQ LSTGEPCLRY HQTFYTMGK PFDSSDIVFH YRHAQFYIPS KK

5' ATATATCTGCAGTGATAAATTGCCAAGCGTGAC Seq. ID No: 35

5' ATATATGAGCTCTCTTGACAGATTAGGTGGC Seq. ID No: 36

Fig. 1a

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Seq. ID No: 3

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1 ATGGCACTTT ATGGATTGCG CCAAGGACTT ATTCAGAAG CAGGAATTAG AATTAAACAA TTGATGGAGC AAAATTTAAC AATTGAAACA AAGTCAAATC
101 CGAATGACCT TGTTACAAAT GTAGATAAAG CAACAGAAGA TTTCATTTT GATACAAATT TAGAAACATA TCCCAATCAT CAAGTATTAG GTGAAGAAGG
201 GCATGGTCAT GACATCGATA CTTCCAAGG TACGGTATGG ATTGTTGACC CAATAGACGG TACATTGAAT TTTGTTTCATC AACAGAATAA TTTCGCAATT
301 TCAATTGGTA TTTATATCGA TGGTAAACCT TATGCAGGTT TTGTATATGA TGTATATGCT GATGCTTAT ATCATGCTAA AGTAGGGGAA GGTGCATATC
401 GTGGTAGCCA ACCCTTGAAA CCAITGAATG ATTCCTAATC AAGACAAAGC ATTATIGGGA TCAATCCGAA CTGGTTAACT AAACCAATT TAGGAGAAAT
501 CTTTAAAGAA ATTGTTAATG ATTCCTAGAAG TGCAAGGGCA TATGTTAGTG CAGCGCTTGA AATCGTTTCA GTTGCTACAG GTAATTTAGA AGCATATATG
601 ACGCCAAGAC TTCAACCATG GGAATTGCT GTGGGATTGG TTAATTTATA TGAAGTAAAT GGACAAGCTT CCAATTACT AGGAGGACCA TTAACAATTA
701 GTGGTCCAAA TTCAATCTTA GTTGGAAATC GTTGGTCTCCA TCAAGAAATT AGCAATGATT ATTTAGAGCC CCACCATGAT GCGTTAATAC AATTACATGA
801 ACAACGATTT AAAAGAAAT CAAAATAA

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Seq. ID No: 4

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1 MALYGFAOGL IQEAGIRIKQ LMEONLTJET KSNPNDLVTN VDKATEDFIF DTILETYPNH QVLGEEGHGH DIDTSKGTWV IVDPIDGTLN FVHQENFAI
101 SIGIYIDGKP YAGFVYDVMA DVLVHAKVGE GAYRGSQPLK PLNDSNLRQS IIGINPNWLT KPILGEIFKE IVNDSRSARA YGSAALEIVS VATGNLEAYM
201 TPRLQPWDFP GGLVILYEVN GQASNLLGGP LTISGPNLIL VGNRGLHQEI SNDYLEPHHD ALIQLHEQRF KRKSK*

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ATATATTCGAGCAAGTATTAGTGAAGAAGG Seq. ID No: 37
 ATATATGAGCTCAGCGATTGATCCCAATAATGC Seq. ID No: 38

Fig. 1b

Seq. ID No: 5
1 ATGGGATTCA AAAACAATTT AACATCAAAT TTAACAAATA AAATCGGTAA TTCAGTCTTT AAAATAGAAA ATGTTGACGG AAAAGGTGCA ATGCCAACGA
101 CGATTCAAGA ATTGAGAGAA AGACGACAAC GTGCTGAAGC AATTGTAAAG AGAAAGTCTT TAATGTCATC AACAAATGAGC GTTGTTCCTT TTCCGGGTTT
201 AGATTTTGGT GTTGATTAA AATTAATGAA AGATATTATC GAAGATGTTA ATAAATTTA TGGTTTAGAT CATAAGCAAG TTAATAGCCT TGGGATGAT
301 GTGAAAGAAA GAATTATGTC TGCAGCAGCA ATTCAAGGTA GTCAATTTAT TGGTAAAGA ATTTCAAATG CATTTTTAAA AATTGTAATT AGAGATGTAG
401 CTAACCGTAC TGCTGCAAAA CAACAAAAAT GGTTCCTGT TGTAGGACAA GCTGTGCTG CATCTATTAG TTAATATTTT ATGAATAAAA TTGGAAAAAGA
501 TCACATTCAA AAATGCGAAA ATGTTATTAA AAATGTCATG TAG

Seq. ID No: 6
1 MGFKNNLTSN LTNKIGNSVF KIENVGKGA MPTTIQELRE RRQRAEAIK RKSLMSSTMS VVPIPLDFG VDLKLMKDII EDVWNKIYGLD HKQVNSLGDD
101 VKERIMSAIA IQGSQFIGKR ISNAFLKIVI RDVAKRTAAK QTKWFPVVGQ AVSASISYYF MNKIGKDHQ KCENVIKNMV*

5' ATATATCTGCAGGGGATTCAAAAACAATTTAACATC Seq. ID No: 39
5' ATATATGAGCTCAGGCTATTAACTTGCTTAIGATC Seq. ID No: 40

Fig. 1c

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Seq ID No: 7

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1  GTGTTTCATC ATATCAGCGT TATGTTAAAC GAAACCATTTG ATTATTTAAA TGTAAAAGAA AATGGTGTGT ACATTGACTG TAGCTAGGT GGAGCGGGAC
101 ATGCCCTTTA TTACTAAAT CAATTAATG ACGACGGAG ATTAATAGCA ATCGATCAAG ACCAACTGC AATTGATAAT GCTAAAGAGG TATTAAAGGA
201 TCATTTCGAT AAGTGACTT TTGTTTCATG CAACTTCCGT GAATTAAGTC AAATATTAAA AGACTTAAC ATTGAAAAAG TAGATGGAAT TTATTACGAC
301 TTGGGTGTTT CAAGCCACCA ACTCGACATT CCAGAACGAG GATTCAGTTA TCACCATGAC GCAACATTAG ACATGCGTAT GGACCAAAAC CAAGAACTAA
401 CAGCATATGA AATTGTTAAT AATTGGTCAT ATGAAGCGTT AGTGAAGATT TTTTATCGCT ATGGCGAGGA GAAATTTTCA AAACAGATAG CTCGAAGAAT
501 CGAAGCACAT CGCGAACAA ACACAATAAC AACCACTTA GAATTAGTTG ACATTATAAA AGAAGGTATT CCTGCAAAAG CAAGAAGAAA AGCGGGACAT
601 CCTGCAAAAC GAGTATTTC AAGCACTACGA ATTCAGTAA ACGATGAATT GTCAGCTTTT GAAGATTCAA TAGAACAAAG GATTGAATTA GTGAAAAGTAG
701 ATGGCAGGAT TTCGGTAATC ACTTTCCATT CTTTAGAAGA TCGTTTATGT AAACAGGTGT TCCAAAGAATA TGAAAAAGGT CCAGAGGTAC CAAGAGGATT
801 ACCAGTTATA CCAGAAGCAT ATACACCTAA GTTAAAGCGT GTTAATCGTA AACCGATTAC CGCTACAGAA GAAGATTTAG ATGACAATAA CAGAGCACGA
901 AGCGCGAAAT TAGGTGTAGC TGAAATACTT AAATAA

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Seq ID No: 8

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1  VFHHISVMLN ETIDYLVNKE NGVYIDCTLG GAGHALYLLN QLNDGRLIA IDQDQTAIDN AKEVLKDHLL KVFVHSNFR ELTQILKDLN IEKVDGIYYD
101 LGVSSPQLDI PERGFSYHHD ATLDMRMDQT QELTAVEIVN NWSYEALVKI FYRYGEEKFS KQIARRIEAH REQQPITTTT ELVDIIKEGI PAKARRKGGH
201 PAKRVFQALR IAVNDELSAF EDSIEQAIEL VKVDGRISVI TFHSLEDRLC KQVFQYEEKG PEVPRGLPVI PEAYTPKLKR VNRKPITATE EDLDDNNRAR
301 SAKLRVAEIL K

```

5' TGGTGTGTACATTGACTGTAC
5' GCTGTTAGTTCTTGTGTTGG

Seq ID No: 41
 Seq ID No: 42

Fig. 1d

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	Seq. ID No: 9	
1	ATGATAAATA ATCATGAATT ACTAGGTATT CACCATGTTA CTGCAATGAC AGATGATGCA GAACGTAATT ATAAATTTTT TACAGAAGTA CTAGGCATGC	
101	GTTTAGTTAA AAAGACAGTC AATCAAGATG ATATTTATAC GTATCATACT TTTTTTGAG ATGATGTAGG TTCGCAGGT ACAGACATGA CGTCTTTTGA	
201	TTTTCCAAAT ATTACAAAG GGCAGGAGG AACAAATTCC ATTACAAGAC CGTCTTTTAG AGTGCCTAAC GATGACGAT TAACATATTA TGAACAGCGC	
301	TTTGATGAGT TTGGTGTAA ACACGAAGT ATTCAGAAT TATTGGTAA AAAAGTGTG CCATTTGAAG AAGTGGATGG CCAAGTGAT CAATTAATTT	
401	CAGATGAGT AAATGAAGG GTAGACCTG GTGTACCTG GAAGAATGGA CCGGTTCCAG TAGATAAAGC GATTATGGA TTAGGCCCCA TTGAAATTA	
501	AGTAAGTTAT TTGACGACT TTAATAATAT TTTAGAGACT GTTTACGGTA TGACAACAT TCGGCATGAA GATAATGTCG CATTACTTGA AGTTGGCGAA	
601	GGAGGCAATG GTGCCAGGT AATCTTAATA AAAGATGATA AAGGCCAGC AGCACGTCAA GGTATGGTG AGGTACATCA TGTGTCAATT CGTGTGAAAG	
701	ATCATGATGC AATAGAAGCG TGGGCAACGA AATATAAGA GGTAGGTATT AATAACTCAG GCATCGTTAA TCGTTCTAT TTTGAAGCAT TATATGCACG	
801	TGTGGGGCAT ATTTAATAG AAATTCAAC AGATGGACCA GGATTATGG AAGATGAAC TTATGAAACA TTAGCGGAAG GGTATCCTT ACCACCATTT	
901	TTAGAAAATA AAAGAGAATA TATTGAATCG GAAGTTAGAC CTTTAAATAC GAAGCGTCAA CATGGTTAA	
	Seq. ID No: 10	
1	MINNHELLGI HHVTAMTDDA ERNYKFFTEV LGMRLVKTV NQDDIYTYHT FFADDVGSAG TDMTFFDFPN ITKQAGTNS ITRPSFRVPN DDALTYEQR	
101	FDEFVKGHEG IQELFGKKVL PFEEVDGQVY QLISDELNEG VAPGVPWNG PVPVDKAIYG LGPIEIKVSY FDDFKNILET VYGMTTIAHE DNVALLEVGE	
201	GGNGGQVILI KDDKGPAARQ GYGEVHHVSF RVKDHDAIEA WATKYKEVGI NNSGIVNRFY FEALYARVGH ILIEISTDGP GFMEDEPYET LGEGLSLPPF	
301	LENKREYIES EVRPFNTKRQ HG	

5' ATATATGTCAGAGGTATTCACCATGTTACTGC Seq. ID No: 43
5' ATATATGAGCTCAATTGATACACTTGGCCATCG Seq. ID No: 44

Fig. 1e

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Seq. ID No: 11	GGGACATTTTAAATCATGCG	1
101	ATGGGTATCT TAAAAGAGTC	CTACTGGTCA AGAATTTTC CAGTTTTTCA
201	CAAGTCATGG CGCATATAGC	TGTCATGCATC ACAGGTCATC ATCTAAATGTC
301	CAGAAATCAT TCTGATTCAA	ACAAATGTTTA TGTTGTCTTT AGCTAATGTC
401	ATGACTGCGAG AACCATTCAT	TAGTCGCCCTT TATTTTAGCA ACACGTGTTTC
501	TAAAATTCGA TCGTTTAATT	TATTTACAAA CAAGTCATCT
601	TGATTTTACT GCGCTAATA	ACTATGCAAG CTTGCAAAAT
701	GCTGCTGCC TCACTTCTT	GATCGGATTTG CGTGTAAATC ATTACATTTT
801	TACTCATCAT GATTAATCTA	AAAATTAGCGT ACACAAATGT CTCCTGCAAT
901	TGGTATATTAT ATGTCGTGTC	CGGTCAAGTTT TCACGGTTCC ATTCAGCAGA
1001	CGTTACTTCA TCATATTAT	TAATTGGAAA AGTATTCCTT ATTAATGGGAT
1101	TGTTTCGGTTT CATCTTACTC	TATCGATTAA

	Seq. ID No: 12
1	MRILKESIIV AFAPVGVVVG AGFATGQEIF QFFTSHGAYS ISGLIIVTGIL ITLGGMVVMH TGHHLKSRNH SDSINYFLYP SIARGFDIIL TMFMLSLAI I
1101	MTAGGASTIH QSFNLPYWL S ALILVAFATL TLFUKFDRLI AVLGGVTPFL IAIVIMIAY YFTTSHLDFT AANDAQIHK QKSLSPGWWF DAINVASLQI
2201	AAAGASFLVM GSKVKYRDST LYGLLIGGLI IITFLLMMNL GLISQFDKIK HVDLPTLKLA TQWSPSIGII MSVIMILVIY NTVVGLMYAF ASRFSVPFSR
3301	RYFIIITMA VITYIISTFPI FISLIGKVFP IMGLFGFILL IPVLYKGLIK RITGKSHID

5' ATATATCTGCAGGGGACATTTTAAATCATGCTATGC Seq. ID No: 45
5' ATATATGAGCTCGCAGCTCATATAATAATAGCTAAAGAC Seq. ID No: 46

Fig. 1f

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Seq. ID No: 13	
1	ATGTTAATCG ATACACATGT CCATTTAAAT GATGAGCAAT ACGATGATGA TTTGAGTGAA GTGATTACAC GTGCTAGAGA AGCAGGTGTT GATCGTATGT
101	TTGTAGTTGG TTTTAACAAA TCGACAATTG AACGCGCGAT GAAATTAATC GATGAGTATG ATTTTTTATA TGGCATTATC GGTGGCATC CAGTTGACGC
201	AAATTGATTT ACAGAAGAAC ACTTGAATG GATTGAATCT TTAGCTCAGC ATCCAAAAGT GATTGGTATT GGTGAAATGG GATTAGATTA TCACTGGGAT
301	AAATCTCCTG CAGATGTTCA AAAGGAAGTT TTTAGAAAGC AAATTGCTTT AGCTAAGCGT TTGAAGTTAC CAATTATCAT TCATAACCGT GAAGCAACTC
401	AAGACTGTAT CGATATCTTA TTGGAGGAGC ATGCTGAAGA GGTAGGCGGG ATTATGCATA GCTTTAGTGG TTCTCCAGAA ATTGCAGATA TTGTAACATA
501	TAAGCTGAAT TTTTATATTT CATTAGGTGG ACCTGTGACA TTTAAAATG CTAAACAGCC TAAAGAAGTT GCTAAGCATG TGTCAAATGA GCGTTTGCTA
601	GTTGAAACCG ATGCACCGTA TCTTTCGCCA CATCCGTATA GAGGGAAGCG AAATGAACCG GCGAGAGTAA CTTTAGTAGC TGAACAAATT GCTGAATTAA
701	AAGGCTATC TTATGAAGAA GTGTGCGAAC AAACAACATAA AAATGTGTTA ATTTAAATTC ATAA
Seq. ID No: 14	
1	MLIDTHVLN DEQYDDDLSE VITRAREAGV DRMFVVGFNK STIERAMKLI DEYDFLYGII GWHFVDAIDF TEHLEWIES LAQHPKVICI GEMGLDYHWD
101	KSPADVQKEV FRQIALAKR LKLPILIIHR EATQDCIDIL LEEHAEVGG IMHSFSGSPE IADIVTNKLN FYISLGGPVT FKNKQPKVEV AKHVSMERLL
201	VETDAPYLSP HPYRGKRNEP ARVTLVAEQI AELKGLSYEE VCEQTTKNAE KLFNLNS
Seq. ID No: 47	
5' ATATATCTGCAGTGTAAATCGATACACATGTCC	
Seq. ID No: 48	
5' ATATATGAGCTCCTTCAAAACGCTTAGCTAAAGC	

Fig. 1g

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Seq. ID No: 15	Seq. ID No: 16	Seq. ID No: 49	Seq. ID No: 50
1 ATGATAATAT ATTGGTGTAT GACAGTTAAT GGAGGGAACG AAATGAAAGC TTTATTACTT AAAACAAGTG TATGGCTCGT TTGGCTTTT AGTGTAAATG	1 MIIYWCMTVN GGNEMKALLL KTSVWLVLFF DVDTQQASTQ KPTHATATFKL SVMLWQVSN AAEQHTPMKA HAVTTIDKAT TDKQQVPEPTK EAAHSGKEA ATNVSASAQG TADDTNSKVT	101 SNAPSNKPST VVSTKVNETR DVTQQAQSTQ KPTHATATFKL SVMLWQVSN AAEQHTPMKA HAVTTIDKAT TDKQQVPEPTK EAAHSGKEA ATNVSASAQG TADDTNSKVT	101 SNAPSNKPST VVSTKVNETR DVTQQAQSTQ KPTHATATFKL SVMLWQVSN AAEQHTPMKA HAVTTIDKAT TDKQQVPEPTK EAAHSGKEA ATNVSASAQG TADDTNSKVT
101 GATTATGGCA AGTCTCGAAC GCGGTGTAGC AGCATACACC AATGAAAGCA CAACGATAGA CAAGCTAAGC ATACATAAGC AACAAGTACC	101 LDAGDAFQGL PLNSQSGEE PLQSVTAEMM RIYKDVDTFV VENVTNPKAL AEQINQADQT FRAQTAEVII PNTIDFKGE RDDVTRTN LGNAIADAME AYGVKNFSKK TDFAVTNGSG	101 LDAGDAFQGL PLNSQSGEE PLQSVTAEMM RIYKDVDTFV VENVTNPKAL AEQINQADQT FRAQTAEVII PNTIDFKGE RDDVTRTN LGNAIADAME AYGVKNFSKK TDFAVTNGSG	101 LDAGDAFQGL PLNSQSGEE PLQSVTAEMM RIYKDVDTFV VENVTNPKAL AEQINQADQT FRAQTAEVII PNTIDFKGE RDDVTRTN LGNAIADAME AYGVKNFSKK TDFAVTNGSG
201 GCAACAAGG GAAGCGGCTC ATCATCTGAG CAAAGCAACG CGAACCAACG TATCAGCATC AGCGCAGGGA CACAGCTGATG ATACATAAGC AACAAGTACC	201 EGIKGVEFRD PLQSVTAEMM RIYKDVDTFV VENVTNPKAL AEQINQADQT FRAQTAEVII PNTIDFKGE RDDVTRTN LGNAIADAME AYGVKNFSKK TDFAVTNGSG	201 EGIKGVEFRD PLQSVTAEMM RIYKDVDTFV VENVTNPKAL AEQINQADQT FRAQTAEVII PNTIDFKGE RDDVTRTN LGNAIADAME AYGVKNFSKK TDFAVTNGSG	201 EGIKGVEFRD PLQSVTAEMM RIYKDVDTFV VENVTNPKAL AEQINQADQT FRAQTAEVII PNTIDFKGE RDDVTRTN LGNAIADAME AYGVKNFSKK TDFAVTNGSG
301 TCCAAACGAC CATCTAACAA ACCATCTACA ACCATCTACA CAAAGCAACG CGAACCAACG TATCAGCATC AGCGCAGGGA CACAGCTGATG ATACATAAGC AACAAGTACC	301 FNYRNGEVSN IKPSLINVKD TRYDLISVLP FGNTIAQIDV KGSVDVWTAPE HSLGAPTTQK DGKTVLTANG GLLHISDSIR VYDINKPSG KRINAIQILN KETGKFENID	301 FNYRNGEVSN IKPSLINVKD TRYDLISVLP FGNTIAQIDV KGSVDVWTAPE HSLGAPTTQK DGKTVLTANG GLLHISDSIR VYDINKPSG KRINAIQILN KETGKFENID	301 FNYRNGEVSN IKPSLINVKD TRYDLISVLP FGNTIAQIDV KGSVDVWTAPE HSLGAPTTQK DGKTVLTANG GLLHISDSIR VYDINKPSG KRINAIQILN KETGKFENID
401 ACACAGCAAC GTTCAAAATTA TCAAAATGCTA AAACAGCATC AACTTTCACCA CAAATGTTTG CTGCTAATGC ACCACAACAA AATATTATTA	401 IRASIAKGV TRYDLISVLP FGNTIAQIDV KGSVDVWTAPE HSLGAPTTQK DGKTVLTANG GLLHISDSIR VYDINKPSG KRINAIQILN KETGKFENID	401 IRASIAKGV TRYDLISVLP FGNTIAQIDV KGSVDVWTAPE HSLGAPTTQK DGKTVLTANG GLLHISDSIR VYDINKPSG KRINAIQILN KETGKFENID	401 IRASIAKGV TRYDLISVLP FGNTIAQIDV KGSVDVWTAPE HSLGAPTTQK DGKTVLTANG GLLHISDSIR VYDINKPSG KRINAIQILN KETGKFENID
501 TACAAATGAT ATCCATGGCC GACTAGCCGA AGAAAAGGG CGTGTCTACG GTATGGCTAA ATTAATAACA GTAAAAGAAC AAGAAAAGCC TGATTTAATG	501 LKRVYHVTMN DFTASGGDGY SMFGGPREEG ISLDQVLASY LKTANLAKYD TTEPQRMLLG KPAVSEQPAK GQQGSKGSKS GKDTQPIGDD KVMDDPAKKPA	501 LKRVYHVTMN DFTASGGDGY SMFGGPREEG ISLDQVLASY LKTANLAKYD TTEPQRMLLG KPAVSEQPAK GQQGSKGSKS GKDTQPIGDD KVMDDPAKKPA	501 LKRVYHVTMN DFTASGGDGY SMFGGPREEG ISLDQVLASY LKTANLAKYD TTEPQRMLLG KPAVSEQPAK GQQGSKGSKS GKDTQPIGDD KVMDDPAKKPA
601 TTAGACGCAG GAGACGCCCT CCAGGTTTA CCACCTTCAA ACCAGTCTAA AGGTGAAGAA ATGGCTAAAG CAATGAATGC AGTAGGTTAT GATGCTATGG	601 PGKVLL	601 PGKVLL	601 PGKVLL
701 CAGTCGGTAA CCATGAATTT GACTTTGGAT ACGATCAGTT GAAAAGTTA GAGGTATGT TAGACTTCCC GATGCTAAGT ACTAACGTTT ATAAAGATGG			
801 AAAACGGCG TTTAAGCCCT CAACGATTGT AACAAAAAT GGTATTCGTT ATGGAATTAT TGGTGTAAAG ACACCAAGAA AAGACGACCA AACAAGACCT			
901 GAAGGCATTA AAGCGTTGA ATTTAGAGAT CCATTACAAA CATGGCGTGG TGATTACTTA GTGAACAAT TAAGTCAATG AAGAACGTA TTACAGTTAT			
1001 ATTTAGGAAT TGATCCTTCA ACACAAGAAA CATGGCGTGG TGATTACTTA GTGAACAAT TAAGTCAATG AAGAACGTA TTACAGTTAT			
1101 TGATGGTCAT TCACATACAG TACTTCAAAA TGGTCAAAAT TATTAACAATG ATGCATTGGC ACAAACAGGT ACAGCACTTG CGAATATCGG TAAGATTACA			
1201 TTTAATTATC GCAATGGAGA GGTATCGAAT ATTAACCGT CATTGATTA TGTAAAGAC GTTGAATATG TAACACCGAA CAAAGCATTA GCTGAACAA			
1301 TTAATCAAG TGATCAACA TTTAGAGCAC AAACGTCAGA GGTAAATTTT CCAACAATA TTAAGAAATG CCAAGGAGAA AGAGATGACG TTAGAACGG			
1401 TGAACAATAA TTAGGAAACG CGATTGCAGA TGCTATGGAA CCGTATGGCG ATTTAATCTC AGTATTACCA CAGTGTAAAC AGCGAATGGC GGTTTACTAC ATATCTCTGA			
1501 ATTCGTGCCT CTATCGCAA AGGTAAGGTG ACAGGTATG ATTTAATCTC AGTATTACCA CAGTGTAAAC AGCGAATGGC GGTTTACTAC ATATCTCTGA			
1601 AGCTCTGGAC GGCTTTTCGAA CATAGTTTAG GCGACCAAC ACACAAAAAG GACGGTAAGA ATGCTATTCA AATTTTAAAT GTATGTTCCG TATATTAGGTA			
1701 TTTCAATCCGT GTTTACTATG ATATAAATAA ACCGCTGGC AAACGAATTA ATGCTATTCA AATTTTAAAT GTATGTTCCG TATATTAGGTA			
1801 TTAACAACGT TATATCAGT AACGATGAAT GACTTCACAG CATCAGGTGG GACGGATATA GACGAGTATG TATATTAGGTA AACAGCAGT AAGTGAACAA			
1901 TCAAGTACTA GCAAGTTAT TAAAAACAGC TAACCTAGCT AAGTATGATA CGACAGAACC ACAACCAATT GGTGACGACA AAGTGAATGGA			
2001 CCAGCTAAAG GACAACAAGG TAGCAAAGGT AGTAAGTCTG GTAAAGATAC ACAACCAATT GGTGACGACA AAGTGAATGGA			
2101 CAGGTAAAGT TGTATTGTTG TAG			

Fig. 1h

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Seq. ID No: 17

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1  ATCGGATTTA CATTTTCAAA CGATTAGGA ACGTTATTTA CTATTATTTT AGCCATTGGA TTCATCATTG ATTTAGTATT GGCTTTTATT ATTATCTTTT
101 TAGAAAGAAA TAGGCGTACA GCGAGTTCAA CTTGGGCATG GCTATTGTGA CTTTTTGTCT TACCATTGAT TGGTTTATT TTTTGGTAG
201 AACCGTTTCG GCACGCAAAAT TGAATAAAAA CAATGGTAAC GTGTTAACGG ATTTTCGATGG ACTTTTAAAA CAACAATAG CAAGCTTTGA TAAAGGTAAT
301 TATGGTACTG ATAACAAACA AGTTCRAAAA CATCATGATT TAGTACGTAT GCITTTGATG GATCAAGATG GTTTTAAAC TGAATAAAT AAAGTTGATC
401 ATTTCAATTG TGGAAATGAT TTATATGATC AAGTTTAAAA AGATATTAAA AGATGCAAAAG AATATATCCA TTTAGAGTAC TATACTTTTCG CTTTAGATGG
501 TTTAGGTAAA AGAATTTTAC ATGCTTTTGA AGAAAAATTG AAGCAAGGTC TAGAAGTAAA AATATTATAT GATGATGTTG GATCTAAAA GATCTAAAAA TGTAAAGATG
601 GCAAAATTTG ATCAATTTTAA ATCGTTTAGT GGAGAAAGTG AAGCAATTTT TGCTTCAAAA TTACCGTTAT TGAATTTTTC AATGAATAAT AGAAATCATA
701 GAAAAATCAT CGTAATCGAT GGTCAACTAG GTTATGTCGG AGGATTTAAC ATTGGIGATG AATATCTAGG ATTAGGAAAA TTAGGATATT GGAGAGATAC
801 GCATTTACGT ATACAAGGGG ATGCGGTTGA TGCACTGCAG TTGCAATTTA TTTTAGACTG GAATTCGCAA GCGCACCGTC CACAATTTGA ATATGATGTT
901 AAGTATTTCC CTAAAAAGAA CCGACCAATTG GGCAATTCAC CAATTCAAAT AGCTGCAAGT GGCCCGGCTA GTGACTGGCA TCAAATTTGA TACGGTTATA
1001 CAAAAATGAT TATGAGTGCA AAGAAATCTG TATATTTACA ATCACCATAT TTCAATCCGG ATAATTCATA TATAAATGCC ATTAATAATTG CTGCTAAATC
1101 AGGTGTAGAT GTACATTTAA TGATTTCCATG TAAGCCAGAT CATCCATTAG TATATTGGC GACATTTTCA AATGCCCTCG ACTTATTATC AAGTGGTGT
1201 AAAATTTTATA CGTATGAAA TGGATTTTAA CATTTTAAAA TGTGCTTAAT TGATGATGAA ATCGTATCAG TGGGCACAGC AAATATGGAC TTAGAAGTT
1301 TTGAATTTAA TTTGAAGTA AATGCCCTTG TATATGATGA AATCTTGCT AAAGATTTAA GGGTGGCTTA TGAACATGAT ATTACAAAAA CAAAACAACT
1401 AACCAGAGAA TCATATGCCA ATAGACCGCT GTCTGTAAA TTCAAGAAT CGTTAGCAAA ATTAGTTTCG CCAATTTTAT AA

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Seq. ID No: 18

MRFTSNDLGTFTIIILAIGFIINLVLAFFIIIFLENRRTASSTWAWLFVLFVLIPLIGFILYLFFGRTVSARKLNKNNGNVLTFDFGLLKQOIESFDKNGYGTDNKQVQKHDLVRMLL
MDQDGLTENNKVDHFDGNDLYDQVLKDIKNAKEYIHLEYTFALDGLGKRILHALEEKLKQGLEVKILYDDVGSKNVKMANFDFHFKSLGGEVEAFASFKLPLNFRMNNRHRKIIIV
IDQQLGVVGGFNIGDEYIGLGLGYWRDTHLRIOGDAVDALQLRFILDWNSQARHPQFEYDVKYFPKKNGLGNSPIQIAASGPASDWHQIEYGYTKMIMSAKSVYLQSPYFIPDNSY
INAIKIAKSGVDVHLMIPCKPDHPLVYWATFSNASDLLSSGVKIITYENGFIHSKNCLIDDEIVSVGTANMDFRSFELNFEVNAFYDENLAKDLRVAYEHDIITKSQLTKESEYANRP
LSVKFKESLAKLVSPIL

5' ATATATCTGCAGAGAGTACATACCTTCGCTTTAG Seq. ID No: 51
5' ATATATGAGCTCCCTAATCCTAGATATTCATCAC Seq. ID No: 52

Fig. 1i

Seq. ID No: 19
1 ATGAAGATTT TATTCGTTTG TACAGGTAAC ACATGTCGTA GCCCATTAGC GGAAAGTATT GCAAAAGAGG TTATGCCAAA TCATCAATTT GAATCAAGAG
101 GTATATTTCG TGGAACAAT CRAAGGIGTT CGAATTATGT TGAAGACTTA GTTGAAGAAC ATCATTTAGC TGAACCGACC TTATCGCAAC AATTACTGA
201 AGCAGATTTG AAAGCAGATA TTATTTTGAC GATGTCGTAT TCGCACAAAG AATTAATAGA GGCACACTTT GGTTTGCAA ATCATGTTTT CACATTGCAT
301 GAATATGTAA AAGAAGCAGG AGAAGTTATA GATCCATACG GTGGAACAAA AGAAATGTAT GTACATACCT ATGAAGAACT TGTAAGTTTA ATTTAAAAA
401 TAAAGATAT TATTGCTAG

Seq. ID No: 20
1 MKILFVCTGN TCRSPLESI AKEVMPNHQF ESRGIFAVNN QGVSNYVEDL VEEHHLAETT LSQQFTEADL KADIILTMSY SHKELIEAHF GLQNHVFTLH
101 EYVKEAGEVI DPGGTKEMY VHTYEELVSL ILKLDIIC

5' ATATATCTGCAGTTGTACAGGTAACACATGTCG Seq. ID No: 53
5' ATATATGAGCTCCTGCTTTCAAATCTGCTCAG Seq. ID No: 54

Fig. 1j

Seq. ID No: 21

1 ATGACAAAAC AGATTATAGT AACAGACTCA ACATCCGATT TATCTAAAGA ATACTTAGAA GCAAACAACA TTCAATGTAAT TCCTTTAAGT TTAACATTATG
101 AAGGAGCTTC ATACGTTGAC CAAGTAGATA TTACATCAGA AGAATTTATT AATCATATTG AAAATGATGA AGATGTAAG ACAAGTCAGC CAGCCATAGG
201 TGAATTTATA TCTGCTTATG AAGAACTAGG AAAAGATGGC TCTGAAATCA TAAGTATTCA TCTTTCTTCA GGATTAAGTG GTACATATAA CACTGCTTAC
301 CAAGCAAGTC AAATGGTAGA TGCTAATGTA ACTGTTATTG ATTCAAAATC TATTTCTTTT GGTTTAGGGT ATCAATACA ACACCTAGTA GAGCTTGTA
401 AAGAAGGTGT CTCACCTTCT GAAATAGTTA AAAAGTTAAA TCATTTAAGA GAAAACATTA AATTATTGT AGTTATAGG CAATTGAATC AATTAATTAA
501 AGGTGGCAGA ATTAGTAAAA CAAAAGGTTT GATTGGTAAT CTTATGAAAA TTAAACCAAT TGGTACACTA GATGATGGTC GCTTAGAGCT TGTGCACAAT
601 GCGAGAACTC AAAATTCTAG TATCCAATAC TTGAAGAAAG AAATTGCTGA ATTTATAGGA GATCATGAAA TCAATCCAT TGGTGTGCGA CATGCTAACG
701 TCATTGAATA TGTGATAAAA TTGAAGAAAG TTTTAAATGA AGCTTTTCAT GTGAATAAAT ACGATATAAA TGTAACATAA CCAGTTATTT CTGCACATAC
801 TGGTCAAGGT GCGATTGGCC TCGTAGTCCT TAAGAAG

Seq. ID No: 22

1 MTKQIIIVTDS TSDLSKEYLE ANNIHVIPLS LTIEGASYVD QVDITSEEFI NHIENDEVDK TSQPAIGEFI SAYEELGKD SEIISHLSS GLSGTYNTAY
101 QASQMVDANV TVIDSKSISF GLGYQIQHLV ELVKEGVSTS EIVKLNHLR ENIKLFVWIG QLNQLIKGR ISKTKGLIGN LMKIKPIGTL DDGRLELVHN
201 ARTQNSSIQY LKKEIAEFIG DHEIKSIGVA HANVIEYVDK LKKVFNEAFH VNNYDINVT PVISAHTGQG AIGLVVLKK

5' CTATTGAAGGAGCTTCATACG Seq. ID No: 55
5' TACAAGCTCTACTAGGTGTTG Seq. ID No: 56

Fig. 1k

Seq. ID No: 23

1 ATGAATTTAT TTTACAATCC TAAATATGTA GGAGATGTCG CATTITTACA AATTGAACCA GTTGAAGGTG AATTAAACTA CAATAAAAAA GGTAATGTTG
101 TTGAAATTAC TAATGAAGGT AATGTTGTAG GTTATAATAT TTTTGAAATT TCAAAAGATA TAACAATTGA AGAAAAAGGT CATATTAAAT TAACTGATGA
201 ACTTGTAAT GTATTCCAAA AGCGTATTTC AGAAGCTGGT TTTGATTATA AATTAAATGC TGATCTATCA CCGAAATTTG TAGTTGGCTA CGTTGAAACT
301 AAAGACAAAC ATCCTGATGC AGATAAATTA AGTGTAATAA AGTAAACGT TGGAATGAC ACATTACAAA TTGTATGTGG CGGCGCTAAC GTTGAAGCTG
401 GACAGAAAGT TGTGTTGCT AAAGTAGGTG CAGTGATGCC TAGCGGTATG GTAATTAAAG ATGCTGAATT ACGTGGTGTT GCCTCAAGCG GTATGATTTG
501 TTCAATGAAA GAATTGAATT TACCTAATGC ACCTGAAGAA AAAGGTATTA TGGTATTAAA TGACAGCTAT GAAATTGGAC AAGCATTTTT TGAA

Seq. ID No: 24

1 MNLFYNPKYV GDVAFLLQIEP VEGELNYNKK GNVVEITNEG NVVGNIFEI SKDITIEEG HIKLTDELVN VFQKRISEAG FDYKLNADLS PKFVVGIVET
101 KDKHPDADKL SVLNVNVDND TLQIVCGAPN VEAGQKVVA KVGAVMPSGM VIKDAELRGV ASSGMICSMK ELNLPNAPPE KGIMVLNDSY EIGQAFPE

5' CCTAAATATGTAGGATGTC Seq. ID No: 57
5' TTATCTGCATCAGGATGTTG Seq. ID No: 58

Fig. 11

Seq. ID No: 25

1 ATGACTGTAG AATGGTTAGC AGAACAAATTA AAAGAACATA ATATTCAATT AACTGAGACT CAAAACAAC AGTTCAAAC ATATTATCGT TTAATTGTTG

101 AATGGAATGA AAAGATGAAT TTGACAAGTA TTACAGATGA ACACGATGTA TATTGGAAC ATTTTATGA TTCCATTGCA CCTAGTTTTT ATTTTGATTT

201 TAATCAGCCT ATAAGTATAT GTGATGTAGG CGCTGGAGCT GGTTTTCCAA GTATTCCGT AAAAATAATG TTCCGCAGT TAAAAGTGAC GATTGTTGAT

301 TCATTAAATA ACGGTATTCA ATTTTAAAC CATTAGCGT CAGAATTACA ATTACAGAT GTACAGCTTTA TACACGATAG AGCAGAAAAC TTGTTAAGG

401 GTGCTACAG GGAGTCTTAT GATGTTGTTA CTGCAAGAGC AGTAGCTAGA TTATCCGTGT TAAGTGAATT GTGTTACCG CTAGTTAAA AAGGTGGACA

501 GTTTGTTGCA TTAATACTT CAAAAGTGA AGAAGAATTA GAAGAAGCAA AATTGCAAT TAGTGTAAATG TTACAGAAAC ACATACCTTT

601 GAATTGCCAG AAGATGCTGG AGAGCGCCAG ATGTTTCAAT TTGATAAAA AAGACAGACG CCGAAAAAGT ATCCAAGAAA ACCAGGGACG CCTAATAAGA

701 CTCCTTTACT TGA AAAA

Seq. ID No: 26

1 MTVEWLAEQL KEHNIQLTET QKQFQTYR LLVEWNEKMN LTSITDEHDV YLKHFYDSIA PSFYDFDNQP ISICDVGAGA GFPSIPLKIM FPQLKVTIVD

101 SLNKRIQFLN HLAELQLQD VSFHIDRAET FGKGVYRESY DVVTARAVAR LSVLSELCLP LVKKGQFVA LKSSKGEEEL EEAKFAISVL GGNVTETHTF

201 ELPEDAGERQ MFLIDKKRQT PKKYPRKPGT PNKTPLLEK

5' CTGTAATGGTTAGCAGAAC Seq. ID No: 59

5' CAATCGTCACTTTTAACTGCG Seq. ID No: 60

Fig. 1m

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Seq. ID No: 27

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1  ATGATAATAT ATTGGTGTAT GACAGTTAAT GGAGGAACG AATGAAAGC TTTATTACTT TATGGCTCGT TTTGCTTTTT AGTGTATGG
101 GATTATGGCA AGTCTCGAAC GCGGTGAGC AGCATACACC AATGAAAGCA CATGCAGTAA CAACGATAGA CAAAGCAACA ACAGATACC
201 GCCAACAAAG GAAGCGGCTC ATCATTTCTGG CAAAGAGAGG GCAACCAACG TATCAGCATC CGAACACCGC GACGTAGATA CACAACAAGC CTCAACACAA AACCCAACTC
301 TCCAACGCAC CATCTAACAA ACCATCTACA GTAGTTTCAA CAAAAGTAAA CAAAGTAAAG TATCAGCATC CGAACACCGC GACGTAGATA CACAACAAGC CTCAACACAA AACCCAACTC
401 ACACAGCAAC GTTCAAAATTA TCAAATGCTA AAACAGCATC ACTTTTCAAC CAAATGTTTG CTGCTAATGC ACCACAAAACA ACAACACATA AAATATTACA
501 TACAAATGAT ATCCATGGCC GACTAGCCGA AGAAAAAGGG CGTGTCAATG GTATGGCTAA ATTAAAAACA GTAAAAGAAC AAGAAAAGCC TGATTTAATG
601 TTAGACGCAG GAGACGCCCT CCAAGGTTTA CCACCTTCAA ACCAGTCTAA AGGTGAAGAA ATGGCTAAAG CAATGAATGC AGTAGGTTAT GATGCTATGG
701 CAGTCGGTAA CCATGAATTT GACTTTGGAT AACGATTGT CAACGATTGT AACAATAAAT GGTATTCGTT ATGGAATTAT TGGTGTAACG ACACCAGAAA CAAAGACGAA AACAGACCT
801 AAAACGGCGG TTTAAGCCTT TTAAGCCTT AAGCGTTGA ATTTAGAGAT CCATTACAAA GTGTGACAGC GGAATGATG CGTATTTATA AAGACGTAGA TACATTTGTT GTTATATCAC
901 GAAGGCATTA AAGCGTTGA ATTTAGAGAT CCATTACAAA GTGTGACAGC GGAATGATG CGTATTTATA AAGACGTAGA TACATTTGTT GTTATATCAC
1001 ATTTAGGAAT TGATCCTTCA ACACAAGAA CATGGCGTGG TGATTACTTA GTGAACAAT TAAAGTCAAAA TCCACAATTG AAGAAAAGTA TTACAGTTAT
1101 TGATGGTCAT TCACATACAG TACTTCAAAA TGGTCAAAAT TATAACAATG ATGCATTGGC ACAACACAGT ACAGCATTTG CGAATATCGG TAAGATTACA
1201 TTTAATTATC GCAATGGAGA GGTATCGAAT ATTAACCGT CATTGATTAA TGTTAAAGAC GTTGAAAATG TAACACCGAA CAAAGCATTA GCTGAACAAA
1301 TTAATCAAGC TGATCAACA TTTAGAGCAC AAACGCGAGA GGTAAATTAT CCAACAATA CCATTGATTT CAAAGGAGAA AGAGATGACG TTAGAAGCGG
1401 TGAACAATAA TTAGGAAACG CGATTGCAGA TGCTATGGAA CCGTATGGCG TTAAGAATTT CTCTAAAAAG ACTGACTTTG CCGTGACAAA TGGTGAGGTT
1501 ATTCGTGCTT CTATCGCAA AGGTAAGGTG ACAGCTATG ATTTAATCTC AGTATTACCA TTTGGAATAA CGATTGCGCA AATTGATGTA AAAGGTTGAG
1601 ACGTCTGGAC GGCTTTGGA CATAGTTTAG GCGCACCAAC AACACAAAAG GACGGTAAGA CAGTGTAAAC AGCGAATGGC GGTTTACTAC ATATCTCTGA
1701 TTCAATCCGT GTTTACTATG ATATAATAA ACCGTCTGGC AAACGAATTA ATGCTATTCA AATTTTAAAT AAAGAGACAG GTAAAGTTTG AATATTGAT
1801 TTAACACGTG TATATCACGT AACGATGAAT GACTTCACAG CATCAGGTGG CGACGGATAT AGTATGTTTG GTGGTCTAG AGAAGAAGGT ATTTTCATTAG
1901 ATCAAGTACT AGCAAGTTAT TTAACAAACAG CTAACCTTAGC TAAGTATGAT ACGACAGAAC CACAACGTAT GTTATTAGGT AAACAGCAG TAAGTGAACA
2001 ACCAGCTAAA GGACAACAAG GTAGCAAAGG TAGTAAGTCT GGTAAAGATA CACAACCAAT TGGTGACGAC AAAGTGATGG ATCCAGCGAA AAAACAGCT
2101 CCAGGTAAG TTGTATTGTT GCTAGCGCAT AGAGGAAGTG TTAGTAGCGG TACAGAAGGT TCTGGTGGCA CAATAGAAGG AGCTACTGTA TCAAGCAAGA
2201 GTGGGAAACA ATTGGCTAGA ATGTCAGTGC CTAAGGTTAG CGGCATGAG AAACAGTTAC CAAAAACTGG AACTAATCAA AGTTCAAGCC CAGAAGCGAT
2301 GTTTGTATTA TTAGCAGGTA TAGGTTTAAAT CGCGACTGTA CGACGTAGAA AAGCTAGC

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Seq. ID No: 28

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1  MIIYWCMTVN GGNEMKALLL KTSVWLVLFF SVMGLWQVSN AAEQHTPMKA HAVTTIDKAT TDKQOVPPPTK EAAHSGKEA ATNVSASAQG TADDTNSKVT
101 SNAPSNKPST VVSTKVNETR DVDTQQASTQ KPHTTATFKL SNAKTASLSP RMFAANAPQT TTHKILHTND IHGRLAEEKG RVIGMAKLKT VKEQEKPDLM

```

Fig. 1n

201 LDAGDAFQGL PLSNQSGEE MAKAMNAVGY DAMAVGNHEF DFGYDQLKKL EGMLDFPMLS TNYKDGKRA FKPSTIVTKN GIRYGIIGVT TPETKTKTRP
301 EGIKGVEFRD PLQSVTAEMM RIYKDVDTFV VISHLGIDPS TOETWRGDYL VKQLSQNPQL KKRITVIDGH SHTVLONGQI YNNDALAQTG TALANIGKIT
401 FNYRNGEVSN IKPSLINVKD VENVTNPKAL AEQINQADQT FRAQTAEVII PNNTIDFKGE RDDVRTRETN LGNAIADAME AYGVKNFSSK TDFAVTNGGG
501 IRASIAKGKV TRYDLISVLP FGNTIAQIDV KGSVDWTAPE HSLGAPTTQK DGKTVLTANG GLLHISDSIR VYYDINKPSG KRINAIQILN KETGKFENID
601 LKRVYHVTMN DFTASGGDGY SMFGGPREEG ISLDQVLASY LKTANLAKYD TTEPQRMLLG KPAVSEQPAK GQQGSKGSKS GKDTQPIGDD KVNDFPAKKPA
701 PGKVVLLAH RGTVSSGTEG SGRTIEGATV SSKSGKQLAR MSVPKGSAAE KQLPKTGTNQ SSSPEAMFVL LAGIGLIA TV RRRKAS

5'ACAAGTGATAGGCTCGTTTTC Seq. ID No: 61
5'ATTGAACGTTGCTGTGTGAG Seq. ID No: 62

Fig. 1n, cont.

Seq. ID No: 29

1 ATGAGTCATTATTACGATGAAGATCCAGTGTAATTAGCAATGAACAACGTATTCAATAT
61 CAATTAAACCATCATAAATTGATTTAATACTGATAACGGAGTGTTCGAAAGATAAA
121 GTAGATTATGGTTCAGATGTTCTTGTTCAACTTTTAAAGCGCATCCACCTGGTCCA
181 AGTAAGCGAATTGCCGATGTTGGTTGCGTTACGGACCAATTGGTTTGATGATTGCTAAA
241 GTATCACCACATCATTCAATTACAATGCTAGATGTTAATCACAGAGCGCTAGCCTTAGTT
301 GAAAAAACAAAAATTAAATGGTATTGATAATGTGATCGTAAAGGAAAGTGATGCTTTG
361 TCTGCTGTGGAAGACAAAAAGTTTGTATTTTATTTAACCAATCCACCAATAAGAGCAGGG
421 AAAGAAACCGTGCAATCGTATATTTCGAGCAAGCATTACATAGATTAGACTCGAACGGTGAA
481 CTATTCGTTGTAATTCAGAAGAAGCAAGGTATGCCATCTGCAAAAGAAAGAAATGAATGAA
541 CTTTTTGAAATGTAGAAGTGGTAAATAAAGATAAAGGATATTACATTCTGAGAAGTATA
601 AAAGCTTGA

Seq. ID No: 30

1 MSHYYDEDPVISNEQRIQYQLNHHKIDLITDNGVFSKDKVDYGSVDLVQTFLKAHPPGP
61 SKRIADVCGYGPIGLMIKVPSPHSITMLDVNHRALALVEKNKKLNGIDNVIVKESDAL
121 SAVEDKSFDILTNPPIRAGKETVHRIFEQALHRLDSNGELFVVIRKQGMPSAKKRMNE
181 LFGNVEVNVKDKGYIILRSIKA

5' ATTACGATGAAGATCCAAGTG Seq. ID No: 63
5' TTTTTTCAACTAAGGCTAGCG Seq. ID No: 64

Fig. 10

Seq. ID No: 31

1 ATCGAGTTG ATTTGAATTG TGATTTAGGC GAAGCATTTG GAAATTATTC CTTGGTGGT GATCATCAAA TTATTCCGTT AATTACAAGT GCGAATGTTG
101 CTTGTGTTT TCACGCTGGT GATGAAAATG TAATGAATGA AACGGTAAAA ACGGTAAAG CACATAATGT TGCAGTAGGT GCACATCCTG GTTTACCTGA
201 TTTGAAGGC TTTGGCAGC GAAATATAGA TATCTCTAAC GACGAGATTI ATAATTGAT GATTTATCAA TTAGGTGCAT TACAAGGGTT TTGTCGCATT
301 CATCAAGTTA AAATTAATCA TGTTAAACCG CATGGTGCAT TGTATCAGAT GGTGCAAAA GACAGAGAAA TAGCAAAACGT TATAGCACAA GCTGTTTATG
401 ACTTTGATCC ATCACTAGTG TTAGTAGGAT TAGCAAAATTC ATATCTAATT TCAGAAGCAA AGAATGTCGG ATTAATTACA GCTTCTGAAG TGTTCGCTGA
501 TAGACGATAC GAAGATGATG GGCAGCTCGT TAGTAGGAAA GAAAGTGATG CTGTGATTAC TGATACTGAC GAAGCACTTA AGCAGGTTTT AAAGATGGTG
601 AAGGAAAATA AAGTTATTTT AAAAAACAAT AAGGAAGTAA CGTTACAAGC AGATACAATT TGTGTGCATG GTGATGGAGA ACATGCATTA TTATTTGTTT
701 CGAAAATTAG AGAAATTTTA ATGAAAGAAG GCATTGATAT TCAATCCTTA

Seq. ID No: 32

1 MRVDLNCDLG EAFGNYSFGG DHQIPLITS ANVACGFHAG DENVMNETVK LAKAHNVAVG AHPGLPDLKG FGRNIDISN DEIYNLMYQ LGALQGFERI
101 HQVKINHVKP HGALYQMGAK DREIANVIAQ AVYDFDPSLV LVGLANSYLI SEAKNVGLIT ASEVFADRRY EDDGQLVSRK ESDAVITDTD EALKQVLKMV
201 KENKVISKNN KEVTLQADTI CVHGDGEHAL LFVSKIREIL MKEGIDIQSL

5'GAATTGTGATTAGGCGAAGC Seq. ID No: 65
5'ATGAATCGACAAAACCCCTTG Seq. ID No: 66

Fig. 1p

Seq. ID No: 33

1 ATGGCTCAA TTTCTAATA TAAACGTGTA GTTTTGAAAC TAAGTGGTGA AGCGTTAGCT GGAGAAAAAG GATTGGCAT AAATCCAGTA ATTATTAATA
101 GTGTTGCTGA GCAAGTGGCT GAAGTTGCTA AAATGGACTG TGAATCGCA GTAATCGTTG GTGGCGGAAA CATTGGAGA GGTAACACAG GTAGTGACTT
201 AGGTATGGAC CGTGGAACTG CTGATTACAT GGGTATGCTT GCAACTGTAA TGAATGCCCT AGCATTACAA GATAGTTTAG AACATTGGA TTGTGATACA
301 CGAGTATTAA CATCTATTGA AATGAAGCAA GTGGCTGAAC CTTATATTCT TCGTCGTGCA ATTAGACACT TAGAAAAAGAA ACGCGTAGTT ATTTTGTCTG
401 CAGGTATTGG AAACCCATAC TTCTCTACAG ATACTACAGC GGCATTACGT GCTGCAGAG TTGAAGCAGA TGTATTTTA ATGGGCAAAA ATAATGTAGA
501 TGGTGTATAT TCTGCAGATC CTAAGATAA CAAAGATGCG GTAAATATG AACATTAAAC GCATATTCAA ATGCTTCAAG AAGTTTACA AGTAATGGAT
601 TCAACAGCAT CCTCATTCTG TATGGATAAT AACATTCCGT TAACTGTTTT CTCTATTATG GAAGAAGGAA ATATTAAACG TGCTGTTATG GGTGAAAAAGA
701 TAGGTACGTT AATTACAAA

Seq. ID No: 34

1 MAQISKYKRV VLKLSGEALA GEKGFGINPV IIKSVAEQVA EVAKMDCEIA VIVGGNIWR GKTGSDLGMD RGTADYMGML ATVMNALALQ DSLEQLDCDT
101 RVLTSIEMKQ VAEPYIRRRR IRHLEKKRVV IFAAGIGNPY FSTDTTAALR AAEVEADVIL MGKNNVDGVY SADPKVINKDA VKYEHLETHIQ MLQEGQLQVMD
201 STASSFCMDN NIPLTVFSIM EEGNIKRAVM GEKIGTLITK

5' TTGAACTAAGTGGTGAAGCG Seq. ID No: 67
5' GCAGCAAAATAACTACCGGT Seq. ID No: 68

Fig. 1q

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Seq. ID No: 109

1 ATGGTGGCAT ATTAAATAT TCATACGGCT TATGATTGT TAAATTCAAG CTTAAAAATA GAAGATGCG TAAGACTTGC TGTGTCTGAA AATGTTGATG
 101 CACTTGGCAT AACTGACACC AATGTATTGT ATGGTTTTCC TAAATTTTAT GATGCAATGA TAGCAATATA CATTAACCG ATTTTGGTA TGACAATATA
 201 TGTGACAAAT GGATTAAATA CAGTCGAAAC AGTTGTTCTA GCTAAAAATA ATGATGGATT AAAAGATTG TATCAACTAT CATCGGAAAT AAAAATGAAT
 301 GCATTAGAAC ATGTGTCGTT TGAATTATTA AAACGATTTT CTAACAATAT GATTATCATT TTTAAAAAG TCGGTGATCA ACATCGTGAT ATTGTACAAG
 401 TGTTTGAAAC CCATAATGAC ACATATATGG ACCACCTTAG TATTTGATT CAAGGTAGAA AACATGTTG GATTCAAAAT GTTGTACC AAACACGTCA
 501 AGATGCGCAT ACGATTTCTG CATTAGCAGC TATTAGAGAC AATACAAAAT TAGACTTAAT TCATGATCAA GAAGATTTTG GTGCACATTT TTTAACTGAA
 601 AAGGAAATTA ATCAATTAGA TATTAACCAA GAATATTAA CGCAGGTTGA TGTATAGCT CAAAAGTGTG ATGCAGAAAT AAAATATCAT CAATCTCTAC
 701 TTCCTCAATA TGAGACACCT AATGATGAAT CAGCTAAAAA ATATTGTGG CGTGTCTTAG TTACACAAT GAAAAAATTA GAACTTAAT ATGACGTCTA
 801 TTTAGAGCGA TTGAAATATG AGTATAAAGT TATTACTAAT ATGGGTTTTG AAGATTATTT CTTAATAGTA AGTGATTTAA TCCATTATGC GAAAAACGAAT
 901 GATGTGATGG TAGGTCTCTG TCGTGGTTCT TCAGCTGGCT CACTGGTCAG TTATTATTG GGAATTACAA CGATTGATCC TATTAAATTC AATCTATTAT
 1001 TTGAACGTTT TTTAAACCCA GAACGTGTAA CAATGCCCTGA TATTGATATT GACTTTGAAG ATACACGCG AGAAAGGTC ATTCACTAG TCCACAGAAA
 1101 ATATGGCGAG CTACATGTAT CTGGAATTGT GACTTTCGGT CATCTGCTTG CAAGAGCAGT TGCTAGAGAT GTTGGAAGAA TTATGGGGTT TGATGAAGTT
 1201 ACATTAAATG AAATTTCAAG TTAAATCCCA CATAAATTAG GAATTACACT TGATGAAGCA TATCAAAATG ACGATTTTAA AGAGTTTGT CATCGAAACC
 1301 ATCGACATGA ACGCTGGTTC AGTATTGTGA AAAAGTTAGA AGGTTTACCA AGACATACAT CTACACATGC GGCAGGAAT ATTATTAAAG ACCATCCATT
 1401 ATATCAATAT GCCCCTTTAA CGAAAGGGA TACAGATTA TTAACGCAAT GGACAATGAC TGAAGCCGAA CGTATTGGGT TATTAAAAAT AGATTTTCTA
 1501 GGGTTGAGAA ACTTATCGAT TATTCATCAA ATCTTAACAC AAGTCAAAA AGATTAGGT ATTAATATTG ATATCGAAAA GATTCCGTTT GATGATCAAA
 1601 AAGTGTGTA ATTGTTGTG CAAGGAGATA CGACTGGCAT ATTCCAATTA GAGTCTGACG GTGTAAGAAG TGTATTAAAA AAATTAAAGC CGGAACACTT
 1701 TGAAGATATT GTTGCTGTAA CTTCTTTGTA TAGACCAGGT CCAATGGAAG AAATTTCCAAC TTACATTACA AGAAGACATG ATCCAAGCAA AGTTCAATAT
 1801 TTACATCCGC ATTTAGAAC TATATTAAAA AATACTTACG GTGTTATTAT TTATCAAGAG CAAATTATGC AAATAGCGAG CACATTGCA AACCTCAGTT
 1901 ATGTTGAAGC GGATATTTTA AGAAGAGCAA TGAGTAAAAA AAATAGAGCT GTTCTTGAAA GTGAGCGTCA ACATTTTATA GAAGGTGCAA AGCAAAATGG
 2001 TTATCACCAG GACATTAGTA AGCAAATATT TGATTTGATT CTGAAATTTG CTGATTATGG TTTTCTCTAGA GCACATGCTG TCAGCTATT TCATAATTGCA
 2101 TACATTATGA GCTTTTAAA AGTCCATTAT CCAAAATTAT TTTACGCAAA TATTTTAAGT AATGTTATTG GAAGTGAGAA GAAAACTGCT CAAATGATAG
 2201 AAGAGCAAA AAAACAAGGT ATCACTATAT TGCCACCGAA CATTAACGAA AGTCATTGGT TTTATAAAACC TTCCCAAGAA GGCATTTATT TATCAATTGG
 2301 TACAATTAAA GGTGTTGGTT ATCAAAGTGT GAAAGTGAAC GTTATCAGAA CGGCAAAATTT AAAGATTTCT TTGATTTTGC TAGACGTATA
 2401 CCGAAGAGAG TCAAAACGAG AAAGTTACTT GAAGCACTGA TTTTAGTGGG ACGGTTTGTAT GCTTTTGGTA AAACACGTTT AACGTTGTTG CAAGCTATTG
 2501 ATCAAGTGT GGATGGCGAT TTTAAACAT TGGAACAAGA TGGTTTTTTA TTTGATATTT TAACGCCAAA ACAGATGAT GAAGATAAAG AAGAATTGCC
 2601 TGATGCACTT ATTAGTCAGT ACGAAAAAGA ATATTAGGA TTTTATGTTT CGCAACACCC AGTAGATAAA AAGTTTGTG CCAAAACAATA TTTAACGATA
 2701 TTTAAATTGA GTAACGGCA GAATTATAAA CCTATATTAG TACAGTTTGA TAAAGTTAAA CAAATTGAA CTAATAATAG TCAATAATAG GCATTGCTCA

Fig. 1r

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2801 CATTAAATGA TGGCATTGAA ACTTTAGATG GTGTGATTTT CCTAATCAG TTTAAAAAGT ACGAAGAGTT GTTATCACAT AATGACTTGT TTATAGTTAG
 2901 CGGGAATTT GACCATAGAA AGCAACAACG TCAACTAATT ATAAATGAGA TTCAGACATT AGCCACTTTT GAAGAACAAA AATTAGCATT TGCCAACAAA
 3001 ATTATAATTA GAAATAAATC ACAAATAGAT ATGTTTGAAG AGATGATTAA AGCTACGAAA GAGAATGCTA ATGATGTTGT GTTATCCTTT TATGATGAAA
 3101 CGATTAAACA AATGACTACT TTAGGCTATA TTAATCAAAA AGATAGTAGT TTAATAAATT TTATACAATC CTTTAAACCCT AGTGATATTA GGCTTATA

Seq. ID No: 110

1 MVAYLNIHTA YDLLNSSLKI EDAVRLAVSE NVDALAITDT NVLYGFPKFY DACIANNIKP IFGMTIYVTN GLNTVETVVL AKNNDGLKDL YQLSSEIKMN
 101 ALEHVSPELL KRFSNNMII FKKVGDQHRD IVQVFETHND TYMDHLSISI QGRKHVWION VCQTRQDAD TISALAAIRD NTKLDLIHQ EDFGAHFLTE
 201 KEINQLDINQ EYLTQVDVIA QKCDAAELKYH QSLLPQYETP NDESAKKYLW RVLVTQLKKL ELNVDVYLER LKYEYKVITN MGFEDYFLIV SDLIHYAKTN
 301 DVMVGPGRGS SAGSLVSILL GITTIDPIKF NLLFERFLNP ERVTMPDIDI DFEDTRRERV IQYVQEKYGE LHSVGIIVTFG HLLARAVARD VGRIMGFDEV
 401 TLNEISSLIP HKLGITLDEA YQIDDFKEFV HRNHRHERWF SICKKLEGLP RHTSTHAAGI IINDHPLYEY APLTKGDTGL LTQWTMTAE RIGLLKIDFL
 501 GLRNLSTIHK ILTQVKKDLG INIDIEKIPF DDQKVFEELS QDGTGIFQL ESDGVRSVLK KLPKPEHEDI VAVTSLYRPG PMEEIPTYIT RRHDPKVVQY
 601 LHPHLEPILK NTYGVIIYQE QIMQIASTFA NFSYGEADIL RRAMSKKNRA VLESERQHF I EGAKQNGYHE DISKQIFDLI LKFADYGFPR AHAVSYSKIA
 701 YIMSFLKVHY PNYFYANILS NVIGSEKTA QMIEEAKKQG ITILPPNINE SHWFYKPSQE GIYLSIGTIK GVGYSQSVKVI VDERYQNGKF KDFDFFARRI
 801 PKRVKTRKLL EALILVGAFD AFGKTRSTLL QAIDQVLDGD FKTLEQDGLF FDILTPKQMY EDEKEELPDAL ISQYEKEYLG FYVSQHPVDK KFAVAKQYLT
 901 FKLSNAQNYK PILVQFDKVK QIRTKNGQNM AFVTLNDGIE TLDGVIFFNQ FKKEEELLSH NDUFIVSGKF DHRKQQRQLI INEIQTATF EEOKLAFAPAK
 1001 IIRNKSQID MFEEMIKATK ENANDVLSF YDETIKQMTT LGYINQKDSM FNNFIQSFNP SDIRLI

TAGAAGATGCCGTAAGACTTG Seq. ID No: 111

ATATCACGATGTTGATCACCG Seq. ID No: 112*Fig. 1r, cont.*

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Seq. ID No: 113

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1  ATGAAGAAA  AAGCGTACT  ACCATTATTT  TTAGGTATTA  TGGTCTTTT  GGCTGGTTGT  GACTATTCTA  AACCTGAAA  ACGTAGTGG  TTTTCTACA
101 ATACATTGCT  AGATCCAATG  AAAATGTAT  TGGATTGGTT  GGAATTAAC  TTATTAAACG  TTTAGCTATT  ATTATCCTG  TATTGGTAAT
201 TCGTATTATT  TTATTACCAT  TCATGTTGTC  AAATATATA  AATAGTCATA  TGATGCGTCA  AAAAATGAAA  GTTGCAAGC  CAGAAGTTGA  AAAAATTCAA
301 GAAAAAGTGA  AACGTGCGG  TACACAAGAA  GAAAAAATGG  CTGCAAAACCA  AGAATTAATG  CAAGTATATA  AAAAGTATGA  CATGAACCCG  ATTAAGAGTA
401 TGTGGGTTG  TTTACCAATG  CTAATCCAAT  TACCAATCAT  CATGGGATTA  TACTTTGTAC  TTAAGACCA  ACTTGTAGAT  GGTGTTTGA  AATATCCACA
501 CTTCTTATGG  TTCGATTAG  GACGTCCTGA  TATTGGGATT  ACAATTATG  CCGGTGTTT  ATACTTTATC  CAAGCATATG  TATCAAGTAA  AACGATGCCA
601 GACGAACAAC  GTCAAAATGG  TTACATGATG  ATGGTCATT  CACCAATTAT  GATTATCTGG  ATTCATTAA  GCTCAGCATC  AGCACTTGGT  TTGTACTGGT
701 CAGTCAGTGC  GCGGTTCTT  GTAGTTCAA  CACACTTTC  GAACATTTAT  TATGAAAAAG  TCGCTAAAA  AGAAGTACAA  CCTTTCATTG  AAGGTTATGA
801 AAGAGAGCAC  AACGGCGCA  GCAAT

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Seq. ID No: 114

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1  MKKALLPLF  LGIMVFLAG  DYSKPEKRS  FFYNTFVDP  KNVLDWLGNN  LLNDNYGLAI  IILVLVIRII  LLPFMLSNYK  NSHMMRQMK  VAKPEVEKIQ
101 EKVKRARTQE  EKMAANQELM  QVYKKYDMNP  IKSMLGCLPM  LIQLPIIMGL  YFVLKDQLVD  GLFKYPHFLW  FDLGRPDIWI  TIIAGVLYFI  QAYVSSKTMP
201 DEQRQMGYMM  MVISPIMI  ISLSSASALG  LYWSVSAFL  VVQTHFANIY  YEKVAKKEVQ  PFIEAYEREH  NGGSN

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TATGGTCTTTTGGCTGGTG Seq. ID No: 115
TTTTTCTTCTGTGTACGCGC Seq. ID No: 116

Fig. 1s

Seq. ID No: 117

1 ATGGATTTT CCAACTTTT TCAAAACCTC AGTACGTTAA AAATTGTAAC GAGTATCCTT GATTACTGA TAGTTGGTA TGTACTTTAT CTTCTCATCA

101 CGGTCTTTAA GGGAACTAAA GCGATACAAAT TACTTAAAGG GATATTAGTA ATTGTTATTG GTCAGCAGAT AAGTATGATA TTGAACCTGA CTGCAACATC

201 TAAATTATTC GATATCGTTA TTCAATGGGG GGTATTAGCT TTAATAGTAA TATTCACACC AGAAATTAGA CGTGGGTTAG AACAACTTGG TAGAGGTAGC

301 TTTTAAAC GCTATACCTC TAATACGTAT AGTAAAGATG AAGAGAAATT GATTCAAATCG GTTTCAAAGG CTGTGCAATA TATGGCTAAA AGACGTATAG

401 GTGCATTAAAT TGTCTTTGAA AAAGAAACAG GTCCTTCAAGA TTATATTGAA ACAGGTATTG CAATGGATTG AAATATTTCG CAAGAACCTT TAATTAATGT

501 CTTTATACCT AACACACCTT TACATGATGG TGCAATGATT ATTCAAGGCA CGAAGATTGC AGCAGCAGCA AGTTATTTCG CATTGTCTGA TAGTCCTAAG

601 ATATCTAAA GTTGGGTAC AAGACATAGA GCTGCGGTG GTATTCAGA AGTATCTGAT GCATTTACCG TTATTGTATC TGAAGAACT GGTGATATTT

701 CCGTAACATT TGATGGAAAA TTACGACGAG ACATTTCAAA CGAAATTTT GAAGAGTTGC TTGCTGAACA TTGGTTGGC ACACGCTTTC AAAAGAAAAGG

801 TGTGAAA

Seq. ID No: 118

1 MDFSNTFQNL STLKIVTSIL DLLIVWVLY LLITVFKGTK AIQLKGLV IVIGQQISM I LNLATSKLF DIVIQWGLA LIVIFQPEIR RALEQLGRGS

101 FLKRYTSNTY SKDEEKLIQS VSKAVQYMAK RRGALIVFE KETGLQDYIE TGIAMDSNIS QELLINVFIP NTPLHDGAMI IQGTKIAAAA SYLPLSDSPK

201 ISKSLGTRHR AAVGISEVSD AFTVIVSEET GDISVTFDGK LRRDISNEIF EELLAHWFPG TRFQKKGVK

CTTTATCTTCTCATCACGGTC Seq. ID No: 119
TGCACCTATACGCTCTTTTAGC Seq. ID No: 120

Fig. 1t

Seq. ID No: 121	
1	ATGATGATAA TCGTCATGTT ACTACTAAGT TATCTTATCG GCGCTTTCCC AAGTGGATTC GTAATTGGAA AATTATTTTT CAAAAAAGAT ATTAGACAAT
101	TTGGTAGTGG TAATACTGGC GCTACTAATA GCTTTAGAGT ATTAGGTCGT CCTGCAGGAT TCTTGGTAAC ATTTCTAGAT ATTTTCAAAG GGTTCATAAC
201	TGTTTTCTTC CCTTTATGGT TACAAGTTCA GCGAGATGGC CCTATTAGTA CTTTTTTTAC AAATGGTTTA ATTGTTGGCT TATTCGGCTAT ACTTGGACAC
301	GTTTATCCTG TTTATTTAAA ATTCCAAGGT GGCAAAGCTG TTGCAACTAG TGCAGGTGTC <u>GTCTTGGGAG</u> TCAATCCGAT ACTTTTACTA ATACTTGCAA
401	TTATCTTCTT TATTGTATTG AAGATTTTAA AATATGTTTC TTTAGCAAGT ATCGTTGCAG CAATTGCTG TGTGATTGGC TCGCTTATCA TTCAAGACTA
501	TATTTTATTA GTCGTTAGTT TCTTAGTTTC AATCATATTG ATAATTAGAC ATCGCTCTAA TATCGCAAGG ATTTTATAGAG GCGAAGAACCC TAAATAAAAA
601	TGGATG
Seq. ID No: 122	
1	MMIIVMLLS YLIGAFPSGF VIGKLEFKD IRQFGSNTG ATNSPRVLGR PAGFLVTFLD IFKGFITVFF PLWLQVHADG PISTFFFTNGL IVGLFAILGH
101	VYPVYLKFOG GKAVATSAGV VLGVPNPILL ILAIIFFIVL KIFKYVSLAS IVAAICCVIG SLIIQDYILL VVSFLVSILL IIRHRSNIAR IFRGEEP KIK
201	WM
Seq. ID No: 123	
<u>GTTATCTTATCGGCGCTTTCC</u>	
Seq. ID No: 124	
<u>GCCTAGTTGCAACAGCTTTG</u>	

Fig. 1u

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Seq. ID No: 125

1 ATGCAGTTAA ATAGTAATGG TTGGCATGTT GATGACCATA TTGTTGTGCG TGTCTTCTACA GGTAATGATA GTATGTGTTT ATTGTATCAA CTACTAAATG
 101 ATTATAAGA TAGTTATAGA AAACATAACAT GCTTACATGT CAATCATGGC GTTAGGTGAG CTTCATATGA GGAAGCCAGA TTTTATAGAAG CATACTGCGA
 201 ACGTCATCAC ATCGATTTAC ATATCAAAAA GTTAGATTG TCGCATAGTC TCGACCGAAA TAACAGCATT CAGAATGAAG CTGGAATTAA ACGTTACGAA
 301 TGGTTTGATG AAATGATGAA TGTATTAGAA GCGGATGTAT TGCTAACGGC GCATCATTTG GACGATCAAT TAGAACTAT TATGTATCGT ATTTTAAATG
 401 GGAATCAAC ACGTAATAAA CTAGGATTG ATGAGTTATC GAAGCGAAAA GGTATCAGA TTTATCGACC ACTTTAGCT GTCTTAAAA AAGAATAAAA
 501 ACAATTCCAA GAGAGATATC ATATTCCATA TTTTGAAGAT GAATCTAATA AAGATAACAA ATATGTTAGA AATGATATTC GTAATAGAAT TATTCAGCT
 601 ATTGATGAA ATAATCAACT TAAAGTATCG CATTTATTAA AATTAAAAA ATGGCATGAT GAACATATG ATATTTTGA ATATTCAGCT AAACAATTAA
 701 TTCAAGAATT TGTGAAGTTT GATGAACAGT CAAAATATTT AGAGTTTCT AGACAAGCTT TTAATAACTT ACCAACTCA TTAAGATGG TTTGTGTTGA
 801 CTGCTATTA TCAAGTATT ATGAGTTGTT TAATATTAGT GCTAAAAACAT ACGAAGAGTG GTTTAAACAA TTTAGTAGTA AGAAAGCACA ATTCAGTATT
 901 AATCTCAGG ATAAATGGAT AATTCAAATC GCATATGGTA AATTAATAAT AATGGCTAAA AATAATGGCG ATACATATTT TAGAGTTCAA ACAATTAAAA
 1001 AGCCAGGTAA TTATATTTT AACAAATATC GATTAGAGAT ACATTCTAAT TTACCAAAAT GTTTATTTC GCTTACAGTG AGAACACGAC AAAGTGCGGA
 1101 TACATTTAAA CTGAATGGG CCGATGGTTA TAAGAAAGTG AATCGCCTGT TTATAGATTG TAAAGTGCCA CAGTGGGTTT GGGATCAAAT GCCAATCGTA
 1201 TTGGATAAAC AACAGCGCAT TATTGCGGTA GGAGATTAT ATCAACAACA AACAATAAAA AAATGGATTA TAATTAGTAA AAATGGAGAT GAA

Seq. ID No: 126

1 MQLNSGWHV DDHIVAVST GIDSMCLLYQ LLNDYKDSYR KLTCLHVNHG VRSASIEEAR FLEAYGERHH IDLHIKKLDL SHSLDRNNSI QNEARIKRYE
 101 WFDEMNVLE ADVLLTAHL DDQLETIMYR IFNGKSTRNK LGFDELSKRK GYQIYRPLLA VSKKEIKQFQ ERYHIPYFED ESNKDNKYR NDIRNRIIPA
 201 IDENNQLKVS HLLKLKQWHD EYDILQYSA KQFIOEFVKF DEQSKYLEVS RQAFNNLPNS LKMVLDCLL SKYELFNIS AKTYEWFQ FSSKKAQPSI
 301 NLTDKWIQI AYGLIIMAK NNGDTYFRVQ TIKKPGNYIF NKYRLEIHSN LPKCLFPLTV RTRQSGDTFK LNGRDGYKKV NRLFIDCKVP QWVRDQMPIV
 401 LDKQQRILAV GDLYQQQTIK KWIISKNGD E

AATGTTGGCATGTTGATGAC Seq. ID No: 127
 ATTGATCGTCCAAATGATGCG Seq. ID No: 128

Fig. 1v

Seq. ID No: 129	
1	ATGTTTCATGG GAGAAATACGA TCATCAATTA GATACAAAG GACGTATGAT TATACCGTCC AAGTTTCGTT ATGACTTAAA TGAGCGTTTT ATTATCACAA
101	GAGGCCCTGA TAAATGTTTA TTCGGTTTACA CTCTAGACGA ATGGCAACAG ATTGAAGAGA AAATGAAAC CTTACCTATG ACAAAAAAAG ACGCACGTAA
201	GTTTATGCGT ATGTTCTTCT CTGGTGCTGT TGAAGTAGAA CTTGATAAGC AAGGGCGTAT TAACATCCCT CAAAACTTGA GGAATACGC TAATTTAACT
301	AAAGAAATGA CAGTAATCGG TGTTCAAAT CGTATTGAGA TTTGGGATAG AGAAACTTGG AATGATTCT ATGAAGAATC TGAAGAAAAGT TTCGAAGATA
401	TTGCTGAAGA TTTAATAGAT TTTGATTTT
Seq. ID No: 130	
1	MFMGEYDHL DTKGRMIIPS KFRYDLNERF IITRGLDKCL FGYTLDEWQQ IEKMKTLPM TKKDARKEMR MFFSGAVEVE LDKQGRINIP QNLKRYANLT
101	KECTVIGVSN RIEIWDRETW NDFYEESEES FEDIAEDLID FDF
TTCATGGGAGAAATACGATCATC Seq. ID No: 131	
<u>GTATTCTCTCAAGTTTGTGAGG Seq. ID No: 132</u>	

Fig. 1w

Seq. ID No: 133

1 ATGCTAGAGG CACAATTTT TACTGATACT GGACAACATA GAGATAAGAA TGAAGATGCG GGTGGTATTT TTTATAATCA AACTAATCAA CAACTTTTAG
101 TTCTGTGTA TGGTATGGT GCCATAAAG CAGGAGAAGT TGCAAGTAAA TTGTGTACAG ATGAGTTGAA ATCCCGTTTT GAAGCGGAAA ATCTTATAGA
201 ACAACATCAA GCTGAAAATT GGTGCGTAA TAATATAAAA GATATAAATT TTCAGTTATA TCACATATGCA CAAGAAAATG CAGAATATAA AGGTATGGGT
301 ACAACATGT TTTGTGCACT TGTTTTGGAA AAATCAGTTG TGATAGCAAA TGTCGGTGAT TCTAGAGCCT ATGTTATTAA TAGTCGACAA ATTGAACAAA
401 TTACTAGTGA TCACTCAATT GTTAATCATC TTGTTTTAAC GGGTCAAAAT ACGCCGGAAG AAGCATTAC ACATCCACAA CGTAATATTA TTACGAAGGT
501 GATGGGCACA GATAAACGTG TGAGTCCAGA TTTGTTTATT AAGCGATTAA ATTTTATGA TTATTATTA TTAATTCAG ATGGATTAAAC TGATTATGTT
601 AAAGACAATG AAATTAAGCG TTTGTTAGTA AAAGAAGGTA CAATAGAAGA TCATGGTGAT CAATTAATGC AATTGGCATT AGATAACCAT TCGAAAGATA
701 ACGTACTTT CATACTCGCG GCTATTGAAG GTGATAAAGT A

Seq. ID No: 134

1 MLEAQFFTDT GQHRDKNEDA GGIFYNQTNQ QLLVLCDGMG GHKAGEVASK FVTDELKSRF EAENLIEQHQ AENWLRNNIK DINFQLYHYA QENAEYKGMG
101 TTCVCALVFE KSVVIANVGD SRAYVINSRQ IEQITSDHSF VNLVLTGQI TPEEAFTHPQ RNIITKVMGT DKRVSPDLFI KRLNFYDYLL LNSDGLTDYV
201 KDNEIKRLLV KEGTIEDHGD QLMQLALDNH SKDNVTFILA AIEGDKV

CTGATACTGGACAACATAGAG Seq. ID No: 135
ACCGACATTTGCTATCAAC Seq. ID No: 136

Fig. 1x

Seq. ID No: 137

1 ATGAAAAGA TAGTACTTTA CGGGGTCAG TTTAACCCCTA TCCTACTGC ACATATGATA GTAGCTAGCG AAGTATTTC TGAATTACAG CCAGATGAAT

101 TTTATTTTTT ACCTAGTTTT ATGCTCCAT TGAAAAAGCA CCATGATTTT ATAGCGTTC AGCACAGATT AACATGATA CAGATGATTA TCGACGAGCT

201 TGGTTTTTGA GATATTTGTG ACGATGAAAT TAAACGTGGT GGTCAAAGTT ATACCTATGA CACGATCAAG GCATTCAAGG AGCAACACAA AGACAGTGAG

301 TTGTACTTTG TTATTTGGAC GGATCAGTAT AACCAACTAG AGAAATGGTA TCAAATTGAA TACTTAAAG AATGGTTAC TTTTGTAGTT GTAAATCGAG

401 ACAAATAG TCAAATGTT GAAAATGCTA TGATTGCAAT TCAGATACCT AGGTTAGATA TAAGTCGAC AATGATTGCA CAAAGAGTTA GTGAAGGGAA

501 ATCTATCCAA GTTCTGTTC CTAAATCCGT TGAAACTAT ATTAAGGGG AAGGATTATA TGAACAT

Seq. ID No: 138

1 MKKIVLYGGQ FNPHTAHMI VASEVFHELQ PDEFYFLPSF MSPLKXHHDF IDVQHRLTMI QMIIDELGFG DICDEIKRG GQSYTYDTIK AFKEQHKDSE

101 LYFVIGTDQY NQLEKNYQIE YLKEMVTFV VNRDKNSQNV ENAMIAIQIP RVDISSTMIR QRVSEKSIQ VLVFKSVENY IKGEGLYEH

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GTTTAACCCCTATCCTACTGC Seq. ID No: 139

CTAGTTGGTTACTATGATCCG Seq. ID No: 140

Fig. 1y

Seq. ID No: 141
1 ATGGTAACAT TATTACTTC ACCAAGTTGC ACATCTTGCC GTAAAGCGAA AGCATGGTTA CAAGAACATG ACATTCCGTA TAGGAGCGT AATATTTTTT
101 CTGAACATTT AACCAATTGAT GAAATTAGC AAATATTAAA AATGACTGAA GACGGTACTG ATGAATCAT TTCTACACGT TCTAAACAT ACCAAAAATT
201 AAATGTTGAT ATTGATTCAC TACCATTACA AGACTTATAT TCAATCATT AAGATAATCC TGGCTTATTA CGTCGTCCAA TTATTTTGA TAATAAACGA
301 CTACAAGTTG GTTATAATGA GGACGAGATT CGACGTTTCT TACCTAGAAA AGTTCGTACG TTCCAATTAC AAGAAGCACA ACGTATGGTT GAC

Seq. ID No: 142
1 MVTLTSPSC TSCRKAKAWL QEHDIPYTER NIFSEHLTID EIKQILKMT E DGTDEIISTR SKTYQKLNVD IDSLPLQDLY SIIQDNPGLL RRPILDNKR
101 LQVGYNEDEI RRFLPRKVRT FQLQEAQRMV D

ATTACTTCACCAAGTTGCAC Seq. ID No: 143
TAATTGGACGACGTAATAAGC Seq. ID No: 144

Fig. 1z

Seq. ID No: 69

ATGGGATTAAAGTATGAACATATTGCTAAGCAACTTAATGCGTTTATACATCAATCTAATTTCAAACCCGGTGATAAATTGCCAAGCGTGACGCAATTAAAGAACGTTATCAAGTAAGT
AAGAGTACTATCAATTAAGCATTAGGCTTATTGGAACAAGATGGTTTGATCTATCAAGCACAGCAGTGATTTATGTGAGAAATATTGCTGATGCCAATCGTATCAACGTCCTTTAAG
ACTAATGGTTTCTCTAAAAGTTTAGGTGAACACCGAATGACAAGTAAGGTACTTGTGTTTTAAGGAGATTGCAACGCCACCTAAATCTGTACAAGATGAGCTCCAATTAAATGCAGATGAT
ACCGTCTACTATTAGAGCGATTAAAGATTTCGTGGACGATGATGTTTATGTATCGAATATTCTTATTATCATAAAGAAATCGTGAAATATTTTAAATGATGATATTGCTAAGGGCTCTATC
TTCGACTATTAGAATCAAACATGAAACTTCGTATTGGTTTTTCAGATATTTCCTTAATGTAGATCAACTCACTTCAAGTGAAGCTTCATTACTACAATTGTCTACAGGTGAACCATGT
TTACGTTACCAACGACTTTTTTATACAATGACTGGCAACCCCTTTGATTTCATCTGCATCGTATTCATTATTCCTAGTAAAAAGAGATCTCATCACCAT
CACCATCACTAA

Seq. ID No: 70

MGLKYEHIKQLNAFIHQSNFKPGDKLPSTQLKERYQVSKSTIIKALGLLEQDGLIYQAQSGIYVRNIADANRINVFKNFGFSKSLGEHRMTSKVLVFEIATPPKSVQDELQLNADD
TVYYLERLRFVDDDLVLCIEYSYYHKEIVKYLNDDDIAKGSIFDYLESNMKLRIGFSDIFFNVQDLTSSEASLLQLSTGEPCLRYHQTFYTMGTGKPFDDSDIVFHYRHAQFYIPSKKRSHHH
HHH

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5' - CCATGGGATTAAAGTATGAACATATTGCTAAGC Seq. ID No: 91
5' - GAGATCTCTTTTACTAGGAATATAAACTGTGCATGACG Seq. ID No: 92

Fig. 2a

Seq. ID No: 71
ATGCTGACCTTTATGGATTGCCCCAAGGACTTATTCAAGAAGCAGGAATTAGAATTAAACAATTGATGGAGCAAAAATTAAACAATTGAAAACAAGTCAAATCCGAATGACCTTGTTACA
AATGTAGATAAAGCAACAGAGATTTCATTTTGTATACAAATTTAGAAACATATCCCAATCATCAAGTATTAGTGAAGAAGGCATGGTCATGACATCGATACCTTCCAAAGGTACGGTA
TGGATTGTTGACCCCAATAGACGGTACATTGAATTTTGTTCATCAACAAGAAAATTTCCGAATTTCAATTGGTATTATATCGATGGTAAACCTTATGCAGGTTTGTATATGATGTTATG
GCTGATGCTTATATCATGCTAAAGTAGGGGAGGTGCATATCGTGGTAGCCCAACCTTGAAACCATTTGAATGATCTAAATCTAAGACAAGCATTAATGGGATCAATCCGAACTGGTTA
ACTAAACCAATTTTAGGAGAAATCTTTAAAGAAATTTGTTAATGATTTAGAAAGTCAAGGCATATGGTAGTGCAGCGCTTGAAATCGTTTCAGTTGCTACAGGTAATTTAGAAGCATAT
ATGACGCCAAGACTTCAACCATGGGATTTTGCTGCGGATTGGTTATTTATATGAAGTAAATGGACAAGCTTCCAAATTACTAGGAGGACCATTAACAATTAGTGGTCCAAATTCAAATC
TTAGTTGGAAATCGTGGTCTCCATCAAGAAATTAGCAATGATTTATAGAGCCCCACCATGATGCGTTAATACAATTACATGAACAACGATTTTAAAGAAAAATCAAAAAGATCTCATCA
CCATCACCATCACTAA

Seq. ID No: 72
MLALYGAQGLIOEAGIRIKOLMEQNLTIETKSNPNDLVTNVDKATEDFIFDTILETYPNHQVLGEEGHGHDIDTSKGTWIVDPIDGTLNFVHQQENFAISIGIYIDGKPYAGFVYDVM
ADVLVHAKVGEYRGSQPLKPLNDSNLRQSIIGINPNWLTQPKILGEIFKEIVNDSRSRARAYGSAALEIVSVATGNLEAYMTPRLQPWDFAAGLVILYEVNGQASNLLGGPLTISGPNSI
LVGNRGLHQEISNDYLEPHHDALIQLHEQRFKRKSRSHHHHH

5' - GCATGCTGGCACTTTATGGATTGCCCCAAGG Seq. ID No: 93
5' - GAGATCTTTTGTGATTTTCTTTTAAATCGTTGTTCAATGATT Seq. ID No: 94

Fig. 2b

Seq. ID No: 73

ATGGGATTCAAACAAATTAAACATCAAAATTTAAACAAATCGGTAATTACAGTCTTTAAATAGAAAATGTTGACGGAAAAGGTGCAATGCCAACGACGATTCAAGAATTGAGAGAA
 AGACGACAACGCTGCTGAAGCAATTGTAAAGAGAAAGTCTTTAAATGTCAACAATGAGCGTTGTTCCAAATCCGGGTTTAGATTTTGGTGTGATTTAAATTAATGAAGATATTATC
 GAAGATGTTAAATAAATTTATGGTTTAGATCAAGCAAGTTAATAGCCTGGGGATGATGTAAGAAAAGAAATTAATGTCGACGACGCAATTCAGGTAGTCAATTTATTGGTAAAGA
 ATTTCAAATGCATTTTAAATAATTGTAATTAGAGATGTAGCTAAACGTACTGTGCAAAACAACAATAATGGTTTCCCTGTTGTAGGACAAGCTGTGCTGCATCTATTAGTTACTATTTT
 ATGAATAAAATTGGAAAAGATCACATTCAAAAATGCGAAAATGTTATTAAAAATGTCATGAGATCTCATCACCATCACCACTAA

Seq. ID No: 74

MGFKNLTSLTNKIGNSVFKIENVGKGAMPTTIQELRERRQRAEAIIVKRKSLMSSTMSVVPPIGLDFGVDLKLMKDIIEDVNKIYGLDVKQVNSLGLDDVKERIMSAAIQGSQFIGKR
 ISNAFLKIVIRDVAKRTAAKQTKWFPVVGQAVSASISYYFMNKIGKDHQKCNVINKVMRSHHHHH

5'- CCATGGGATTCAAAAAACAATTTAACATCSeq. ID No: 95

5'- GAGATCTCATGACATTTTAAATAACATTTTCGcSeq. ID No: 96

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Fig. 2c

Seq. ID No: 75
ATGGGAATAAATCATGAAATTACTAGGTATTCACCATGTTACTGCAATGACAGATGATGCAGAACGTAATTATAAATTTTTACAGAACTACTAGGCATGCGTTTAGTTAAAAAGACA
GTCAATCAAGATGATATTTATACGATATCATACATTTTTTTTGCAGATGATGATAGTTTCGGCAGGTACAGACATGACGTTCTTTTGATTTTCCAAATATTACAAAAGGCGCAGGAGCAAAAT
TCCATTACAGACCGTCTTTTAGAGTGCCCTAACGATGACGCAATTAAACATATTATGAACAGCGCTTTGATGAGTTTGGTGTAAACACGAAGGTATTCAGAATATTATTTGGTAAAAAAGTG
TTGCCATTTGAAGAAGTCGATGGCCAAAGTGATCAATTAATTTCCAGATGAGTTAAATGAAGGGGTAGCACCTGGTGTAACCTTGGAGAATGGACCGGTTCCAGTAGATAAAGCGATTAT
GGATTAGGCCCATTTGAAATTAAAGTAAGTTATTTTGACGACTTAAAAAATATTTTAGAGACTGTTTACGGTATGACAACTATTGCGCATGAAGATAATGTCCGATTACTTGAAGTTGGC
GAAGAGCAATGGTGGCCAGGTAATCTTAATAAAGATGATAAAGGCCAGCAGCACGTCGAAGGTTATGGTGAGGTACATCATGTGTCAATTCGTGTGAAGATCATGATGCAATAGAA
GCGTGGGCAACGAAATATAAAGAGGTAGGTATTAAATACTCAGGCATCGTTAATCGTTTCTATTTTGAAGCAATTATGACGCTGTGGGCATATTTAATAGAAATTTCAACAGATGGA
CCAGGATTTATGGAAGATGAACCTTATGAACATTTAGGCGAAGGTTATCCTTACCACCATTTTGTAGAAAATAAAAGAGAAATATATTGAATCGGAAGTTAGACCTTTTAAATACGAAGCGT
CAACATGGTATCTCATCACCATCACCATCACTAA

Seq. ID No: 76
MGINNHELLGIHHVTAMTDDAERNYKFFTEVLGMRLVKKTVNODDIYTYHTFFADDDVGSAGTDMTFFDFPNI TKGOAGTNSITRPSFRVPNDDALTYEQRDFDFGVKHEGLOELFGKKV
LPFEVDGQVYQLISDELNEGVA PGVPWKNGPVPVDKAIYGLGPIEIKVSYFDDFKNI LETVYGMTTIAHEDNVALLEVGEGNGGQVILIKDDKGPAAARQGYGEVHHVSFRVKDHAIE
AWATKYEVGINNSGIVNRFYFEALYARVGHILIEISTDGPGEWDEPEYETLGEGLSLPPFLENKREYIESEVRPENTKRQHGRSHHHHH

5' - CCATGGGAATAAATAATCATGAATTACTAGGSeq. ID No: 97
5' - GAGATCTACCATGTTGACGCTTCGTATTAAAGGTCSeq. ID No: 98

Fig. 2d

Seq. ID No: 77
AIGGGACGATCTTAAAGAGTCCATTATTGTGGCATTGTCCTTGTGTTGGTGGTCCAGAAAATTTCCAGTTTTTCAAGTCATGGCGCATAT
AGCATTTCCAGCATATTGTAACAGGACTATTGATTACTTTAGGTGAATGGTTGTTCATGCATACAGGTTCATCATCTAAAGTCCAGAAATCATCTGATTCATTAACATATTCTTATAC
CCCTCTATTGCAAGAGGTTTTTGATATTATTAAACAATGTTTATGTTGCTTTTAGCTATTATATGACTGCGGTGGTGGCTCAACCATTCATCAAGTTTCAACTTACCGTATTGGCTG
AGCGCACTCATATTAGTCGCCCTTTATTAGCAACAACACTGTTTCTAAATTCGATCGTTTAAATGCTGTGCTTGGCGGTGTTACCCCATTTTAAATTGGGATTGTCATTATGATGGGCTC
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5' - CCATGGGACGTATCTTAAAGAGTCCATTATTGTGG Seq. ID No: 99
5' - GGATCCATCGATATGAGATTTGCCGGTAATACGC Seq. ID No: 100

Fig. 2e

Seq. ID No: 79
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5' - CCATGGGATTAATCGATACACATGTCCAT Seq. ID No: 101
5' - GAGATCTTGAATTAAATTAAACAATTCTCTGCATTTTATGTTG Seq. ID No: 102

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Fig. 2f

Seq. ID No. 81

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5' - CCATGGGAATAATATATTGGTGTATGACAG Seq. ID No. 103

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Fig. 2g

Seq. ID No: 83

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5' - CCATGGGACGATTTACATTTTCAAACGATTTAGG Seq. ID No: 105
 5' - GAGATCTTAAAAATGGCGAAACTAATTTTGCTAACG Seq. ID No: 106

Fig. 2h

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Seq. ID No: 85
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5' - CCATGGGAAAGATTTTATTTCGTTGTACAGGTAACSeq. ID No: 107
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Fig. 2i

Seq. ID No: 87

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Fig. 3

SEQUENCE LISTING

<110> TOMICH, Che-Shen
 QUINN, Cheryl
 ARVIDSON, Staffan
 HARRIS, Douglas
 MOTT, John

<120> ANTIMICROBIAL METHODS AND MATERIALS

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<211> 311

<212> PRT

<213> Staphylococcus aureus

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50     55     60
Leu Lys Asp His Leu His Lys Val Thr Phe Val His Ser Asn Phe Arg
65     70     75     80
Glu Leu Thr Gln Ile Leu Lys Asp Leu Asn Ile Glu Lys Val Asp Gly
85     90     95
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Arg Gly Phe Ser Tyr His His Asp Ala Thr Leu Asp Met Arg Met Asp
115    120    125
Gln Thr Gln Glu Leu Thr Ala Tyr Glu Ile Val Asn Asn Trp Ser Tyr
130    135    140
Glu Ala Leu Val Lys Ile Phe Tyr Arg Tyr Gly Glu Glu Lys Phe Ser
145    150    155    160
Lys Gln Ile Ala Arg Arg Ile Glu Ala His Arg Glu Gln Gln Pro Ile

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165 170 175
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 225 230 235 240
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 Tyr Glu Lys Gly Pro Glu Val Pro Arg Gly Leu Pro Val Ile Pro Glu
 260 265 270
 Ala Tyr Thr Pro Lys Leu Lys Arg Val Asn Arg Lys Pro Ile Thr Ala
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<213> Staphylococcus aureus

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

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<212> DNA

<213> Staphylococcus aureus

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<213> Staphylococcus aureus

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 65 70 75 80
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 Gln Ile His Lys Gln Lys Ser Leu Ser Pro Gly Trp Trp Phe Asp Ala
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 Ile Asn Tyr Ala Ser Leu Gln Ile Ala Ala Ala Phe Ser Phe Leu Ser
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 Phe Ile Ser Leu Ile Gly Lys Val Phe Pro Ile Met Gly Leu Phe Gly
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340 345 350

Thr Gly Lys Ser His Ile Asp
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<210> 13

<211> 774

<212> DNA

<213> Staphylococcus aureus

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<211> 2123

<212> DNA

<213> Staphylococcus aureus

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<213> Staphylococcus aureus

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<213> Staphylococcus aureus

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

Tyr Trp Ala Thr Phe Ser Asn Ala Ser Asp Leu Leu Ser Ser Gly Val
 385 390 395 400
 Lys Ile Tyr Thr Tyr Glu Asn Gly Phe Ile His Ser Lys Met Cys Leu
 405 410 415
 Ile Asp Asp Glu Ile Val Ser Val Gly Thr Ala Asn Met Asp Phe Arg
 420 425 430
 Ser Phe Glu Leu Asn Phe Glu Val Asn Ala Phe Val Tyr Asp Glu Asn
 435 440 445
 Leu Ala Lys Asp Leu Arg Val Ala Tyr Glu His Asp Ile Thr Lys Ser
 450 455 460
 Lys Gln Leu Thr Lys Glu Ser Tyr Ala Asn Arg Pro Leu Ser Val Lys
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<210> 19

<211> 420

<212> DNA

<213> Staphylococcus aureus

<400> 19

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 caaggtgttt cgaattatgt tgaagactta gttgaagaac atcatttagc tgaaacgacc 180
 ttatcgcaac aatttactga agcagatttg aaagcagata ttattttgac gatgtcgtat 240
 tcgcacaaag aattaataga ggcacacttt ggtttgcaaa atcatgtttt cacattgcat 300
 gaatatgtaa aagaagcagg agaagttata gatccatacg gtggaacaaa agaaatgtat 360
 gtacatacct atgaagaact tgtaagttta attttaaaat taaaagatat tatttgctag 420

<210> 20

<211> 139

<212> PRT

<213> Staphylococcus aureus

<400> 20

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 20 25 30
 Arg Gly Ile Phe Ala Val Asn Asn Gln Gly Val Ser Asn Tyr Val Glu
 35 40 45
 Asp Leu Val Glu Glu His His Leu Ala Glu Thr Thr Leu Ser Gln Gln
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50 55 60
 Phe Thr Glu Ala Asp Leu Lys Ala Asp Ile Ile Leu Thr Met Ser Tyr
 65 70 75 80
 Ser His Lys Glu Leu Ile Glu Ala His Phe Gly Leu Gln Asn His Val
 85 90 95
 Phe Thr Leu His Glu Tyr Val Lys Glu Ala Gly Glu Val Ile Asp Pro
 100 105 110
 Tyr Gly Gly Thr Lys Glu Met Tyr Val His Thr Tyr Glu Glu Leu Val
 115 120 125
 Ser Leu Ile Leu Lys Leu Lys Asp Ile Ile Cys
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<210> 21

<211> 837

<212> DNA

<213> Staphylococcus aureus

<400> 21

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caagtagata ttacatcaga agaatttatt aatcatattg aaaatgatga agatgtaaag      180
acaagtcagc cagccatagg tgaatttata tctgcttatg aagaactagg aaaagatggc      240
tctgaaatca taagtattca tctttcttca ggattaagtg gtacatataa cactgcttac      300
caagcaagtc aaatggtaga tgctaattgta actggttattg attcaaaatc tatttctttt      360
ggtttagggg atcaaataca acacctagta gagcttgtaa aagaagggtgt ctcaacttct      420
gaaatagtta aaaagttaaa tcatttaaga gaaaacatta aattatttgt agttataggg      480
caattgaatc aattaattaa aggtggcaga attagtaaaa caaaagggtt gatttggaat      540
cttatgaaaa ttaaaccaat tggtagacta gatgatggtc gcttagagct tgtgcacaat      600
gcgagaactc aaaattctag tatccaatac ttgaaaaagg aaattgctga atttatagga      660
gatcatgaaa tcaaattcat tgggtgctgca catgctaacg tcattgaata tgttgataaa      720
ttgaagaaag tttttaatga agcttttcat gtgaataatt acgatataaa tgtaactaca      780
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<210> 22

<211> 279

<212> PRT

<213> Staphylococcus aureus

<400> 22

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 20 25 30
 Ile Glu Gly Ala Ser Tyr Val Asp Gln Val Asp Ile Thr Ser Glu Glu
 35 40 45
 Phe Ile Asn His Ile Glu Asn Asp Glu Asp Val Lys Thr Ser Gln Pro
 50 55 60
 Ala Ile Gly Glu Phe Ile Ser Ala Tyr Glu Glu Leu Gly Lys Asp Gly
 65 70 75 80
 Ser Glu Ile Ile Ser Ile His Leu Ser Ser Gly Leu Ser Gly Thr Tyr
 85 90 95
 Asn Thr Ala Tyr Gln Ala Ser Gln Met Val Asp Ala Asn Val Thr Val
 100 105 110
 Ile Asp Ser Lys Ser Ile Ser Phe Gly Leu Gly Tyr Gln Ile Gln His
 115 120 125
 Leu Val Glu Leu Val Lys Glu Gly Val Ser Thr Ser Glu Ile Val Lys
 130 135 140
 Lys Leu Asn His Leu Arg Glu Asn Ile Lys Leu Phe Val Val Ile Gly
 145 150 155 160
 Gln Leu Asn Gln Leu Ile Lys Gly Gly Arg Ile Ser Lys Thr Lys Gly
 165 170 175
 Leu Ile Gly Asn Leu Met Lys Ile Lys Pro Ile Gly Thr Leu Asp Asp
 180 185 190
 Gly Arg Leu Glu Leu Val His Asn Ala Arg Thr Gln Asn Ser Ser Ile
 195 200 205
 Gln Tyr Leu Lys Lys Glu Ile Ala Glu Phe Ile Gly Asp His Glu Ile
 210 215 220
 Lys Ser Ile Gly Val Ala His Ala Asn Val Ile Glu Tyr Val Asp Lys
 225 230 235 240
 Leu Lys Lys Val Phe Asn Glu Ala Phe His Val Asn Asn Tyr Asp Ile
 245 250 255
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 260 265 270
 Gly Leu Val Val Leu Lys Lys
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<210> 23

<211> 594

<212> DNA

<213> Staphylococcus aureus

<400> 23

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gttgaagggtg aattaaacta caataaaaaa ggtaatgttg ttgaaattac taatgaaggt 120

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aatgtttag gttataatat ttttgaaatt tcaaaagata taacaattga agaaaaaggt    180
catattaaat taactgatga acttgtaa atgtattccaaa agcgtatttc agaagctggt    240
tttgattata aattaaatgc tgatctatca ccgaaatttg tagttggcta cgttgaaact    300
aaagacaaac atcctgatgc agataaatta agtgtactaa atgtaaacgt tggaaatgac    360
acattacaaa ttgtatgtgg cgcgcctaac gttgaagctg gacagaaagt tgttgttgct    420
aaagtaggtg cagtgatgcc tagcggtatg gtaattaaag atgctgaatt acgtgggtgtt    480
gcctcaagcg gtatgatttg ttcaatgaaa gaattgaatt tacctaatgc acctgaagaa    540
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<210> 24

<211> 198

<212> PRT

<213> Staphylococcus aureus

<400> 24

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Met Asn Leu Phe Tyr Asn Pro Lys Tyr Val Gly Asp Val Ala Phe Leu
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20     25     30
Val Val Glu Ile Thr Asn Glu Gly Asn Val Val Gly Tyr Asn Ile Phe
35     40     45
Glu Ile Ser Lys Asp Ile Thr Ile Glu Glu Lys Gly His Ile Lys Leu
50     55     60
Thr Asp Glu Leu Val Asn Val Phe Gln Lys Arg Ile Ser Glu Ala Gly
65     70     75     80
Phe Asp Tyr Lys Leu Asn Ala Asp Leu Ser Pro Lys Phe Val Val Gly
85     90     95
Tyr Val Glu Thr Lys Asp Lys His Pro Asp Ala Asp Lys Leu Ser Val
100    105    110
Leu Asn Val Asn Val Gly Asn Asp Thr Leu Gln Ile Val Cys Gly Ala
115    120    125
Pro Asn Val Glu Ala Gly Gln Lys Val Val Val Ala Lys Val Gly Ala
130    135    140
Val Met Pro Ser Gly Met Val Ile Lys Asp Ala Glu Leu Arg Gly Val
145    150    155    160
Ala Ser Ser Gly Met Ile Cys Ser Met Lys Glu Leu Asn Leu Pro Asn
165    170    175
Ala Pro Glu Glu Lys Gly Ile Met Val Leu Asn Asp Ser Tyr Glu Ile
180    185    190
Gly Gln Ala Phe Phe Glu
195

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<210> 25

<211> 717

<212> DNA

<213> Staphylococcus aureus

<400> 25

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ttgacaagta ttacagatga acacgatgta tatttgaaac atttttatga ttccattgca    180
cctagttttt attttgattt taatcagcct ataagtatat gtgatgtagg cgctggagct    240
ggttttccaa gtattccggt aaaaataatg tttccgcagt taaaagtgac gattgttgat    300
tcattaaata agcgtattca atttttaaac catttagcgt cagaattaca attacaggat    360
gtcagcttta tacacgatag agcagaaaca tttggtaagg gtgtctacag ggagtcttat    420
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ctagttaaaa aagggtggaca gtttgttgca ttaaaatctt caaaagggtga agaagaatta    540
gaagaagcaa aatttgcaat tagtgtgtta ggtggtaatg ttacagaaac acataccttt    600
gaattgccag aagatgctgg agagcgccag atgttcatta ttgataaaaa aagacagacg    660
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<210> 26

<211> 239

<212> PRT

<213> Staphylococcus aureus

<400> 26

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

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115	120	125
Glu Thr Phe Gly Lys Gly Val Tyr Arg Glu Ser Tyr Asp Val Val Thr		
130	135	140
Ala Arg Ala Val Ala Arg Leu Ser Val Leu Ser Glu Leu Cys Leu Pro		
145	150	155
Leu Val Lys Lys Gly Gly Gln Phe Val Ala Leu Lys Ser Ser Lys Gly		
165	170	175
Glu Glu Glu Leu Glu Glu Ala Lys Phe Ala Ile Ser Val Leu Gly Gly		
180	185	190
Asn Val Thr Glu Thr His Thr Phe Glu Leu Pro Glu Asp Ala Gly Glu		
195	200	205
Arg Gln Met Phe Ile Ile Asp Lys Lys Arg Gln Thr Pro Lys Lys Tyr		
210	215	220
Pro Arg Lys Pro Gly Thr Pro Asn Lys Thr Pro Leu Leu Glu Lys		
225	230	235

<210> 27

<211> 2358

<212> DNA

<213> Staphylococcus aureus

<400> 27

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gcggtgagc agcatacacc aatgaaagca catgcagtaa caacgataga caaagcaaca	180
acagataagc aacaagtacc gccacaag gaagcggctc atcattcttg caaagaagcg	240
gcaaccaacg tatcagcatc agcgcaggga acagctgatg atacaaacag caaagtaaca	300
tccaacgcac catctaaca accatctaca gtagtttcaa caaaagtaaa cgaaacacgc	360
gacgtagata cacaacaagc ctcaacacaa aaaccaactc acacagcaac gttcaaatta	420
tcaaatgcta aaacagcatc actttcacca cgaatgtttg ctgctaatgc accacaaaca	480
acaacacata aaatattaca tacaaatgat atccatggcc gactagccga agaaaaaggg	540
cgtgtcatcg gtatggctaa attaaaaaca gtaaaagaac aagaaaagcc tgatttaatg	600
ttagacgcag gagacgcctt ccaaggttta ccactttcaa accagtctaa aggtgaagaa	660
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gactttggat acgatcagtt gaaaaagtta gaggggtatgt tagactttccc gatgctaagt	780
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ggtattcgtt atggaattat tgggtgaacg acaccagaaa caaagacgaa aacaagacct	900
gaaggcatta aaggcgttga atttagagat ccattacaaa gtgtgacagc ggaaatgatg	960
cgtatttata aagacgtaga tacatttggt gttatatcac atttaggaat tgatccttca	1020
acacaagaaa catggcgtgg tgattactta gtgaaacaat taagtcaaaa tccacaattg	1080

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tataacaatg atgcattggc acaaacaggt acagcacttg cgaatatcgg taagattaca 1200
tttaattatc gcaatggaga ggtatcgaat attaaaccgt cattgattaa tggttaaagac 1260
gttgaaaatg taacaccgaa caaagcatta gctgaacaaa ttaatcaagc tgatcaaaca 1320
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aaaccagcag taagtgaaca accagctaaa ggacaacaag gtagcaaagg tagtaagtct 2040
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agttcaagcc cagaagcgat gtttgtatta ttagcaggta taggtttaat cgcgactgta 2340
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<210> 28

<211> 786

<212> PRT

<213> Staphylococcus aureus

<400> 28

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20          25          30
Met Gly Leu Trp Gln Val Ser Asn Ala Ala Glu Gln His Thr Pro Met
35          40          45
Lys Ala His Ala Val Thr Thr Ile Asp Lys Ala Thr Thr Asp Lys Gln
50          55          60

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

Gln Ile Asn Gln Ala Asp Gln Thr Phe Arg Ala Gln Thr Ala Glu Val
 435 440 445
 Ile Ile Pro Asn Asn Thr Ile Asp Phe Lys Gly Glu Arg Asp Asp Val
 450 455 460
 Arg Thr Arg Glu Thr Asn Leu Gly Asn Ala Ile Ala Asp Ala Met Glu
 465 470 475 480
 Ala Tyr Gly Val Lys Asn Phe Ser Lys Lys Thr Asp Phe Ala Val Thr
 485 490 495
 Asn Gly Gly Gly Ile Arg Ala Ser Ile Ala Lys Gly Lys Val Thr Arg
 500 505 510
 Tyr Asp Leu Ile Ser Val Leu Pro Phe Gly Asn Thr Ile Ala Gln Ile
 515 520 525
 Asp Val Lys Gly Ser Asp Val Trp Thr Ala Phe Glu His Ser Leu Gly
 530 535 540
 Ala Pro Thr Thr Gln Lys Asp Gly Lys Thr Val Leu Thr Ala Asn Gly
 545 550 555 560
 Gly Leu Leu His Ile Ser Asp Ser Ile Arg Val Tyr Tyr Asp Ile Asn
 565 570 575
 Lys Pro Ser Gly Lys Arg Ile Asn Ala Ile Gln Ile Leu Asn Lys Glu
 580 585 590
 Thr Gly Lys Phe Glu Asn Ile Asp Leu Lys Arg Val Tyr His Val Thr
 595 600 605
 Met Asn Asp Phe Thr Ala Ser Gly Gly Asp Gly Tyr Ser Met Phe Gly
 610 615 620
 Gly Pro Arg Glu Glu Gly Ile Ser Leu Asp Gln Val Leu Ala Ser Tyr
 625 630 635 640
 Leu Lys Thr Ala Asn Leu Ala Lys Tyr Asp Thr Thr Glu Pro Gln Arg
 645 650 655
 Met Leu Leu Gly Lys Pro Ala Val Ser Glu Gln Pro Ala Lys Gly Gln
 660 665 670
 Gln Gly Ser Lys Gly Ser Lys Ser Gly Lys Asp Thr Gln Pro Ile Gly
 675 680 685
 Asp Asp Lys Val Met Asp Pro Ala Lys Lys Pro Ala Pro Gly Lys Val
 690 695 700
 Val Leu Leu Leu Ala His Arg Gly Thr Val Ser Ser Gly Thr Glu Gly
 705 710 715 720
 Ser Gly Arg Thr Ile Glu Gly Ala Thr Val Ser Ser Lys Ser Gly Lys
 725 730 735
 Gln Leu Ala Arg Met Ser Val Pro Lys Gly Ser Ala His Glu Lys Gln
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 785

<210> 29

<211> 609

<212> DNA

<213> Staphylococcus aureus

<400> 29

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ctattcgttg taattcagaa gaagcaaggat atgccatctg caaagaaaag aatgaatgaa      540
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<210> 30

<211> 202

<212> PRT

<213> Staphylococcus aureus

<400> 30

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      20      25      30
Asn Gly Val Phe Ser Lys Asp Lys Val Asp Tyr Gly Ser Asp Val Leu
      35      40      45
Val Gln Thr Phe Leu Lys Ala His Pro Pro Gly Pro Ser Lys Arg Ile
      50      55      60
Ala Asp Val Gly Cys Gly Tyr Gly Pro Ile Gly Leu Met Ile Ala Lys
      65      70      75      80
Val Ser Pro His His Ser Ile Thr Met Leu Asp Val Asn His Arg Ala
      85      90      95
Leu Ala Leu Val Glu Lys Asn Lys Lys Leu Asn Gly Ile Asp Asn Val
      100      105      110
Ile Val Lys Glu Ser Asp Ala Leu Ser Ala Val Glu Asp Lys Ser Phe
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115 120 125
 Asp Phe Ile Leu Thr Asn Pro Pro Ile Arg Ala Gly Lys Glu Thr Val
 130 135 140
 His Arg Ile Phe Glu Gln Ala Leu His Arg Leu Asp Ser Asn Gly Glu
 145 150 155 160
 Leu Phe Val Val Ile Arg Arg Lys Gln Gly Met Pro Ser Ala Lys Lys
 165 170 175
 Arg Met Asn Glu Leu Phe Gly Asn Val Glu Val Val Asn Lys Asp Lys
 180 185 190
 Gly Tyr Tyr Ile Leu Arg Ser Ile Lys Ala
 195 200

<210> 31

<211> 750

<212> DNA

<213> Staphylococcus aureus

<400> 31

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gatgaaaatg taatgaatga aacggtaaaa cttgccaaag cacataatgt tgcagtaggt      180
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gcttctgaag tgtttgctga tagacgatac gaagatgatg ggcagctcgt tagtagaaaa      540
gaaagtgatg ctgtgattac tgatactgac gaagcactta agcagggttt aaagatgggtg      600
aaggaaaata aagttatttc aaaaaacaat aaggaagtaa cgttacaagc agatacaatt      660
tgtgtgcatg gtgatggaga acatgcatta ttatttgttt cgaaaattag agaaatttta      720
atgaaagaag gcattgatat tcaatcctta                                     750
  
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<210> 32

<211> 250

<212> PRT

<213> Staphylococcus aureus

<400> 32

Met Arg Val Asp Leu Asn Cys Asp Leu Gly Glu Ala Phe Gly Asn Tyr
 1 5 10 15

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

<210> 33

<211> 720

<212> DNA

<213> Staphylococcus aureus

<400> 33

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atggctcaaa tttctaaata taaacgtgta gttttgaaac taagtgggtga agcggttagct      60
ggagaaaaag gatttggcat aaatccagta attattaaaa gtgttgctga gcaagtggct      120
gaagttgcta aaatggactg tgaaatcgca gtaatcgttg gtggcggaaa catttggaga      180
ggtaaaacag gtagtgactt aggtatggac cgtggaactg ctgattacat gggtagctt      240
gcaactgtaa tgaatgcctt agcattacaa gatagtttag aacaattgga ttgtgataca      300
cgagtattaa catctattga aatgaagcaa gtggctgaac cttatattcg tcgtcgtgca      360
  
```

attagacact tagaaaagaa acgcgtagtt atttttgctg caggtattgg aaaccatac 420
 ttctctacag atactacagc ggcattacgt gctgcagaag ttgaagcaga tgttatttta 480
 atgggcaaaa ataatgtaga tgggtgtatat tctgcagatc ctaaagtaaa caaagatgcg 540
 gtaaaatatg aacatttaac gcatattcaa atgcttcaag aaggtttaca agtaatggat 600
 tcaacagcat cctcattctg tatggataat aacattccgt taactgtttt ctctattatg 660
 gaagaaggaa atattaaacg tgctgttatg ggtgaaaaga taggtacggt aattacaaaa 720

<210> 34

<211> 240

<212> PRT

<213> Staphylococcus aureus

<400> 34

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

<210> 35

<211> 33

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 35

atatatctgc agtgataaat tgccaagcgt gac 33

<210> 36

<211> 33

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 36

atatatgagc tctcttgtagc agatttaggt ggc 33

<210> 37

<211> 33

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 37

atatatctgc agcaagtatt aggtgaagaa ggg 33

<210> 38

<211> 33

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 38
atatatgagc tcacggattg atcccaataa tgc 33

<210> 39

<211> 36

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 39
atatatctgc aggggattca aaaacaattt aacatc 36

<210> 40

<211> 36

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 40
atatatgagc tcaaggctat taacttgctt atgatc 36

<210> 41

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 41
tggtgtgtac attgactgta c 21

<210> 42

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 42

gctgttagtt cttgtgttg g

21

<210> 43

<211> 33

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 43

atatactgc agaggtattc accatgttac tgc

33

<210> 44

<211> 33

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 44

atatacgagc tcaattgata cacttgcca tcg

33

<210> 45

<211> 35

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 45

atatactgc aggggacatt tttaatcatg catgc

35

<210> 46

<211> 36

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 46

atatatgagc tcgcagtcac aataatagct aaagac

36

<210> 47

<211> 33

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 47

atatatctgc agtggttaac gatacacatg tcc

33

<210> 48

<211> 33

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 48

atatatgagc tccttcaaac gcttagctaa agc

33

<210> 49

<211> 33

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 49

atatatctgc agacaagtgt atggctcggt ttg

33

<210> 50

<211> 33

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 50

atatatgagc tcatttgaac gttgctgtgt gag

33

<210> 51

<211> 34

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 51

atatatctgc agagagtaca tactttcgct ttag

34

<210> 52

<211> 34

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 52

atatatgagc tccctaattcc tagatattca tcac

34

<210> 53

<211> 33

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 53

atatatctgc agttgtacag gtaacacatg tcg

33

<210> 54

<211> 32

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 54

atatatgagc tcctgctttc aaatctgctc ag

32

<210> 55

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 55

ctattgaagg agcttcatac g

21

<210> 56

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 56

tacaagctct actaggtggt g

21

<210> 57

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 57

cctaaatag taggagatgt c

21

<210> 58

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 58

ttatctgcat caggatgtt g

21

<210> 59

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 59

ctgtagaatg gtttagcagaa c

21

<210> 60

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 60

caatcgtcac ttttaactgc g

21

<210> 61

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 61
acaagtgtat ggctcgtttt g 21

<210> 62

<211> 21

<212> DNA

<213> Artificial

<220>

<223> oligonucleotide Primer

<400> 62
atttgaacgt tgctgtgtga g 21

<210> 63

<211> 21

<212> DNA

<213> Artificial

<220>

<223> oligonucleotide Primer

<400> 63
attacgatga agatccaagt g 21

<210> 64

<211> 21

<212> DNA

<213> Artificial

<220>

<223> oligonucleotide Primer

<400> 64
ttttttcaac taaggctagc g 21

<210> 65

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 65

gaattgtgat ttaggcgaag c

21

<210> 66

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 66

atgaatgcga caaaaccctt g

21

<210> 67

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 67

ttgaaactaa gtggtgaagc g

21

<210> 68

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 68

gcagcaaaaa taactacgcg t

21

<210> 69

<211> 731

<212> DNA

<213> Artificial

<220>

<223> Nucleotide sequence of *S. aureus* coding region cloned for expression in *E. coli*

<400> 69

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atgggattaa agtatgaaca tattgctaag caacttaatg cgtttataca tcaatctaatt      60
ttcaaaccgc gtgataaatt gccaaagcgtg acgcaattaa aagaacgtta tcaagtaagt      120
aagagtacta tcattaaagc attaggctta ttggaacaag atggtttgat ctatcaagca      180
caaggcagtg gtatttatgt gagaaatatt gctgatgcca atcgtatcaa cgtctttaag      240
actaatgggt tctctaaaag tttagggtgaa caccgaatga caagtaaggt acttggtttt      300
aaggagattg caacgccacc taaatctgta caagatgagc tccaattaaa tgcagatgat      360
accgtctact atttagagcg attaagattc gtggacgatg atgttttatg tatcgaatat      420
tcttattatc ataaagaaat cgtgaaatat ttaaattgatg atattgctaa gggctctatc      480
ttcgactttt agaatcaaac atgaaacttc gtattgggtt ttcagatatt ttctttaatg      540
tagatcaact cacttcaagt gaagcttcat tactacaatt gtctacaggt gaaccatggt      600
tacgttacca ccagactttt tatacaatga ctggcaaacc ctttgattca tctgacatcg      660
tatttcatta tcgtcatgca cagttttata ttctagtaa aaagagatct catcaccatc      720
accatcacta a                                     731

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<210> 70

<211> 243

<212> PRT

<213> Artificial

<220>

<223> Amino acid sequence encoded by *S. aureus* coding region cloned for expression in *E. coli*

<400> 70

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

```

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Val Leu Val Phe Lys Glu Ile Ala Thr Pro Pro Lys Ser Val Gln Asp
 100 105 110
 Glu Leu Gln Leu Asn Ala Asp Asp Thr Val Tyr Tyr Leu Glu Arg Leu
 115 120 125
 Arg Phe Val Asp Asp Asp Val Leu Cys Ile Glu Tyr Ser Tyr Tyr His
 130 135 140
 Lys Glu Ile Val Lys Tyr Leu Asn Asp Asp Ile Ala Lys Gly Ser Ile
 145 150 155 160
 Phe Asp Tyr Leu Glu Ser Asn Met Lys Leu Arg Ile Gly Phe Ser Asp
 165 170 175
 Ile Phe Phe Asn Val Asp Gln Leu Thr Ser Ser Glu Ala Ser Leu Leu
 180 185 190
 Gln Leu Ser Thr Gly Glu Pro Cys Leu Arg Tyr His Gln Thr Phe Tyr
 195 200 205
 Thr Met Thr Gly Lys Pro Phe Asp Ser Ser Asp Ile Val Phe His Tyr
 210 215 220
 Arg His Ala Gln Phe Tyr Ile Pro Ser Lys Lys Arg Ser His His His
 225 230 235 240
 His His His

<210> 71

<211> 855

<212> DNA

<213> Artificial

<220>

<223> Nucleotide sequence of *S. aureus* coding region cloned for expression in *E. coli*

<400> 71

atgctggcac tttatggatt tgcccaagga cttattcaag aagcaggaat tagaattaaa	60
caattgatgg agcaaaattt aacaattgaa acaaagtcaa atccgaatga ccttggtaca	120
aatgtagata aagcaacaga agatttcatt tttgatacaa ttttagaaac atatcccaat	180
catcaagtat taggtgaaga agggcatggt catgacatcg atacttccaa aggtacggta	240
tggattgttg acccaataga cggtagattg aattttgttc atcaacaaga aaatttcgca	300
atttcaattg gtatttatat cgatggtaaa cttatgcag gttttgtata tgatgttatg	360
gctgatgtct tatatcatgc taaagtaggg gaaggtgcat atcgtggtag ccaacccttg	420
aaaccattga atgattctaa tctaagacaa agcattattg ggatcaatcc gaactgggta	480
actaaaccaa ttttaggaga aatcttttaa gaaattgtta atgattctag aagtgaagg	540
gcatatggta gtgcagcgct tgaaatcggt tcagttgcta caggtaattt agaagcatat	600
atgacgcaa gacttcaacc atgggatttt gctggcggat tggttatttt atatgaagta	660

```

aatggacaag cttccaattt actaggagga ccattaacaa ttagtggtcc aaattcaatc      720
ttagttggaa atcgtggtct ccatcaagaa attagcaatg attatttaga gccccaccat      780
gatgcgttaa tacaattaca tgaacaacga tttaaagaa aatcaaaaag atctcatcac      840
catcaccatc actaa                                                         855

```

<210> 72

<211> 284

<212> PRT

<213> Artificial

<220>

<223> Amino acid sequence encoded by S. aureus coding region cloned for expression in E. coli

<400> 72

```

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

```

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<210>	73
<211>	567
<212>	DNA
<213>	Artificial

<223> Nucleotide sequence of S. aureus coding region cloned for expression in E. coli

<210>	74
<211>	188
<212>	PRT
<213>	Artificial

<223> Amino acid sequence encoded by S. aureus coding region cloned for expression in E. coli

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

<210> 75

<211> 996

<212> DNA

<213> Artificial

<220>

<223> Nucleotide sequence of *S. aureus* coding region cloned for expression in *E. coli*

<400> 75

atgggaataa ataatcatga attactaggt attcaccatg ttactgcaat gacagatgat	60
gcagaacgta attataaatt ttttacagaa gtactaggca tgcgtttagt taaaaagaca	120
gtcaatcaag atgatattta tacgtatcat actttttttg cagatgatgt aggttcggca	180
ggtacagaca tgacgttctt tgattttcca aatattacaa aagggcaggc aggaacaaat	240
tccattacaa gaccgtcttt tagagtgcct aacgatgacg cattaacata ttatgaacag	300
cgctttgatg agtttggtgt taaacacgaa ggtattcaag aattatttgg taaaaagt	360
ttgccatttg aagaagtcga tggccaagt tatcaattaa tttcagatga gttaaagaa	420
ggggtagcac ctggtgtacc ttggaagaat ggaccggttc cagtagataa agcgatttat	480
ggattaggcc ccattgaaat taaagtaagt tattttgacg actttaaaaa tattttagag	540
actgtttacg gtatgacaac tattgcgcat gaagataatg tcgcattact tgaagttggc	600
gaaggaggca atggtggcca ggtaatctta ataaaagatg ataaagggcc agcagcacgt	660

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```

caaggttatg gtgaggtaca tcatgtgtca tttcgtgtga aagatcatga tgcaatagaa    720
gcgtgggcaa cgaaatataa agaggtaggt attaataact caggcatcgt taatcgtttc    780
tattttgaag cattatatgc acgtgtgggg catattttta tagaaatttc aacagatgga    840
ccaggattta tggaagatga accttatgaa acattaggcg aagggttatc cttaccacca    900
tttttagaaa ataaaagaga atatattgaa tcggaagtta gaccttttaa tacgaagcgt    960
caacatggta gatctcatca ccatcaccat cactaa                                996

```

<210> 76

<211> 331

<212> PRT

<213> Artificial

<220>

<223> Amino acid sequence encoded by S. aureus coding region cloned for expression in E. coli

<400> 76

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

```

Ile Leu Ile Lys Asp Asp Lys Gly Pro Ala Ala Arg Gln Gly Tyr Gly
 210 215 220
 Glu Val His His Val Ser Phe Arg Val Lys Asp His Asp Ala Ile Glu
 225 230 235 240
 Ala Trp Ala Thr Lys Tyr Lys Glu Val Gly Ile Asn Asn Ser Gly Ile
 245 250 255
 Val Asn Arg Phe Tyr Phe Glu Ala Leu Tyr Ala Arg Val Gly His Ile
 260 265 270
 Leu Ile Glu Ile Ser Thr Asp Gly Pro Gly Phe Met Glu Asp Glu Pro
 275 280 285
 Tyr Glu Thr Leu Gly Glu Gly Leu Ser Leu Pro Pro Phe Leu Glu Asn
 290 295 300
 Lys Arg Glu Tyr Ile Glu Ser Glu Val Arg Pro Phe Asn Thr Lys Arg
 305 310 315 320
 Gln His Gly Arg Ser His His His His His His
 325 330

<210> 77

<211> 1113

<212> DNA

<213> Artificial

<220>

<223> Nucleotide sequence of *S. aureus* coding region cloned for expression in *E. coli*

<400> 77

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atgggacgta tcttaaaaga gtccattatt gtggcatttg cctttgttgg tgttgctggt      60
gggtgccggct ttgctactgg tcaagaaatt ttccagtttt tcacaagtca tggcgcatat      120
agcatttcag gcattattgt aacaggacta ttgattactt taggtggaat gggtgtcatg      180
catacaggtc atcatctaaa gtccagaaat cattctgatt caattaacta tttcttatac      240
ccctctattg caagagggtt tgatattatt ttaacaatgt ttatgttgtc tttagctatt      300
attatgactg caggtggtgc gtcaaccatt catcaaagtt tcaacttacc gtattggctg      360
agcgcactca tattagtcgc ctttatttta gcaacactgt ttctaaaatt cgatcgttta      420
attgctgtgc ttggcgggtg taccccatTT ttaattgcga ttgtcattat gattgcggtc      480
tactatttca caacaagtca tcttgatttt actgccgcta ataatgatgc tcagattcat      540
aagcagaaat cattatcacc tggatggtgg tttgatgcga ttaactatgc aagcttgcaa      600
attgctgctg ccttcagctt cttatcagtg atgggtagta aagttaaata tcgtgactca      660
acgttatacg ggggcttgat tggcggttta atcattacat ttttactcat gatgattaat      720
ctaggtttaa tttctcaatt cgataaaatt aaacacgtag atctacctac attaaaatta      780
gcgacacaaa tgtctccgtc aattggtatt attatgtctg tcattatgat acttgtcatc      840

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tacaatactg ttgttggtt aatgtatgca tttgcgtcac gtttcagcgt tccattcagc 900
 agacgttact tcatcattat tattacaatg gctgtcatca cttatattag tacattttatc 960
 ggttttcattt cattaattgg aaaagtattc cctattatgg gattgttcgg tttcatctta 1020
 ctcatacctg tactctataa aggtttaatt aagcgtatta ccggcaaadc tcatatcgat 1080
 ggatccagat ctcatcacca tcaccatcac taa 1113

<210> 78

<211> 370

<212> PRT

<213> Artificial

<220>

<223> Amino acid sequence encoded by S. aureus coding region cloned for expression in E. coli

<400> 78

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

Gly Leu Ile Gly Gly Leu Ile Ile Thr Phe Leu Leu Met Met Ile Asn
 225 230 235 240
 Leu Gly Leu Ile Ser Gln Phe Asp Lys Ile Lys His Val Asp Leu Pro
 245 250 255
 Thr Leu Lys Leu Ala Thr Gln Met Ser Pro Ser Ile Gly Ile Ile Met
 260 265 270
 Ser Val Ile Met Ile Leu Val Ile Tyr Asn Thr Val Val Gly Leu Met
 275 280 285
 Tyr Ala Phe Ala Ser Arg Phe Ser Val Pro Phe Ser Arg Arg Tyr Phe
 290 295 300
 Ile Ile Ile Ile Thr Met Ala Val Ile Thr Tyr Ile Ser Thr Phe Ile
 305 310 315 320
 Gly Phe Ile Ser Leu Ile Gly Lys Val Phe Pro Ile Met Gly Leu Phe
 325 330 335
 Gly Phe Ile Leu Leu Ile Pro Val Leu Tyr Lys Gly Leu Ile Lys Arg
 340 345 350
 Ile Thr Gly Lys Ser His Ile Asp Gly Phe Arg Ser His His His His
 355 360 365
 His His
 370

<210> 79

<211> 801

<212> DNA

<213> Artificial

<220>

<223> Nucleotide sequence of *S. aureus* coding region cloned for expression in *E. coli*

<400> 79

atgggattaa tcgatacaca tgtccattta aatgatgagc aatac gatga tgatttgagt	60
gaagtgatta cacgtgctag agaagcaggt gttgatcgta tgtttgtagt tggttttaac	120
aaatcgacaa ttgaacgcgc gatgaaatta atc gatgagt atgatttttt atatggcatt	180
atcggttggc atccagttga cgcaattgat ttacagaag aacacttgga atggattgaa	240
tctttagctc agcatccaaa agtgattggt attggtgaaa tgggattaga ttatcactgg	300
gataaatctc ctgcagatgt tcaaaaggaa gtttttagaa agcaaattgc ttagctaag	360
cgtttgaagt taccaattat cattcataac cgtgaagcaa ctcaagactg tatcgatatc	420
ttattggagg agcatgctga agaggtaggc gggattatgc atagcttttag tggttctcca	480
gaaattgcag atattgtaac taataagctg aatttttata tttcattagg tggacctgtg	540
acatttaaaa atgctaaaca gcctaaagaa gttgctaagc atgtgtcaat ggagcgtttg	600
ctagttgaaa ccgatgcacc gtatctttcg ccacatccgt atagagggaa gcgaaatgaa	660

ccggcgagag taacttttagt agctgaacaa attgctgaat taaaaggctt atcttatgaa 720
 gaagtgtgcg aacaaacaac taaaaatgca gagaaattgt ttaatttaaa ttcaagatct 780
 catcaccatc accatcacta a 801

<210> 80

<211> 266

<212> PRT

<213> Artificial

<220>

<223> Amino acid sequence encoded by *S. aureus* coding region cloned for
 expression in *E. coli*

<400> 80

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

Glu Val Cys Glu Gln Thr Thr Lys Asn Ala Glu Lys Leu Phe Asn Leu
 245 250 255

Asn Ser Arg Ser His His His His His His
 260 265

<210> 81

<211> 2150

<212> DNA

<213> Artificial

<220>

<223> Nucleotide sequence of S. aureus coding region cloned for expression in E. coli

<400> 81

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cttaaaacaa gtgtatggct cgttttgctt tttagtgtaa tgggattatg gcaagtctcg      120
aacgcggctg agcagcatac accaatgaaa gcacatgcag taacaacgat agacaaagca      180
acaacagata agcaacaagt accgccaaca aaggaagcgg ctcatcattc tggcaaagaa      240
gcggcaacca acgtatcagc atcagcgcag ggaacagctg atgatacaaa cagcaaagta      300
acatccaacg caccatctaa caaacatct acagtagttt caacaaaagt aaacgaaaca      360
cgcgacgtag atacacaaca agcctcaaca caaaaaccaa ctcacacagc aacgttcaaa      420
ttatcaaatg ctaaaacagc atcactttca ccacgaatgt ttgctgctaa tgcaccacaa      480
acaacaacac ataaaatatt acatacaaat gatatccatg gccgactagc cgaagaaaaa      540
gggcgtgtca tcggtatggc taaattaaaa acagtaaaag aacaagaaaa gcctgattta      600
atgttagacg caggagacgc cttccaaggt ttaccacttt caaaccagtc taaaggtgaa      660
gaaatggcta aagcaatgaa tgcagtaggt tatgatgcta tggcagtcgg taaccatgaa      720
tttgactttg gatacgatca gttgaaaaag ttagagggta tgtagactt cccgatgcta      780
agtactaacg tttataaaga tggaaaacgc gcgtttaagc cttcaacgat tgtaacaaaa      840
aatggatttc gttatggaat tattggtgta acgacaccag aaacaaagac gaaaacaaga      900
cctgaaggca ttaaaggcgt tgaatttaga gatccattac aaagtgtgac agcggaaatg      960
atgcgtattt ataaagacgt agatacattt gttgttatat cacatttagg aattgatcct     1020
tcaacacaag aaacatggcg tgggtgattac ttagtgaaac aattaagtca aaatccacaa     1080
ttgaagaaac gtattacagt tattgatggc cattcacata cagtacttca aaatgggtcaa     1140
atttataaca atgatgcatt ggcacaaaca ggtacagcac ttgcgaatat cggtaaagatt     1200
acatttaatt atcgaatgg agaggtatcg aatattaaac cgtcattgat taatgttaaa     1260
gacgttgaaa atgtaacacc gaacaaagca ttagctgaac aaattaatca agctgatcaa     1320
acatttagag cacaaactgc agaggttaatt attccaaaca ataccattga tttcaaagga     1380
gaaagagatg acgttagaac gcgtgaaaca aatttaggaa acgcgattgc agatgctatg     1440

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gaagcgtatg gcgtaagaa tttctctaaa aagactgact ttgccgtgac aaatggtgga 1500
ggtattcgtg cctctatcgc aaaaggtaag gtgacacgct atgatttaat ctgagtatta 1560
ccatttgga atacgattgc gcaaattgat gtaaaagggt cagacgtctg gacggctttc 1620
gaacatagtt taggcgcacc aacaacacaa aaggacggta agacagtgtt aacagcgaat 1680
ggcgggttac tacatatctc tgattcaatc cgtgtttact atgatataaa taaaccgtct 1740
ggcaaacgaa ttaatgctat tcaaatttta aataaagaga caggtaagtt tgaaaatatt 1800
gatttaaaac gtgtatatca cgtaacgatg aatgacttca cagcatcagg tgggacggat 1860
atagtatgtt cggtggtcct agagaagaag gtatttcatt agatcaagta ctagcaagtt 1920
atttaaaaac agctaactta gctaagtatg atacgacaga accacaacgt atgttattag 1980
gtaaacgagc agtaagtga caaccagcta aaggacaaca aggtagcaaa ggtagtaagt 2040
ctggtaaaga tacacaacca attggtgacg acaaagtgat ggatccagcg aaaaaaccag 2100
ctccaggtaa agttgtattg ttgagatctc atcaccatca ccatacctaa 2150

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<210> 82

<211> 716

<212> PRT

<213> Artificial

<220>

<223> Amino acid sequence encoded by *S. aureus* coding region cloned for expression in *E. coli*

<400> 82

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

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

Arg Tyr Asp Leu Ile Ser Val Leu Pro Phe Gly Asn Thr Ile Ala Gln
 515 520 525
 Ile Asp Val Lys Gly Ser Asp Val Trp Thr Ala Phe Glu His Ser Leu
 530 535 540
 Gly Ala Pro Thr Thr Gln Lys Asp Gly Lys Thr Val Leu Thr Ala Asn
 545 550 555 560
 Gly Gly Leu Leu His Ile Ser Asp Ser Ile Arg Val Tyr Tyr Asp Ile
 565 570 575
 Asn Lys Pro Ser Gly Lys Arg Ile Asn Ala Ile Gln Ile Leu Asn Lys
 580 585 590
 Glu Thr Gly Lys Phe Glu Asn Ile Asp Leu Lys Arg Val Tyr His Val
 595 600 605
 Thr Met Asn Asp Phe Thr Ala Ser Gly Gly Asp Gly Tyr Ser Met Phe
 610 615 620
 Gly Gly Pro Arg Glu Glu Gly Ile Ser Leu Asp Gln Val Leu Ala Ser
 625 630 635 640
 Tyr Leu Lys Thr Ala Asn Leu Ala Lys Tyr Asp Thr Thr Glu Pro Gln
 645 650 655
 Arg Met Leu Leu Gly Lys Pro Ala Val Ser Glu Gln Pro Ala Lys Gly
 660 665 670
 Gln Gln Gly Ser Lys Gly Ser Lys Ser Gly Lys Asp Thr Gln Pro Ile
 675 680 685
 Gly Asp Asp Lys Val Met Asp Pro Ala Lys Lys Pro Ala Pro Gly Lys
 690 695 700
 Val Val Leu Leu Arg Ser His His His His His His
 705 710 715

<210> 83

<211> 1509

<212> DNA

<213> Artificial

<220>

<223> Nucleotide sequence of *S. aureus* coding region cloned for expression in *E. coli*

<400> 83

atgggacgat ttacattttc aaacgattta ggaacgttat ttactattat tttagccatt 60
 ggattcatca ttaatttagt attggctttt attattatct ttttagaaag aaataggcgt 120
 acagcgagtt caactgggc atggctatct gtactttttg tcttaccatt gattggtttt 180
 attcttttact tgtttttttg tagaaccgtt tcggcacgca aattgaataa aaacaatggt 240
 aacgtgttaa cggatttcga tggactttta aaacaacaaa tagaaagctt tgataaaggt 300
 aattatggta ctgataacaa acaagttcaa aaacatcatg atttagtacg tatgcttttg 360
 atggatcaag atgggtttttt aactgaaaat aataaagttg atcatttcat tgatggaaat 420

gatttatatg atcaagtttt aaaagatatt aaaaatgcaa aagaatatat ccatttagag 480
 tactatactt tcgctttaga tggtttaggt aaaagaattt tacatgcttt agaagaaaaa 540
 ttgaaacaag gtctagaagt aaaaatatta tatgatgatg ttggatctaa aaatgttaag 600
 atggcaaatt ttgatcattt taaatcgta ggtggagaag ttgaagcatt ttttgcttca 660
 aaattaccgt tattgaattt cagaatgaat aatagaaatc atagaaaaat catcgtaatc 720
 gatggtcaac taggttatgt cggaggattt aacattggtg atgaatatct aggattagga 780
 aaattaggat attggagaga tacgcattta cgtatacaag gggatgcggt tgatgactg 840
 cagttgcat ttattttaga ctggaattcg caagcgcacc gtccacaatt tgaatatgat 900
 gttaagtatt tccctaaaaa gaacggacca ttgggcaatt caccaattca aatagctgca 960
 agtggcccg ctagtgactg gcatcaaatt gaatacgggt atacaaaaat gattatgagt 1020
 gcaaagaaat ctgtatat tacaatcacca tatttcattc cggataattc atatataaat 1080
 gccattaaaa ttgctgctaa atcaggtgta gatgtacatt taatgattcc atgtaagcca 1140
 gatcatccat tagtatattg ggcgacattt tcaaatgcct ctgacttatt atcaagtgggt 1200
 gttaaaattt atacgtatga aaatggattt atacattcta aaatgtgctt aattgatgat 1260
 gaaatcgtat cagtgggcac agcaaatatg gactttagaa gttttgaatt aaattttgaa 1320
 gtaaatgcct ttgtatatga tgaaaatctt gctaaagatt taagggtggc ttatgaacat 1380
 gatattacaa aatcaaaaca actaaccaaa gaatcatatg ccaatagacc gctgtctgtt 1440
 aaattcaaag aatcggttagc aaaattagtt tcgccaattt taagatctca tcaccatcac 1500
 catcactaa 1509

<210> 84

<211> 502

<212> PRT

<213> Artificial

<220>

<223> Amino acid sequence encoded by S. aureus coding region cloned for expression in E. coli

<400> 84

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

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

Arg Ser Phe Glu Leu Asn Phe Glu Val Asn Ala Phe Val Tyr Asp Glu
 435 440 445
 Asn Leu Ala Lys Asp Leu Arg Val Ala Tyr Glu His Asp Ile Thr Lys
 450 455 460
 Ser Lys Gln Leu Thr Lys Glu Ser Tyr Ala Asn Arg Pro Leu Ser Val
 465 470 475 480
 Lys Phe Lys Glu Ser Leu Ala Lys Leu Val Ser Pro Ile Leu Arg Ser
 485 490 495
 His His His His His His
 500

<210> 85

<211> 447

<212> DNA

<213> Artificial

<220>

<223> Nucleotide sequence of S. aureus coding region cloned for expression in E. coli

<400> 85
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 attgcaaaag aggttatgcc aaatcatcaa tttgaatcaa gaggtatatt cgctgtgaac 120
 aatcaaggtg tttcgaatta tgttgaagac ttagttgaag aacatcattt agctgaaacg 180
 accttatcgc aacaatttac tgaagcagat ttgaaagcag atattatttt gacgatgtcg 240
 tattcgcaca aagaattaat agaggcacac tttggtttgc aaaatcatgt tttcacattg 300
 catgaatatg taaaagaagc aggagaagtt atagatccat acggtggaac aaaagaaatg 360
 tatgtacata cctatgaaga acttgtaagt ttaattttta aattaaaaga tattattttgc 420
 agatctcatc accatcacca tcactaa 447

<210> 86

<211> 148

<212> PRT

<213> Artificial

<220>

<223> Amino acid sequence encoded by S. aureus coding region cloned for expression in E. coli

<400> 86

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

<210> 87

<211> 744

<212> DNA

<213> Staphylococcus aureus

<400> 87

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 ggagaaaaag gatttggcat aaatccagta attattaaaa gtgttgctga gcaagtggct 120
 gaagttgcta aaatggactg tgaaatcgca gtaatcggtg gtggcggaag catttgagaga 180
 ggtaaaacag gtagtgactt aggtatggac cgtggaactg ctgattacat gggtagctt 240
 gcaactgtaa tgaatgcctt agcattacaa gatagtttag aacaattgga ttgtgataca 300
 cgagtattaa catctattga aatgaagcaa gtggctgaac cttatattcg tcgtcgtgca 360
 attagacact tagaaaagaa acgcgtagtt atttttgctg caggtattgg aaaccatac 420
 ttctctacag atactacagc ggcattacgt gctgcagaag ttgaagcaga tgttatttta 480
 atgggcaaaa ataatgtaga tgggtgtatat tctgcagatc ctaaagtaaa caaagatgcg 540
 gtaaaatatg aacatttaac gcatattcaa atgcttcaag aaggtttaca agtaatggat 600
 tcaacagcat cctcattctg tatggataat aacattccgt taactgtttt ctctattatg 660
 gaagaaggaa atattaaacg tgctgttatg ggtgaaaaga taggtacggt aattacaaaa 720
 agatctcatc accatcacca tcac 744

<210> 88

<211> 248

<212> PRT

<213> Staphylococcus aureus

<400> 88

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Met Ala Gln Ile Ser Lys Tyr Lys Arg Val Val Leu Lys Leu Ser Gly
1      5      10      15
Glu Ala Leu Ala Gly Glu Lys Gly Phe Gly Ile Asn Pro Val Ile Ile
20     25     30
Lys Ser Val Ala Glu Gln Val Ala Glu Val Ala Lys Met Asp Cys Glu
35     40     45
Ile Ala Val Ile Val Gly Gly Gly Asn Ile Trp Arg Gly Lys Thr Gly
50     55     60
Ser Asp Leu Gly Met Asp Arg Gly Thr Ala Asp Tyr Met Gly Met Leu
65     70     75     80
Ala Thr Val Met Asn Ala Leu Ala Leu Gln Asp Ser Leu Glu Gln Leu
85     90     95
Asp Cys Asp Thr Arg Val Leu Thr Ser Ile Glu Met Lys Gln Val Ala
100    105    110
Glu Pro Tyr Ile Arg Arg Arg Ala Ile Arg His Leu Glu Lys Lys Arg
115    120    125
Val Val Ile Phe Ala Ala Gly Ile Gly Asn Pro Tyr Phe Ser Thr Asp
130    135    140
Thr Thr Ala Ala Leu Arg Ala Ala Glu Val Glu Ala Asp Val Ile Leu
145    150    155    160
Met Gly Lys Asn Asn Val Asp Gly Val Tyr Ser Ala Asp Pro Lys Val
165    170    175
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<213> Staphylococcus aureus

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 180 185 190
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 Ile Val Ser Glu Glu Thr Gly Asp Ile Ser Val Thr Phe Asp Gly Lys
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<213> Artificial

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<400> 120

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21

<210> 121

<211> 606

<212> DNA

<213> Staphylococcus aureus

<400> 121

atgatgataa tcgtcatgtt actactaagt tatcttatcg gcgctttccc aagtggattc 60

gtaattggaa aattatTTTT caaaaaagat attagacaat ttggtagtgg taatactggc 120

gctactaata gcttttagagt attaggctcg cctgcaggat tcttggtaac atttctagat 180

atTTTcaaag ggTtcataac tgttttcttc cttttatggT tacaagttca cgcagatggc 240

cctattagta ctttttttac aaatggTtta attgTtggtt tattcgctat acttggaac 300

gtttatcctg tttatttaaa attccaaggT ggcaaagctg ttgcaactag tgcaggTgtc 360

gtcttgggag tcaatccgat acttttacta atacttgcaa ttatcttctt tattgtattg 420

aagattttta aatatgtttc tttagcaagt atcgTtgcaG caatttgctg tgtgattggc 480

tcgcttatca ttcaagacta tattttatta gtcgttagtt tcttagtttc aatcatattg 540

ataattagac atcgctctaa tatcgcaagg attttttagag gcgaagaacc taaaataaaa 600

tggatg 606

<210> 122

<211> 202

<212> PRT

<213> Staphylococcus aureus

<400> 122

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

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<210> 123

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 123

ggtatcttat cggcgctttc c

21

<210> 124

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 124

gcactagttg caacagcttt g

21

<210> 125

<211> 1293

<212> DNA

<213> Staphylococcus aureus

<400> 125

atgcagttaa atagtaatgg ttggcatggt gatgaccata ttgttgctgc tgtttctaca	60
ggtattgata gtatgtgttt attgtatcaa ctactaaatg attataaaga tagttataga	120
aaactaacat gcttacatgt caatcatggc gttaggctcag cttcaattga ggaagccaga	180
tttttagaag catactgcga acgtcatcac atcgatttac atatcaaaaa gttagatttg	240
tcgcatagtc tcgaccgaaa taacagcatt cagaatgaag ctcgaattaa acgttacgaa	300
tggtttgatg aaatgatgaa tgtattagaa gcggatgtat tgctaacggc gcatcatttg	360
gacgatcaat tagaaactat tatgtatcgt atttttaatg ggaaatcaac acgtaataaa	420
ctaggatttg atgagttatc gaagcgaaaa ggttatcaga tttatcgacc acttttagct	480
gtctctaaaa aagaaataaa acaattccaa gagagatatc atattccata ttttgaagat	540
gaatctaata aagataacaa atatgttaga aatgatattc gtaatagaat tattccagct	600
attgatgaaa ataatcaact taaagtatcg catttattaa aattaaaaca atggcatgat	660
gaacaatatg atattttgca atattcagct aaacaattta ttcaagaatt tgtgaagttt	720
gatgaacagt caaaatattt agagggtttct agacaagctt ttaataactt accaaactca	780
ttaaagatgg ttgtgttggc ctgcctatta tcaaagtatt atgagttggt taatattagt	840
gctaaaacat acgaagagtg gtttaaacaa tttagtagta agaaagcaca attcagtatt	900
aatctcacgg ataaatggat aattcaaadc gcatatggta aattaataat aatggctaaa	960
aataatggcg atacatattt tagagttcaa acaattaaaa agccaggtaa ttatattttt	1020
aacaaatadc gattagagat acattctaatt ttacaaaaat gtttatttcc gcttacagtg	1080
agaacacgac aaagtggcga tacatttaaa ctgaatgggc gcgatgggtta taagaaagtg	1140
aatcgctgtt ttatagattg taaagtgccg cagtgggttc gggatcaaat gccaatcgta	1200
ttggataaac aacagcgcat tattgcggta ggagatttat atcaacaaca aacaataaaa	1260

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aaatggatta taattagtaa aaatggagat gaa

1293

<210> 126

<211> 431

<212> PRT

<213> Staphylococcus aureus

<400> 126

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

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

<210> 127

<211> 21

<212> DNA

<213> Artificial

<220>

<223> oligonucleotide Primer

<400> 127

aatggttggc atgttgatga c

21

<210> 128

<211> 21

<212> DNA

<213> Artificial

<220>

<223> oligonucleotide Primer

<400> 128

attgatcgtc caaatgatgc g

21

<210> 129

<211> 429

<212> DNA

<213> Staphylococcus aureus

<400> 129

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atgttcatgg gagaatacga tcatcaatta gatacaaaag gacgtatgat tataccgtcc      60
aagtttcggt atgacttaaa tgagcgtttt attatcacaa gaggccttga taaatgttta    120
ttcggttaca ctctagacga atggcaacag attgaagaga aaatgaaaac cttacctatg    180
acaaaaaaag acgcacgtaa gtttatgcgt atgttcttct ctggtgctgt tgaagtagaa    240
cttgataagc aagggcgat taacatccct caaaacttga ggaaatacgc taatttaact    300
aaagaatgta cagtaatcgg tgtttcaaat cgtattgaga tttgggatag agaaacttgg    360
aatgatttct atgaagaatc tgaagaaagt ttcgaagata ttgctgaaga tttaatagat    420
tttgattttt                                     429

```

<210> 130

<211> 143

<212> PRT

<213> Staphylococcus aureus

<400> 130

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

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<210> 131

<211> 22

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 131

ttcatgggag aatacgatca tc

22

<210> 132

<211> 22

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 132

gtatttcctc aagttttgag gg

22

<210> 133

<211> 741

<212> DNA

<213> Staphylococcus aureus

<400> 133

atgctagagg cacaattttt tactgatact ggacaacata gagataagaa tgaagatgcg 60

gggtggtatgtt ttataatca aactaatcaa caacttttag ttctgtgtga tggatatgggt 120

ggccataaag caggagaagt tgcaagtaaa ttgtttacag atgagttgaa atcccgtttt 180

gaagcggaaa atcttataga acaacatcaa gctgaaaatt gggtgcgtaa taatataaaa 240

gatataaatt ttcagttata tcactatgca caagaaaatg cagaatataa aggtatgggt 300

acaacatgtg ttgtgacact tgtttttgaa aaatcagttg tgatagcaaa tgtcgggtgat 360

tctagagcct atgttattaa tagtcgacaa attgaacaaa ttactagtga tcactcattt 420

gttaatcatc ttgttttaac ggggtcaaatt acgccggaag aagcatttac acatccacaa 480

cgtaatatata ttacgaaggt gatgggcaca gataaacgtg tgagtccaga ttgttttatt 540

aagcgattaa atttttatga ttattttatta ttaaattcag atggattaac tgattatgtt 600

aaagacaatg aaattaagcg ttgttagta aaagaaggta caatagaaga tcatgggtgat 660

caattaatgc aattggcatt agataacat tcgaaagata acgttacttt catactcgcg 720

gctattgaag gtgataaagt a 741

<210> 134

<211> 247

<212> PRT

<213> Staphylococcus aureus

<400> 134

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

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<210> 135

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 135
ctgatactgg acaacataga g 21

<210> 136

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 136
accgacattt gctatcacia c 21

<210> 137

<211> 567

<212> DNA

<213> Staphylococcus aureus

<400> 137
atgaaaaaga tagtacttta cggcggtcag ttttaacccta tccatactgc acatatgata 60
gtagctagcg aagtatttca tgaattacag ccagatgaat tttatttttt acctagtttt 120
atgtctccat tgaaaaagca ccatgatttt atagacgttc agcacagatt aacaatgata 180
cagatgatta tcgacgagct tggtttttgg gatattttgtg acgatgaaat taaacgtggt 240
ggtcaaagtt atacctatga cacgatcaag gcattcaagg agcaacacaa agacagttag 300
ttgtactttg ttattgggac ggatcagtat aaccaactag agaaatggta tcaaattgaa 360
tacttaaaag aatgggttac tttttagtgg gtaaactcgag aaaaaaatag tcaaatggt 420
gaaaatgcta tgattgcaat tcagatacct agggtagata taagttagac aatgattcga 480
caaagagtta gtgaaggga atctatccaa gttcttggtc cttaatccgt tgaaaactat 540
attaaggggg aaggattata tgaacat 567

<210> 138

<211> 189

<212> PRT

<213> Staphylococcus aureus

<400> 138

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

<210> 139

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 139

gtttaaccct atccatactg c

21

<210> 140

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 140

ctagttgggtt atactgatcc g

21

<210> 141

<211> 393

<212> DNA

<213> Staphylococcus aureus

<400> 141

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atggtaacat tatttacttc accaagttgc acatcttgcc gttaaagcgaa agcatgggta      60
caagaacatg acattccgta tacggagcgt aatatttttt ctgaacattt aacaattgat      120
gaaattaagc aaatattaaa aatgactgaa gacgggtactg atgaaatcat ttctacacgt      180
tctaaaacat accaaaaatt aaatgttgat attgattcac taccattaca agacttatat      240
tcaatcattc aagataatcc tggcttatta cgtcgtccaa ttattttaga taataaacga      300
ctacaagttg gttataatga ggacgagatt cgacgtttct tacctagaaa agttcgtacg      360
ttccaattac aagaagcaca acgtatgggtt gac                                  393

```

<210> 142

<211> 131

<212> PRT

<213> Staphylococcus aureus

<400> 142

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

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<210> 143

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 143

atttacttca ccaagttgca c

21

<210> 144

<211> 21

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 144

taattggacg acgtaataag c

21

<210> 145

<211> 20

<212> DNA

<213> Artificial

<220>

<223> Oligonucleotide Primer

<400> 145

gggccaagc ttagtgatgg

20