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(54) Title: IMMUNOGENIC COMPOSITION

(57) Abstract: The present application relates to immunogenic compositions comprising staphylococcal PNAG and Type 5 and/or 8 capular polysaccharide or oligosaccharide from S. aureus. Vaccines, methods of treatment using and processes to make an immunogenic composition comprising PNAG and Type 5 and/or 8 capsular polysaccharides are also described.

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IMMUNOGENIC COMPOSITION

Technical Field

The present invention relates to the field of Staphylococcal immunogenic compositions and vaccines, their manufacture and the use of such compositions in medicine. More particularly, it relates to vaccine compositions comprising PNAG (PIA) polysaccharide and type 5 and/or 8 polysaccharides from *S. aureus*. Methods for the treatment or prevention of staphylococcal infections using such vaccines are also provided.

Background

The number of both community acquired and hospital acquired infections have increased over recent years with the increased use of intravascular devices. Hospital acquired (nosocomial) infections are a major cause of morbidity and mortality, more particularly in the US, where if affects more than 2 million patients annually. Following various studies, about 6 percent of the US patients will acquire an infection during their stay in hospital. The economic burden in the USA was estimated to be more than $4.5 billion in 1992 (Emori and Gaynes, 1993, Clin. Microbiol. Rev. 6; 428). The most frequent infections are urinary tract infections (UTI-33% of the infections), followed by pneumonia (15.5%), surgical site infections (14.8%) and primary bloodstream infections (13%) Emori and Gaynes, 1993, Clin. Microbiol. Rev. 6; 428).

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

Staphylococcus aureus is the most common cause of nosocomial infections with a significant morbidity and mortality (Romero-Vivas et al 1995, Infect. Dis. 21; 1417). It is the cause of some cases of osteomyelitis, endocarditis, septic arthritis, pneumonia, abscesses and toxic shock syndrome.

S. epidermidis is a normal skin commensal which is also an important opportunistic pathogen responsible for infections of implanted medical devices and infections at sites of

surgery. Medical devices infected by *S. epidermidis* include cardiac pacemakers, cerebrospinal fluid shunts, continuous ambulatory peritoneal dialysis catheters, orthopaedic devices and prosthetic heart valves.

S. aureus and *S. epidermidis* infections are treated with antibiotics, with penicillin being the drug of choice whereas vancomycin is used for methicillin resistant isolates. The percentage of staphylococcal strains exhibiting wide-spectrum resistance to antibiotics has become increasingly prevalent since the 1980's (Panlilo et al 1992, Infect.Control. Hosp. Epidemiol. 13; 582), posing a threat for effective antimicrobial therapy. In addition, the recent emergence of vancomycin resistant *S. aureus* strain has aroused fear that methicillin resistant *S.aureus* strains will emerge and spread for which no effective therapy is available.

An alternative approach of using antibodies against staphylococcal antigens in passive immunotherapy has been investigated. Therapy involving administration of polyclonal antisera are under development (WO 00/15238, WO 00/12132) as well as treatment with a monoclonal antibody against lipoteichoic acid (WO 98/57994).

An alternative approach would be use of active vaccination to generate an immune response against staphylococci. Several candidates for inclusion as vaccine components have been identified. These include Fibronectin binding protein (US5840846), MHC II analogue (US5648240), fibrinogen binding protein (US6008341), GehD (US 2002/0169288), collagen binding protein (US6288214), SdrF, SdrG and SdrH (WO 00/12689), mutant SEA and SEB exotoxins (WO 00/02523) and 52kDa vitronectin binding protein (WO 01/60852).

The *S. aureus* genome has been sequenced and many of the coding sequences have been identified (EP786519, WO02/094868). The same is true for *S. epidermidis* (WO 01/34809). As a refinement of this approach, others have identified proteins that are recognised by hyperimmune sera from patients who have suffered staphylococcal infection (WO01/98499, WO 02/059148).

The first generation of vaccines targeted against *S. aureus* or against the exoproteins it produces have met with limited success (Lee 1996 Trends Microbiol. 4; 162). There remains a need to develop effective vaccines against staphylococcal infections.

Description of Figures

Figure 1 – Polypeptide sequences of preferred proteins. Table 1 provides information on which protein is represented by each SEQ ID.

Figure 2 – Nucleotide sequences encoding preferred proteins. Table 1 provides information on which protein is encoded by each SEQ ID.

Figure 3 – Purification of alpha toxin under native conditions. Panel A shows a coommassie stained SDS-PAGE of samples prepared during the purification of alpha toxin. Lane 1 – molecular weight markers, lane 2 – soluble fraction containing over-expressed alpha toxin, lane 3 – flow through from the Ni-NTA column, lane 4 – fractions eluted with 10% buffer B, lane 5 – fractions eluted with 20% buffer B, lane 6 – fractions eluted with 30% buffer B, lane 7 – fractions eluted with 50% buffer B, lane 8 – fractions eluted with 75% buffer B, lane 9 and 10 fractions eluted with 100% buffer B, lane 11 bacteria at T=0 before induction, lane 12 – bacteria at T=4 hours after induction, lane 13 – cell lysate, lane 14 – soluble fraction, lane 15 – insoluble fraction.
Panel B shows a coommassie stained SDS-PAGE of 10, 5, 2 and 1μl of the purified alpha toxin.

Figure 4 – Purification of SdrC underdenaturing conditions. Panel A shows a coommassie stained SDS-PAGE of samples prepared during the purification of alpha toxin. Lane M – molecular weight markers, lane Start – supernatant fromed from the insoluble fraction containing over-expressed SdrC, lane FT1 – flow through from the Ni-NTA column, lane C – fractions eluted with wash buffer C, lane D – fractions eluted with buffer D, lane E – fractions eluted with buffer E.
Panel B shows a coommassie stained SDS-PAGE of 1, 2, 5 and 10μl of the purified SdrC.

Figure 5 – ELISA results for antisera against staphylococcal proteins in plates coated with purified proteins.

Pool mice pre – result using pooled sera extracted from mice pre-innoculation. Pool mice Post III – result using pooled mouse sera extracted post-immunisation. Pool rabbit pre – result using pooled sera extracted from rabbits pre-innoculation. Pool rabbit Post III – result using pooled rabbit sera extracted post-immunisation. Blc- negative contol.

Figure 6 – ELISA results for mouse antisera raised against staphylococcal proteins in plates coated with killed staphylococci.

Panel A uses plates coated with *S. aureus* serotype 5 killed whole cells. Panel B uses plates coated with *S. aureus* serotype 8 killed whole cells. Panel C uses plates coated with *S. epidermidis* killed whole cells.

The line marked with square signs shows the ELISA result using antisera from mice immunised three times with the indicated staphylococcal protein. The line marked with diamond signs shows the ELISA result for pre-immune mouse sera.

Figure 7 - ELISA results for rabbit antisera raised against staphylococcal proteins in plates coated with killed staphylococci.

Panel A uses plates coated with *S. aureus* serotype 5 killed whole cells. Panel B uses plates coated with *S. aureus* serotype 8 killed whole cells. Panel C uses plates coated with *S. epidermidis* killed whole cells.

The line marked with square signs shows the ELISA result using antisera from rabbits immunised three times with the indicated staphylococcal protein (except for HarA where only one immunisation was given). The line marked with diamond signs shows the ELISA result for pre-immune rabbit sera.

Detailed description

The present invention discloses particular combinations of Staphylococcal antigens which when combined, lead to the production of an immunogenic composition for treating or preventing staphylococcal infection. Immunogenic compositions of the invention incorporate PNAG (PIA) and *S. aureus* polysaccharides type 5 and/or 8. This combination of antigens is capable of eliciting an immune response against a range of staphylococcal infections. PNAG (PIA) is highly conserved among Gram positive bacteria and provides protection against a broad range of bacteria whereas Type 5 and 8 polysaccharides are potent imunogens that elicit an immune response against most strains of *S. aureus* which is the most common cause of nosocomial infection.

Polysaccharides

The immunogenic compositions of the invention comprise PIA (also known as PNAG) and type 5 and 8 polysaccharides from *S. aureus*.

PIA (PNAG)

It is now clear that the various forms of staphylococcal surface polysaccharides identified as PS/A, PIA and SAA are the same chemical entity – PNAG (Maira-Litran et al Vaccine 22; 872-879 (2004)). Therefore the term PIA or PNAG encompasses all these polysaccharides or oligosaccharides derived from them.

PIA is a polysaccharide intercellular adhesin and is composed of a polymer of β-(1 →6)-linked glucosamine substituted with N-acetyl and O-succinyl constituents. This polysaccharide is present in both *S.aureus* and *S. epidermidis* and can be isolated from either source (Joyce et al 2003, Carbohydrate Research 338; 903; Maira-Litran et al 2002, Infect. Imun. 70; 4433). For example, PNAG may be isolated from *S. aureus* strain MN8m (WO 04/43407).

PIA isolated from *S. epidermidis* is a integral constituent of biofilm. It is responsible for mediating cell-cell adhesion and probably also functions to shield the growing colony from the host's immune response.

The polysaccharide previously known as poly-N-succinyl-β-(1 →6)-glucosamine (PNSG) was recently shown not to have the expected structure since the identification of N-succinylation was incorrect (Maira-Litran et al 2002, Infect. Imun. 70; 4433). Therefore the polysaccharide formally known as PNSG and now found to be PNAG is also encompassed by the term PIA.

PIA (or PNAG) may be of different sizes varying from over 400kDa to between 75 and 400kDa to between 10 and 75kDa to oligosaccharides composed of up to 30 repeat units (of β-(1 →6)-linked glucosamine substituted with N-acetyl and O-succinyl constituents). Any size of PIA polysaccharide or oligosaccharide may be use in an immunogenic composition of the invention, however a size of over 40kDa is preferred. Sizing may be achieved by any method known in the art, for instance by microfluidisation, ultrasonic irradiation or by chemical cleavage (WO 03/53462, EP497524, EP497525).

Preferred size ranges of PIA (PNAG) are 40-400kDa, 50-350kDa, 40-300kDa, 60-300kDa, 50-250kDa and 60-200kDa.

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

The term deacetylated PNAG (dPNAG) refers to a PNAG polysaccharide or oligosaccharide in which less than 60%, 50%, 40%, 30%, 20% or 10% of the amino agroups are acetylated.

In an embodiment, PNAG is a deaceylated to form dPNAG by chemically treating the native polysaccharide. For example, the native PNAG is treated with a basic solution such that the pH rises to above 10. For instance the PNAG is treated with 0.1-5M, 0.2-4M, 0.3-3M, 0.5-2M, 0.75-1.5M or 1M NaOH , KOH or NH_4OH. Treatment is for at least 10 or 30 minutes, or 1, 2, 3, 4, 5, 10, 15 or 20 hours at a temperature of 20-100, 25-80, 30-60 or 30-50 or 35-45 °C. dPNAG may be prepared as described in WO 04/43405.

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

Type 5 and Type 8 polysaccharides from *S.aureus*

Most strains of *S.aureus* that cause infection in man contain either Type 5 or Type 8 polysaccharides. Approximately 60% of human strains are Type 8 and approximately 30% are Type 5. The structures of Type 5 and Type 8 capsular polysaccharide antigens are described in Moreau et al Carbohydrate Res. 201; 285 (1990) and Fournier et al Infect. Immun. 45; 87 (1984). Both have FucNAcp in their repeat unit as well as ManNAcA which can be used to introduce a sulfhydryl group. The structures were reported as :

Type 5

→4)-β-D-ManNAcA(3OAc)-(1 →4)-α-L-FucNAc(1 →3)-β-D-FucNAc-(1 →

Type 8

→3)-β-D-ManNAcA(4OAc)-(1 →3)-α-L-FucNAc(1 →3)-β-D-FucNAc-(1 →

Recently (Jones Carbohydrate Research 340, 1097-1106 (2005)) NMR spectroscopy revised to structures to :

Type 5

→4)-β-D-ManNAcA-(1 →4)-α-L-FucNAc(3OAc)-(1 →3)-β-D-FucNAc-(1 →

Type 8

→3)-β-D-ManNAcA(4OAc)-(1 →3)-α-L-FucNAc(1 →3)-α-D-FucNAc(1 →

Polysaccharides may be extracted from the appropriate strain of *S. aureus* using method well known to the skilled man, for instance as described in US6294177. For example, ATCC 12902 is a Type 5 *S. aureus* strain and ATCC 12605 is a Type 8 *S. aureus* strain.

Polysaccharides are of native size or alternatively may be sized, for instance by microfluidisation, ultrasonic irradiation or by chemical treatment. The invention also covers oligosaccharides derived from the type 5 and 8 polysaccharides from *S. aureus*.

The type 5 and 8 polysaccharides included in the immunogenic composition of the invention are preferably conjugated to a carrier protein as described below or are alternatively unconjugated.

The immunogenic compositions of the invention alternatively contains either type 5 or type 8 polysaccharide.

<u>*S. aureus* 336 antigen</u>

In an embodiment, the immunogenic composition of the invention comprises the *S. aureus* 336 antigen described in US6294177.

The 336 antigen comprises β-linked hexosamine, contains no O-acetyl groups and specifically binds to antibodies to *S. aureus* Type 336 deposited under ATCC 55804.

In an embodiment, the 336 antigen is a polysaccharide which is of native size or alternatively may be sized, for instance by microfluidisation, ultrasonic irradiation or by chemical treatment. The invention also covers oligosaccharides derived from the 336 antigen.

The 336 antigen, where included in the immunogenic composition of the invention is preferably conjugated to a carrier protein as described below or are alternatively unconjugated.

<u>Type I, II and III polysaccharides from *S. epidermidis*</u>

Strains ATCC-31432, SE-360 and SE-10 of *S. epidermidis* are characteristic of three different capsular types, I, II and III respectively (Ichiman and Yoshida 1981, J. Appl. Bacteriol. 51; 229). Capsular polysaccharides extracted from each serotype of *S. epidermidis* constitute Type I, II and III polysaccharides. Polysaccharides may be extracted by serval methods including the method described in US4197290 or as described in Ichiman et al 1991, J. Appl. Bacteriol. 71; 176.

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

Polysaccharides are of native size or alternatively may be sized, for instance by microfluidisation, ultrasonic irradiation or chemical cleavage. The invention also covers oligosaccharides extracted from *S. epidermidis* strains.

These polysaccharides are unconjugated or are preferably conjugated as described below.

Conjugation of polysaccharides

Amongst the problems associated with the use of polysaccharides in vaccination, is the fact that polysaccharides *per se* are poor immunogens. Strategies, which have been designed to overcome this lack of immunogenicity, include the linking of the polysaccharide to large protein carriers, which provide bystander T-cell help. It is preferred that the polysaccharides utilised in the invention are linked to a protein carrier which provide bystander T –cell help. Examples of these carriers which are currently used for coupling to polysaccharide or oligosaccharide immunogens include the Diphtheria and Tetanus toxoids (DT, DT Crm197 and TT), Keyhole Limpet Haemocyanin (KLH), *Pseudomonas aeruginosa* exoprotein A (rEPA) and the purified protein derivative of Tuberculin (PPD), protein D from *Haemophilus influenzae*, pneumolysin or fragments of any of the above. Fragments suitable for use include fragments encompassing T-helper epitopes. In particular protein D fragment will preferably contain the N-terminal 1/3 of the protein. Protein D is an IgD–binding protein from *Haemophilus influenzae* (EP 0 594 610 B1).

Despite the common use of these carriers and their success in the induction of anti polysaccharide antibody responses they are associated with several drawbacks. For example, it is known that antigen specific immune responses may be suppressed by the

presence of pre-existing antibodies directed against the carrier, in this case Tetanus toxin (Di John *et al*; Lancet, December 16, 1989). In the population at large, a very high percentage of people will have pre-existing immunity to both DT and TT as people are routinely vaccinated with these antigens. In the UK for example 95% of children receive the DTP vaccine comprising both DT and TT. Other authors have described the problem of epitope suppression to peptide vaccines in animal models (Sad *et al*, Immunology, 1991; 74:223-227; Schutze *et al*, J. Immunol. 135: 4, 1985; 2319-2322).

KLH is known as potent immunogen and has already been used as a carrier for IgE peptides in human clinical trials. However, some adverse reactions (DTH-like reactions or IgE sensitisation) as well as antibody responses against antibody have been observed.

An alternative carrier protein to use in the immunogenic composition of the invention is a single staphylococcal protein or fragment thereof or a fusion protein comprising at least or exactly 1, 2, 3 or 4 or more of the staphylococcal proteins listed in the section below or fragments thereof.

A new carrier protein that would be particularly advantageous to use in the context of a staphylococcal vaccine is staphylococcal alpha toxoid. The native form may be conjugated to a polysaccharide since the process of conjugation reduces toxicity. Preferably a genetically detoxified alpha toxin such as the His35Leu or His 35 Arg variants are used as carriers since residual toxicity is lower. Alternatively the alpha toxin is chemically detoxified by treatment with a cross-linking reagent, formaldehyde or glutaraldehyde. A genetically detoxified alpha toxin is optionally chemically detoxified, preferably by treatment with a cross-linking reagent, formaldehyde or glutaraldehyde to further reduce toxicity. Other staphylococcal proteins or fragments thereof, particularly those listed above may be used as a carrier protein for the polysaccharides listed above. The carrier protein may be a fusion protein comprising at least or exactly 1, 2, 3, 4 or 5 of the staphylococcal proteins listed above.

The polysaccharides may be linked to the carrier protein(s) by any known method (for example, by Likhite, U.S. Patent 4,372,945 by Armor et al., U.S. Patent 4,474,757, and Jennings et al., U.S. Patent 4,356,170). Preferably, CDAP conjugation chemistry is carried out (see WO95/08348).

In CDAP, the cyanylating reagent 1-cyano-dimethylaminopyridinium tetrafluoroborate (CDAP) is preferably used for the synthesis of polysaccharide-protein conjugates. The cyanilation reaction can be performed under relatively mild conditions, which avoids hydrolysis of the alkaline sensitive polysaccharides. This synthesis allows direct coupling to a carrier protein.

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

Proteins

The immunogenic composition of the invention preferably further comprises a staphylococcal protein, more preferably a protein from *S. aureus* or *S. epidermidis*. Some embodiments of the invention contain proteins from both *S.aureus* and *S. epidermidis*. Immunogenic compositions of the invention comprise an isolated protein which comprises an amino acid sequence which has at least 85% identity, preferably at least 90% identity, more preferably at least 95% identity, most preferably at least 97-99% or exact identity, to that of any sequence of figure 1.

Where a protein is specifically mentioned herein, it is preferably a reference to a native or recombinant , full-length protein or optionally a mature protein in which any signal sequence has been removed. The protein may be isolated directly from the staphylococcal strain or produced by recombinant DNA techniques. Immunogenic fragments of the protein may be incorporated into the immunogenic composition of the invention. These are fragments comprising at least 10 amino acids, preferably 20 amino acids, more preferably 30 amino acids, more preferably 40 amino acids or 50 amino acids, most preferably 100 amino acids, taken contiguously from the amino acid sequence of the protein. In addition, such immunogenic fragments are typically immunologically reactive with antibodies generated against the Staphylococcal proteins or with antibodies generated by infection of a mammalian host with Staphylococci or contain T cell epitopes. Immunogenic fragments also includes fragments that when administered at an effective dose, (either alone or as a

hapten bound to a carrier), elicit a protective immune response against Staphylococcal infection, more preferably it is protective against *S. aureus* and/or *S. epidermidis* infection. Such an immunogenic fragment may include, for example, the protein lacking an N-terminal leader sequence, and/or a transmembrane domain and/or a C-terminal anchor domain. In a preferred aspect the immunogenic fragment according to the invention comprises substantially all of the extracellular domain of a protein which has at least 85% identity, preferably at least 90% identity, more preferably at least 95% identity, most preferably at least 97-99% identity, to that a sequence selected from Figure 1 over the entire length of the fragment sequence.

In an embodiment, immunogenic compositions of the invention may contain fusion proteins of Staphylococcal proteins, or fragments of staphylococcal proteins. Such fusion proteins may be made recombinantly and may comprise one portion of at least 2, 3, 4, 5 or 6 staphylococcal proteins. Alternatively, a fusion protein may comprise multiple portions of at least 2, 3, 4 or 5 staphylococcal proteins. These may combine different Staphylococcal proteins or fragments thereof in the same protein. Alternatively, the invention also includes individual fusion proteins of Staphylococcal proteins or fragments thereof, as a fusion protein with heterologous sequences such as a provider of T-cell epitopes or purification tags, for example: β-galactosidase, glutathione-S-transferase, green fluorescent proteins (GFP), epitope tags such as FLAG, myc tag, poly histidine, or viral surface proteins such as influenza virus haemagglutinin, or bacterial proteins such as tetanus toxoid, diphtheria toxoid, CRM197.

Proteins

In an embodiment, the immunogenic composition of the invention further comprises one or more of the proteins mentioned below. Many of the preferred proteins fall into the categories of extracellular component binding proteins, transporter proteins or toxins and regulators of virulence. The immunogenic composition of the invention optionally further comprises a staphylococcal extracellular component binding protein or a staphylococcal transporter protein or a staphylococcal toxin or regulator of virulence. The immunogenic composition of the invention optionally comprises at least or exactly 1, 2, 3, 4, 5 or 6 staphylococcal proteins.

Table 1

The following table sets out the SEQ ID numbers of protein sequences and DNA sequences that are found in Figure 1 and Figure 2 respectively. SA indicates a sequence from *S. aureus* and SE indicates a sequence from *S. epidermidis*.

Name	Protein sequence	DNA sequence
Immunodominant ABC transporter		
SA	SEQ ID 1	SEQ ID 34
SE	SEQ ID 2	SEQ ID 35
Laminin receptor		
SA	SEQ ID 3	SEQ ID 36
SE	SEQ ID 4	SEQ ID 37
Secretory Antigen A SsaA		
SA 1	SEQ ID 5	SEQ ID 38
SA 2	SEQ ID 6	SEQ ID 39
SE	SEQ ID 7	SEQ ID 40
SitC		
SA	SEQ ID 8	SEQ ID 41
SE	SEQ ID 9	SEQ ID 42

IsaA / PisA (IssA)		
SA	SEQ ID 10	SEQ ID 43
SE	SEQ ID 11	SEQ ID 44
EbhA / B		
SA EbhA	SEQ ID 12	SEQ ID 45
SA EbhB	SEQ ID 13	SEQ ID 46
SE EbhA	SEQ ID 14	SEQ ID 47
SE EbhB	SEQ ID 15	SEQ ID 48
Accumulation-assoc pro Aap		
SA	SEQ ID 16	SEQ ID 49
SE	SEQ ID 17	SEQ ID 50
RNA III activating protein RAP		
SA	SEQ ID 18	SEQ ID 51
SE	SEQ ID 19	SEQ ID 52
FIG / SdrG		
SA	SEQ ID 20	SEQ ID 53
SE	SEQ ID 21	SEQ ID 54
Elastin binding protein EbpS		
SA	SEQ ID 22	SEQ ID 55
SE	SEQ ID 23	SEQ ID 56
Extracellular protein EFB **SA**	SEQ ID 24	SEQ ID 57
alpha toxin **SA**	SEQ ID 25	SEQ ID 58
SBI **SA**	SEQ ID 26	SEQ ID 59
IsdA **SA**	SEQ ID 27	SEQ ID 60
IsdB **SA**	SEQ ID 28	SEQ ID 61
SdrC **SA**	SEQ ID 29	SEQ ID 62
ClfA **SA**	SEQ ID 30	SEQ ID 63
FnbA **SA**	SEQ ID 31	SEQ ID 64
ClfB **SA**	SEQ ID 32	SEQ ID 65
Coagulase **SA**	SEQ ID 33	SEQ ID 66
FnbB **SA**	SEQ ID 67	SEQ ID 71
MAP **SA**	SEQ ID 68	SEQ ID 72
SdrC **SA**	SEQ ID 69	SEQ ID 73
SdrG **SA**	SEQ ID 70	SEQ ID 74

Extracellular component binding proteins

Extracellular component binding proteins are proteins that bind to host extracellular components. The term includes, but is not limited to adhesins.

Examples of extracellular component binding proteins include laminin receptor (Naidu et al J. Med. Microbiol. 1992, 36; 177), SitC/MntC/saliva binding protein (US5801234, Wiltshire and Foster Infec. Immun. 2001, 69; 5198), EbhA (Williams et al Infect. Immun. 2002, 70; 6805), EbhB, Elastin binding protein (EbpS) (Park et al 1999, J. Biol. Chem. 274; 2845), EFB (FIB) (Wastfelt and Flock 1995, J. Clin. Microbiol. 33; 2347), SBI (Zhang et al FEMS Immun. Med. Microbiol. 2000, 28; 211), autolysin (Rupp et al 2001, J. Infect. Dis. 183; 1038), ClfA (US6008341, McDevitt et al Mol. Microbiol. 1994, 11; 237), SdrC, SdrG (McCrea et al Microbiology 2000, 146; 1535), SdrH (McCrea et al Microbiology 2000, 146; 1535), Lipase GehD (US2002/0169288), SasA, FnbA (Flock et al Mol Microbiol. 1994, 12; 599, US6054572), FnbB (WO 97/14799, Booth et al 2001 Infec. Immun. 69; 345), collagen binding protein Cna (Visai et al 2000, J. Biol. Chem. 275; 39837), ClfB (WO 99/27109), FbpA (Phonimdaeng et al 1988 J. Gen Microbiol.134; 75), Npase (Flock 2001 J. Bacteriol. 183; 3999), IsaA/PisA (Lonenz et al FEMS Immuno. Med. Microbiol. 2000, 29; 145), SsaA (Lang et al FEMS Immunol. Med. Microbiol. 2000, 29; 213), EPB (Hussain and Hermann symposium on Staph Denmark 14-17th 2000), SSP-1 (Veenstra et al 1996, J. Bacteriol. 178; 537), SSP-2 (Veenstra et al 1996, J. Bacteriol. 178; 537), 17 kDa heparin binding protein HBP (Fallgren et al 2001, J. Med. Microbiol. 50; 547), Vitronectin binding protein (Li et al 2001, Curr. Microbiol. 42; 361), fibrinogen binding protein, coagulase, Fig (WO 97/48727) and MAP (US5648240)

SitC/MntC/saliva binding protein

This is an ABC transporter protein which is a homologue of adhesin PsaA in *S. pneumoniae*. It is a highly immunogenic 32kDa lipoprotein which is distributed through the bacterial cell wall (Cockayne et al Infect. Immun. 1998 66; 3767). It is expressed in *S. aureus* and *S. epidermidis* as a 32kDa lipoprotein and a 40kDa homologue is present in *S. hominis*. In *S. epidermidis*, it is a component of an iron-regulated operon. It shows considerable homology to both adhesins including FimA of Streptococcus parasanguis, and with lipoproteins of a family of ABC transporters with proven or putative metal iron transport functions. Therefore SitC is included as an extracellular biding protein and as a metal ion transporter.

The saliva binding protein disclosed in US5,801,234 is also a form of SitC and can be included in an immunogenic composition of the invention.

ClfA and ClfB

Both these proteins have fibrinogen binding activity and trigger *S. aureus* to form clumps in the presence of plasma. They contain a LPXTG motif common to wall associated proteins.

ClfA is described in US6008341 and ClfB is described in WO 99/27109.

Coagulase (FbpA)

This is a fibrinogen binding protein which triggers *S. aureus* to form clumps in the presence of plasma. It is described in references related to Coagulase : Phonimdaeng et al (J. Gen. Microbio. 1988, 134:75-83), Phonimdaeng et al. (Mol Microbiol 1990; 4:393-404), Cheung et al. (Infect Immun 1995; 63:1914-1920) and Shopsin et al. (J. CLin. Microbiol. 2000; 38:3453-3456).

Preferred fragments for inclusion in the immunogenic composition of the invention include the mature protein in which the signal peptide has been removed (amino acids 27 to the C-terminus).

Coagulase has three distinct domains. Amino acids 59-297 which is a coiled coil region, amino acids 326-505 which is a proline and glycine rich region and the C-terminal domain from amino acid 506 to 645 which has a beta sheet conformation. Each of these domains is a fragment which may be incorporated into the immunogenic composition of the invention.

SdrG

This protein is described in WO 00/12689. SdrG is found in coagulase negative staphylococci and is a cell wall associated protein containing a LPXTG sequence.

SdrG contains a signal peptide (amino acids 1-51), a region containing fibrinogen binding sites and collagen binding sites (amino acids 51-825), two CnaB domains (amino acids 627-698 and 738-809), a SD repeat region (amino acids 825-1000) and an anchor domain (amino acids 1009-1056).

Preferred fragments of SdrG include polypeptides in which the signal peptide and/or the SD repeats and the anchor domain have been removed. These include polypeptides comprising or consisting of amino acids 50-825, amino acids 50-633, amino acids 50-597 (SEQ ID NO 2 of WO 03/76470), amino acids 273-597 (SEQ ID NO 4 of WO 03/76470), amino acids 273-577 (SEQ ID NO 6 of WO 03/76470) amino acids 1-549, amino acids 219-549, amino acids 225-549, amino acids 219-528, amino acids 225-528 of SEQ ID NO: 70 or 20 or 21.

Preferably, an SdrG polypeptide having a sequence at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or 100% homologous to the sequence of SEQ ID NO: 70, 20 or 21 is incorporated into the immunogenic composition of the invention.

The compositions of the invention optionally comprise a fragment of the SdrG polypeptides described above.

Preferred fragments have the signal peptide and/or the SD repeat domain and/or the anchoring domain deleted. For example sequences corresponding to amino acids 1-713 , 1-549, 225-549, 225-529, 24-717, 1-707, 1-690, 1-680, 1-670, 1-660, 1-650, 1-640, 1-630, 1-620, 1-610, 1-600, 34-707, 44-697, 36-689 of SEQ ID 70 or sequences having 85%, 90%, 92%, 95%, 97%, 98%, 99% or 100% identity to SEQ ID 70 or 20 or 21.

Preferred fragments with the signal peptide deleted have a methionine residue at the N-terminus of the fragment to ensure correct translation.

A more preferred fragment has the following sequence:-

MEENSVQDVKDSNTDDELSDSNDQSSDEEKNDVINNNQSINTDDNNQIIKKEETNNYDGIEKRSEDRTESTTN
VDENEATFLQKTPQDNTHLTEEEVKESSSVESSNSSIDTAQQPSHTTINREESVQTSDNVEDSHVSDFANSKI
KESNTESGKEENTIEQPNKVKEDSTTSQPSGYTNIDEKISNQDE
LLNLPINEYENKARPLSTTSAQPSIKRVTVNQLAAEQGSNVNHLIKVTDQSITEGYDDSEGVIKAHDAENLIY
DVTFEVDDKVKSGDTMTVDIDKNTVPSDLTDSFTIPKIKDNSGEIIATGTYDNKNKQITYTFTDYVDKYENIK
AHLKLTSYIDKSKVPNNNTKLDVEYKTALSSVNKTITVEYQRPNENRTANLQSMFTNIDTKNHTVEQTIYINP
LRYSAKETNVNISGNGDEGST
IIDDSTIIKVYKVGDNQNLPDSNRIYDYSEYEDVTNDDYAQLGNNNDVNINFGNIDSPYIIKVISKYDPNKDD
YTTIQQTVTMQTTINEYTGEFRTASYDNTIAFSTSSGQGQGDLPPEKTYKIGDYVWEDVDKDGIQNTNDNEKP
LSNVLVTLTYPDGTSKSVRTDEDGKYQFDGLKNGLTYKITFETPEGYTPTLKHSGTNPALDSEGNSVWVTING
QDDMTIDSGFYQTPKYSLGNY
VWYDTNKDGIQGDDEKGISGVKVTLKDENGNIISTTTTDENGKYQFDNLNSGNYIVHFDKPSGMTQTTTDSGD
DDEQDADGEEVHVTITDHDDFSIDNGYYDDE

EbhA and EbhB

EbhA and EbhB are proteins that are expressed in both *S. aureus* and *S. epidermidis* (Clarke and Foster Infect. Immun. 2002, 70; 6680 , Williams et al Infect. Immun. 2002, 20; 6805) and which bind to fibronectin. Since fibronectin is an important component of extracellular matrix, EbhA and EbhB have an important function in adhering staphylococci to host extracellular matrix.

The Ebh proteins are large, having a molecular weight of 1.1 megadaltons. It is advantageous to use a fragment of the Ebh protein rather than the complete sequence due to ease of

production and formulation. The central region of the protein contains imperfect repeats which contain fibronectin binding sites. Fragments containing one or more of the repeat domains described below are preferred fragments for incorporation into the immunogenic composition of the invention.

Ebh proteins contain imperfect repeats units of 127 amino acids in length which are characterised by containing the consensus sequence:-

L.G.{10}A.{13}Q.{26}L...M..L.{33}A

Preferably

.{19}L.G.{10}A.{13}Q.{26}L...M..L.{33}A.{12}

More preferably

.....I/V..A...I/V..AK.ALN/DG..NL..AK..A.{6}L..LN.AQK..L..QI/V..A..V..V.{6}A..LN/D.AM..L...I/V.D/E...TK.S.NY/F.N/DAD..K..AY/F..AV..A..I/V.N/D.....

Where '.' means any amino acid and '.{10}' means any 10 amino acids and I/V indicates alternative choices of amino acid.

By reference to the sequence disclosed in Kuroda et al (2001) Lancet 357; 1225-1240, and Table 2, the repeat sequences within Ebh proteins are readily deduced.

Preferred fragments to be included in the immunogenic composition of the invention include proteins containing of one, two, three, four, five, six, seven, eight, nine, ten or more than 10 of the 127 amino acid repeat units. Such fragments may consist of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more repeats of the 127 amino acid repeat region or may consist of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more repeats with additional amino acid residues present at either or both ends of the fragment. A further preferred fragment is the H2 polypeptide of about 44kDa spaning three repeats (amino acids 3202-3595) as described in Clarke et al Infection and Immunity 70, 6680-6687, 2002. Such fragments will preferably be able to bind fibronectin and/or to elicit antibodies that are reactive against the whole Ebh protein.

The Ebh proteins are capable of binding to fibronectin. Preferred fragments of these polypeptides sequences retain the ability to bind to fibronectin. Binding to fibronectin can be assessed by ELISA as described by Clarke et al (Infection and Immunity 70; 6680-6687 2002).

Still further preferred fragments are those which comprise a B-cell or T-helper epitope, for example those fragments/peptides described in Tables 3 and 4.

TABLE 2 Repeat sequences in the full-length sequence of Ebh.

The full-length sequence of Ebh is disclosed in Kuroda et al (2001) Lancet 357; 1225-1240. The following table shows the amino acid residues at which the 127 amino acid repeats begin and end within the full length sequence.

	Begin	End
1	3204	3330
2	3331	3457
3	3457	3583
4	3583	3709
5	3709	3835
6	3835	3961
7	3961	4087
8	4200	4326
9	4326	4452
10	4452	4578
11	4578	4704
12	4704	4830
13	4830	4956
14	4956	5082
15	5082	5208
16	5208	5334
17	5334	5460
18	5460	5586
19	5585	5711
20	5711	5837
21	5837	5963
22	5963	6089
23	6089	6215

24	6215	6341
25	6341	6467
26	6467	6593
27	6593	6719
28	6719	6845
29	6845	6971
30	6971	7097
31	7097	7223
32	7223	7349
33	7349	7475
34	7475	7601
35	7601	7727
36	7727	7853
37	7852	7978
38	7978	8104
39	8104	8230
40	8230	8356
41	8356	8482
42	8482	8608
43	8604	8730
44	8858	8984

Table 3 B-cell epitope prediction for a 127 amino acid repeat :

The full-length sequence is disclosed in Kuroda et al (2001) Lancet 357; 1225-1240. One of these repeats, encoded by amino acids 3204-3331of the full-length sequence was chosen to carry out an epitope prediction:-

MDVNTVNQKAASVKSTKDALDGQQNLQRAKTEATNAITHASDLNQAQKNALTQ
QVNSAQNVHAVNDIKQTTQSLNTAMTGLKRGVANHNQVVQSDNYVNADTNKK
NDYNNAYNHANDIINGNAQHPVI

Begin	End	Epitope sequence	Start	Stop
5	10	TVNQKA	3208	3213
14	19	KSTKDA	3217	3222
21	33	DGQQNLQRAKTEA	3224	3236
42	51	DLNQAQKNAL	3245	3254
66	74	DIKQTTQSL	3269	3277
100	112	ADTNKKNDYNNAY	3303	3315
117	123	DIINGNA	3320	3326

- The "Begin" and "End" columns present the position of the predicted B-cell epitopes in the 127 amino acid repeat
- The "Start" and "Stop" columns present the position of the predicted B-cell epitopes in the Ebh full length sequence

Table 4 T-helper cell epitope prediction in Ebh :

The full-length sequence is disclosed in TrEMBL database, sequence reference Q8NWQ6. One of these repeats, encoded by amino acids 3204-3331 of the full-length sequence was chosen to carry out an epitope prediction:-

MDVNTVNQKAASVKSTKDALDGQQNLQRAKTEATNAITHASDLNQAQKNALTQ QVNSAQNVHAVNDIKQTTQSLNTAMTGLKRGVANHNQVVQSDNYVNADTNKK NDYNNAYNHANDIINGNAQHPVI

Position repeat	**Epitope sequence**	**Position sequence**
1	MDVNTVNQK	3204
3	VNTVNQKAA	3206
6	VNQKAASVK	3209
26	LQRAKTEAT	3229
37	ITHASDLNQ	3240
43	LNQAQKNAL	3246
51	LTQQVNSAQ	3254
55	VNSAQNVHA	3258
61	VHAVNDIKQ	3264
64	VNDIKQTTQ	3267
67	IKQTTQSLN	3270
74	LNTAMTGLK	3277
78	MTGLKRGVA	3281
81	LKRGVANHN	3284
85	VANHNQVVQ	3288
91	VVQSDNYVN	3294
92	VQSDNYVNA	3295
97	YVNADTNKK	3301
98	VNADTNKKN	3302
108	YNNAYNHAN	3311
112	YNHANDIIN	3315
118	IINGNAQHP	3321
119	INGNAQHPV	3322

- The "Position repeat" column presents the position of the predicted T-cell epitopes in the repeat
- The "Position sequence" column presents the position of the predicted T-cell epitopes in the Ebh full length sequence

Fragments of the proteins of the invention may be employed for producing the corresponding full-length polypeptide by peptide synthesis; therefore, these fragments may be employed as intermediates for producing the full-length proteins of the invention.

Particularly preferred are variants in which several, 5-10, 1-5, 1-3, 1-2 or 1 amino acids are substituted, deleted, or added in any combination.

Elastin binding protein (EbpS)

EbpS is a protein containing 486 amino acids with a molecular weight of 83kDa. It is associated with the cytoplasmic membrane of *S. aureus* and has three hydrophobic regions which hold the protein in the membrane (Downer et al 2002, J. Biol. Chem. 277; 243; Park et al 1996, J. Biol. Chem. 271; 15803).

Two regions between amino acids 1-205 and 343-486 are surface exposed on the outer face of the cytoplasmic membrane. The ligand binding domain of EbpS is located between residues 14-34 at the N-terminus (Park et al 1999, J. Biol. Chem. 274; 2845).

A preferred fragment to be incorporated into the immunogenic composition of the invention is the surface exposed fragment containing the elastin binding region (amino acids 1-205). Some preferred fragments do not contain the entire exposed loop but should contain the elastin binding region (amino acids 14-34). An alternative fragment which could be used consists of amino acids forming the second surface exposed loop (amino acids 343-486). Alternative fragments containing up to 1, 2, 5, 10, 20, 50 amino acids less at one or both ends are also possible.

Laminin receptors

The laminin receptor of *S. aureus* plays an important role in pathogenicity. A characteristic feature of infection is bloodstream invasion which allows widespread metastatic abscess formation. Bloodstream invasion requires the ability to extravasate across the vascular basement membrane. This is achieved through binding to laminin through the laminin receptor (Lopes et al Science 1985, 229; 275).

Laminin receptors are surface exposed and are present in many strains of staphylococci including *S. aureus* and *S. epidermidis*.

SBI

Sbi is a second IgG binding protein in addition to protein A and it is expressed in most strains of *S.aureus* (Zhang et al 1998, Microbiology 144; 985).

The N-terminus of the sequence of Sbi has a typical signal sequence with a cleavage site after amino acid 29. Therefore a preferred fragment of Sbi to be incorporated into an immunogenic composition of the invention starts at amino acid residue 30, 31, 32 or 33 and continues to the C-terminus of Sbi, for example of SEQ ID NO: 26.

The IgG binding domain of Sbi has been identified as a region towards the N-terminus of the protein from amino acids 41-92. This domain is homologous to the IgG binding domains of protein A.

The minimal IgG binding domain of Sbi contains the following sequence:-

```
QTTQNNYVTDQQKAFYQVLHLKGITEEQRNQYIKTLREHPERAQEVFSESLK
          ** ***  *        ***  *  *   *        *  *
```

* - denotes amino acids which are similar between IgG binding domains

Preferred fragment of Sbi to be included in the immunogenic composition of the invention contains an IgG binding domain. This fragment contains the consensus sequence for an IgG binding domain as designated by * as shown in the above sequence. Preferably the fragment contains or consists of the complete sequence shown above. More preferably, the fragment contains or consists of amino acids 30-92, 33-92, 30-94, 33-94, 30-146, 33-146, 30-150, 33-150, 30-160, 33-160, 33-170, 33-180, 33-190, 33-200, 33-205 or 33-210 of Sbi, for example of SEQ ID NO:26.

Preferred fragment may contain 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 amino acid substitutions from the sequences indicated.

Preferred fragments may contain multiple repeats (2, 3, 4, 5, 6, 7,8, 9 or 10) of the IgG binding domain.

EFB - FIB

Fib is a 19kDa fibrinogen binding protein which is secreted into the extracellular medium by S. aureus. It is produced by all S aureus isolates tested (Wastfelt and Flock 1995, J. Clin. Microbiol. 33; 2347).

S. aureus clumps in the presence of fibrinogen and binds to fibrinogen coated surfaces. This ability facilitates staphylococcal colonisation of catheters and endothelial cells.

Fib contains a signal sequence at the N-terminus of the protein with a putative cleavage site at about amino acid 30. Therefore a preferred fragment to be introduced in the immunogenic composition of the invention would contain the sequence of the mature protein (from about amino acid 30 to the C-terminus of the protein).

Fbe – EfB/FIG

Fbe is a fibrinogen binding protein that is found in many isolates of S. epidermidis and has a deduced molecular weight of 119 kDa (Nilsson et al 1998. Infect. Immun. 66; 2666). Its sequence is related to that of clumping factor from *S. aureus* (ClfA). Antibodies against Fbe can block the binding of *S. epidermidis* to fibrinogen coated plates and to catheters (Pei and Flock 2001, J. Infect. Dis. 184; 52).

Fbe has a putative signal sequence with a cleavage site between amino acids 51 and 52. Therefore a preferred fragment of Fbe contains the mature form of Fbe extending from amino acid 52 to the C-terminus (amino acid 1,092).

The domain of Fbe from amino acid 52 to amino acid 825 is responsible for fibrinogen binding. Therefore a preferred fragment of Fbe consists of or contains amino acids 52-825.

The region between amino acid 373 and 516 of Fbe shows the most conservation between Fbe and ClfA. Preferred fragment will therefore contain amino acids 373-516 of Fbe.

Amino acids 825 – 1041 of Fbe contains a highly repetitive region composed of tandemly repeated aspartic acid and serine residues.

IsaA/PisA

IsaA is a 29kDa protein, also known as PisA has been shown to be a immunodominant staphylococcal protein during sepsis in hospital patients (Lorenz et al 2000, FEMS Immunol. Med. Microb. 29; 145).

The first 29 amino acids of the IsaA sequence are thought to be a signal sequence. Therefore a preferred fragment of IsaA to be included in an immunogenic composition of

the invention would contain amino acid residues 30 onwards, to the end of the coded sequence.

Fibronectin binding protein

Fibronectin binding protein A contains several domains that are involved in binding to fibronectin (WO 94/18327). These are called D1, D2, D3 and D4. Preferred fragments of fibronectin binding protein A or B comprise or consist of D1, D2, D3, D4, D1-D2, D2-D3, D3-D4, D1-D3, D2-D4 or D1-D4.

Fibronectin binding protein contains a 36 amino acid signal sequence. For example:

VKNNLRYGIRKHKLGAASVFLGTMIVVGMGQDKEAA

Optionally, the mature protein omitting this signal sequence is included in the immunogenic composition of the invention.

Transporter proteins

The cell wall of Gram positive bacteria acts as a barrier preventing free diffusion of metabolites into the bacterium. A family of proteins orchestrates the passage of essential nutrients into the bacterium and are therefore essential for the viability of the bacterium. The term transporter protein covers proteins involved in the initial step of binding to metabolites such as iron as well as those involved in actually transporting the metabolite into the bacterium.

Molecular iron is an essential co-factor for bacterial growth. Siderophores are secreted that bind free iron and then are captured by bacterial surface receptors that deliver iron for transport across the cytoplasmic membrane. Iron acquisition is critical for the establishment of human infections so that the generation of an immune response against this class of proteins leads to a loss of staphylococcal viability.

Examples of transporter proteins include Immunodominant ABC transporter (Burnie et al 2000 Infect. Imun. 68; 3200), IsdA (Mazmanian et al 2002 PNAS 99; 2293), IsdB (Mazmanian et al 2002 PNAS 99; 2293), Mg2+ transporter, SitC (Wiltshire and Foster 2001 Infect. Immun. 69; 5198) and Ni ABC transporter.

Immunodominant ABC transporter

Immunodominant ABC transporter is a well conserved protein which may be capable of generating an immune response that is cross-protective against different staphylococcal

strains (Mei et al 1997, Mol. Microbiol. 26; 399). Antibodies against this protein have been found in patients with septicaemia (Burnie et al 2000, Infect. Immun. 68; 3200).

Preferred fragments of imunodominant ABC transporter will include the peptides DRHFLN, GNYD, RRYPF, KTTLLK, GVTTSLS, VDWLR, RGFL, more preferably KIKVYVGNYDFWYQS, TVIVVSHDRHFLYNNV and/or TETFLRGFLGRMLFS since these sequences contain epitopes that are recognised by the human immune system.

IsdA-IsdB

The isd genes (iron-regulated surface determinant) of *S. aureus* encode proteins responsible for haemoglobin binding and passage of haem iron to the cytoplasm , where it acts as an essential nutrient. IsdA and IsdB are located in the cell wall of staphylococci. IsdA appear to be exposed on the surface of bacterium since it is susceptible to proteinase K digestion. IsdB was partially digested suggesting that it is partially exposed on the surface of the bacterium (Mazmanian et al 2003 Science 299; 906).

IsdA and IsdB are both 29kDa proteins which bind heme. Their expression is regulated by the availability of iron via the Fur repressor. Their expression will be high during infection in a host where the concentration of iron will be low.

They are also known as FrpA and FrpB (Morrissey et al 2002, Infect. Immun. 70; 2399). FrpA and FrpB are major surface proteins with a high charge. They have been shown to provide a major contribution to adhesion to plastic.

In an embodiment, the immunogenic composition of the invention comprises a fragment of IsdA and/or IsdB which is described in WO 01/98499 or WO 03/11899.

Toxins and regulators of virulence

Members of this family of proteins include toxin such as alpha toxin, hemolysin, enterotoxin B and TSST-1 as well as proteins that regulate the production of toxins such as RAP.

Alpha toxin (Hla)

Alpha toxin is an important virulence determinant produced by most strains of S.aureus. It is a pore forming toxin with haemolytic activity. Antibodies against alpha toxin have been shown to neutralise the detrimental and lethal effects of alpha toxin in animal models (Adlam et al 1977 Infect. Immun. 17; 250). Human platelets, endothelial cells and mononuclear cells are susceptible to the effects of alpha toxin.

The high toxicity of alpha toxin requires that it should be detoxified before being used as an immunogen. This can be achieved by chemical treatment, for instance by treating with formaldehyde, glutaraldehyde of other cross-linking reagents or by chemically conjugating it to bacterial polysaccharides or to LTA as described below.

A further way of removing toxicity is to introduce point mutations that remove toxicity while retaining the antigenicity of the toxin. The introduction of a point mutation at amino acid 35 of alpha toxin where a histidine residue is replaced with a leucine residue results in the removal of toxicity whilst retaining immunogenicity (Menzies and Kernodle 1996; Infect. Immun. 64; 1839). Histidine 35 appears to be critical for the proper oligomerization required for pore formation and mutation of this residue leads to loss of toxicity.

When incorporated into immunogenic compositions of the invention, alpha toxin is preferably detoxified by mutation of His 35, most preferably by replacing His 35 with Leu or Arg. In an alternative embodiment, alpha toxin is detoxified by conjugation to other components of the immunogenic composition, preferably capsular polysaccharides or LTA, most preferably to S. aureus type V polysaccharide and/or S.aureus Type VIII polysaccharide and/or PIA.

RNA III activating protein (RAP)

RAP is not itself a toxin, but is a regulator of the expression of virulence factors. RAP is produced and secreted by staphylococci. It activates the agr regulatory system of other staphylococci and activates the expression and subsequent release of virulence factors such as hemolysin, enterotoxin B and TSST-1.

An immune response generated against RAP would not kill the bacterium but would interfere with their pathogenicity. This has the advantage of providing less selective pressure for new resistant strains to emerge.

It would have a second advantage of producing an immune response that would be instrumental in reducing the morbidity of the infection.

It is particularly advantageous to combine RAP with other antigens in a vaccine, particularly where the additional antigen would provide an immune response that is able to kill the bacterium.

Other immunodominant proteins

Accumulation-associated protein (Aap)

Aap is a 140kDa protein which is essential for the accumulation of *S. epidermidis* strains on surfaces (Hussain et al Infect. Immun. 1997, 65; 519). Strains expressing this protein produced significantly larger amounts of biofilm and Aap appear to be involved in biofilm formation. Antibodies against Aap are able to inhibit biofilm formation and inhibit the accumulation of *S. epidermidis*.

Staphylococcal Secretory antigen SsaA

SsaA is a strongly immunogenic protein of 30kDa found in both S. aureus and S. epidermidis (Lang et al 2000 FEMS Immunol. Med. Microbiol. 29; 213). Its expression during endocarditis suggested a virulence role specific to the pathogenesis of the infectious disease.

SsaA contains an N-terminal leader sequence and a signal peptidase cleavage site. The leader peptide is followed by a hydrophilic region of approximately 100 amino acids from residue 30 to residue 130.

A preferred fragment of SsaA to be incorporated into the immunogenic composition of the invention is made up of the mature protein (amino acids 27 to the C-terminus or amino acids 30 to the C-terminus).

A further preferred fragments contains the hydrophilic area of SsaA from amino acid 30 to amino acid 130.

Preferred combinations

Staphylococcal infections progress through several different stages. For example, the staphylococcal life cycle involves commensal colonisation, initiation of infection by accessing adjoining tissues or the bloodstream, anaerobic multiplication in the blood, interplay between *S. aureus* virulence determinants and the host defence mechanisms and induction of complications including endocarditis, metastatic abscess formation and sepsis syndrome. Different molecules on the surface of the bacterium will be involved in different steps of the infection cycle. By targeting the immune response against a combination of particular antigens involved in different processes of Staphylococcal infection, multiple aspects of staphylococcal function are affected and this can result in good vaccine efficacy.

In particular, combinations of certain antigens from different classes, some of which are involved in adhesion to host cells, some of which are involved in iron acquisition or other transporter functions, some of which are toxins or regulators of virulence and immunodominant antigens can elicit an immune response which protects against multiple stages of infection.

Some combinations of antigens are particularly effective at inducing an immune response. This can be measured either in animal model assays as described in the examples and/or using an opsonophagocytic assay as described in the examples. Without wishing to be bound by theory, such effective combinations of antigens are thought to be enabled by a number of characteristics of the immune response to the antigen combination. The antigens themselves are usually exposed on the surface of Staphylococcal cells, they tend to be conserved but also tend not to be present in sufficient quantity on the surface cell for an optimal bactericidal response to take place using antibodies elicited against the single antigen. Combining the antigens of the invention can result in a formulation eliciting an advantageous combination of antibodies which interact with the Staphylococcal cell beyond a critical threshold. At this critical level, sufficient antibodies of sufficient quality bind to the surface of the bacterium to allow either efficient killing by complement or neutralisation of the bacterium. This can be measured in either an animal challenge model or an opsonisation assay as described in the examples.

Preferred immunogenic compositions of the invention comprise a plurality of proteins selected from at least two different categories of protein, having different functions within Staphylococci. Examples of such categories of proteins are extracellular binding proteins, transporter proteins such as Fe acquisition proteins, toxins or regulators of virulence and other immunodominant proteins.

In a preferred embodiment, the immunogenic composition of the invention further comprises a number of proteins equal to or greater than 2, 3, 4, 5 or 6 selected from 2 or 3 different groups selected from;

- Group a) extracellular component binding proteins;
- Group b) transporter proteins;
- Group c) toxins or regulators of virulence.

In a preferred embodiment, the immunogenic composition of the invention further comprises a number of proteins equal to or greater than 2, 3, 4, 5 or 6 selected from 2 or 3 of the following groups:

- group a) - at least one staphylococcal extracellular component binding protein or fragment thereof selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrG, SdrH, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig and MAP;
- group b) - at least one staphylococcal transporter protein or fragment thereof selected from the group consisting of Immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC and Ni ABC transporter;
- group c) - at least one staphylococcal regulator of virulence, toxin or fragment thereof selected from the group consisting of alpha toxin (Hla), alpha toxin H35R mutant, RNA III activating protein (RAP).

In a preferred embodiment, the immunogenic composition of the invention contains at least one protein selected from group a) and an additional protein selected from group b) and/or group c).

In a further embodiment, the immunogenic composition of the invention contains at least one antigen selected from group b) and an additional protein selected from group c) and/or group a).

In a further embodiment, the immunogenic composition of the invention contains at least one antigen selected from group c) and an additional protein selected from group a) and/or group b).

A preferred combination of proteins in the immunogenic composition of the invention comprises laminin receptor and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises SitC and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises EbhA and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises EbhB and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises EbpS and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises EFB(FIB) and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises SBI and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises autolysin and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises ClfA and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises SdrC and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises SdrG and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant and RAP.

A further preferred combination of proteins in the immunogenic composition of the invention comprises SdrH and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises Lipase GehD and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises SasA and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises FnbA and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises FnbB and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises Cna and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises ClfB and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises FbpA and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises Npase and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises IsaA/PisA and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises SsaA and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises EPB and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises SSP-1 and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises SSP-2 and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises HPB and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises vitronectin binding protein and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises fibrinogen binding protein and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises coagulase and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises Fig and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of proteins in the immunogenic composition of the invention comprises MAP and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of protein in the immunogenic composition of the invention comprises immunodominant ABC tranporter and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrG, SdrH, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of protein in the immunogenic composition of the invention comprises IsdA and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrG, SdrH, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP,

Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of protein in the immunogenic composition of the invention comprises IsdB and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrG, SdrH, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of protein in the immunogenic composition of the invention comprises SitC and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrG, SdrH, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, alpha toxin, alpha toxin H35L OR H35R mutant, RAP, Aap and SsaA.

A further preferred combination of protein in the immunogenic composition of the invention comprises alpha toxin and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrG, SdrH, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, Aap and SsaA.

A further preferred combination of protein in the immunogenic composition of the invention comprises alpha toxin H35L OR H35R variant and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrG, SdrH, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, Aap and SsaA.

A further preferred combination of protein in the immunogenic composition of the invention comprises RAP and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrG, SdrH, Lipase GehD,

SasA, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC, Ni ABC transporter, Aap and SsaA.

In the above and below combinations, the specified proteins may optionally be present in the immunogenic composition of the invention as a fragment or fusion protein as described above.

Combinations of three proteins

A preferred immunogenic composition of the invention further comprises three protein components in a combination of alpha-toxin, an extracellular component binding protein (preferably an adhesin) and a transporter protein (preferably an iron-binding protein).

In such a combination, the alpha toxin may be chemically detoxified or genetically detoxified by introduction of point mutation(s), preferably the His35Leu point mutation. The alpha toxin is present as a free protein or alternatively is conjugated to a polysaccharide or LTA component of the immunogenic composition.

Preferred combinations include:-

An immunogenic composition comprising alpha toxin, IsdA and an extracellular component binding protein selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrG, SdrH, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig and MAP.

An immunogenic composition comprising alpha toxin, IsdB and an extracellular component binding protein selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrG, SdrH, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig and MAP.

An immunogenic composition comprising alpha toxin, IsdA and an adhesin selected from the group consisting of laminin receptor, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), ClfA, SdrC, SdrG, SdrH, autolysin, FnbA, FnbB, Cna, ClfB, FbpA, Npase, SSP-1, SSP-2, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig and MAP.

An immunogenic composition comprising alpha toxin, IsdB and an adhesin selected from the group consisting of laminin receptor, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), autolysin, ClfA, SdrC, SdrG, SdrH, FnbA, FnbB, Cna, ClfB, FbpA, Npase, SSP-1, SSP-2, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig and MAP.

An immunogenic composition comprising alpha toxin, IsdA and laminin receptor.

An immunogenic composition comprising alpha toxin, IsdA and EbhA.

An immunogenic composition comprising alpha toxin, IsdA and EbhB.

An immunogenic composition comprising alpha toxin, IsdA and EbpS.

An immunogenic composition comprising alpha toxin, IsdA and EFB (FIB).

An immunogenic composition comprising alpha toxin, IsdA and SdrG.

An immunogenic composition comprising alpha toxin, IsdA and ClfA.

An immunogenic composition comprising alpha toxin, IsdA and ClfB.

An immunogenic composition comprising alpha toxin, IsdA and FnbA.

An immunogenic composition comprising alpha toxin, IsdA and coagulase.

An immunogenic composition comprising alpha toxin, IsdA and Fig.

An immunogenic composition comprising alpha toxin, IsdA and SdrH.

An immunogenic composition comprising alpha toxin, IsdA and SdrC.

An immunogenic composition comprising alpha toxin, IsdA and MAP.

An immunogenic composition comprising IsaA and Sbi.

An immunogenic composition comprising IsaA and IsdB.

An immunogenic composition comprising IsaA and IsdA.

An immunogenic composition comprising IsaA and SdrC.

An immunogenic composition comprising IsaA and Ebh or fragment thereof as described above.

An immunogenic composition comprising Sbi and SdrC.

An immunogenic composition comprising Sbi and Ebh or fragment thereof as described above.

An immunogenic composition of the invention comprising IsaA, Sbi or SdrC

Selection of antigens expressed in different clonal lineages

Analysis of the occurrence of virulence factors in relation with the population structure of *Staphylococcus aureus* showed variable presence of virulence genes in natural populations of *S. aureus*.

Among clinical isolates of *Staphylococcus aureus*, at least five clonal lineages were shown to be highly prevalent (Booth *et al.*, 2001 Infect Immun. 69(1):345-52). Alpha-hemolysin (*hla*), fibronectin-binding protein A (*fnbA*) and clumping factor A (*clfA*) were shown to be present in most of the isolates, regardless of lineage identity, suggesting an important role of these proteins in the survival of *S. aureus* (Booth *et al.*, 2001 Infect Immun. 69(1):345-52). Moreover, according to Peacock et al. 2002 the distributions of *fnbA*, *clfA*, coagulase, *spa*, *map*, *pvl* (Panton-Valentine leukocidin), *hlg* (gamma-toxin), alpha-toxin and *ica* appeared to be unrelated to the underlying clonal structure suggesting considerable horizontal transfer of these genes.

In contrary, other virulence genes such as fibronectin binding protein B (*fnbB*), beta-hemolysin (*hlb*), collagen binding protein (*cna*), TSST-1 (*tst*) and methicillin resistance gene (*mecA*) are strongly associated with specific lineages (Booth *et al.*, 2001 Infect Immun. 69(1):345-52). Similarly, Peacock *et al.* 2002 (Infect Immun. 70(9):4987-96) showed that the distributions of the enterotoxins, *tst*, the exfolatins (*eta* and *etb*), beta- and delta-toxins, the *sdr* genes (*sdr*D, *sdr*E and *bbp*), *cna*, *ebp*S and *efb* within the population are all highly significantly related to MLST-derived clonal complexes.

MLST data provide no evidence that strains responsible for nosocomial disease represent a distinct subpopulation from strains causing community-acquired disease or strains

recovered from asymptomatic carriers (Feil *et al.*, 2003 J Bacteriol. 185(11):3307-16).

Preferred immunogenic compositions of the invention are effective against staphylococci from different clonal lineages.

In an embodiment, the immunogenic composition comprises 1, 2, 3, 4, preferably at least 1 protein that is expressed in most isolates of staphylococci. Examples of such proteins include alpha-hemolysin (*hla*), fibronectin-binding protein A (*fnbA*) and clumping factor A (*clfA*), coagulase, *spa*, *map*, *pvl* (Panton-Valentine leukocidin), *hlg* (gamma-toxin) , *ica*, immunodominant ABC transporter, RAP, autolysin (Rupp et al 2001, J. Infect. Dis. 183; 1038), laminin receptors, SitC, IsaA/PisA, SPOIIIE (), SsaA, EbpS, SasF (Roche et al 2003, Microbiology 149; 643), EFB(FIB), SBI, ClfB, IsdA, IsdB, FnbB, Npase, EBP, Bone sialo binding protein II, IsaB/PisB (Lorenz et al FEMS Immuno. Med. Microb. 2000, 29; 145), SasH (Roche et al 2003, Microbiology 149; 643), MRPI, SasD (Roche et al 2003, Microbiology 149; 643), SasH (Roche et al 2003, Microbiology 149; 643), aureolysin precursor (AUR)/Sepp1 and novel autolysin.

In an alternative embodiment, 2 or more proteins which are expressed in different sets of clonal strains are included in the immunogenic composition of the invention. Preferably the combination of antigens will allow an immune response to be generated that is effective against multiple clonal strains, most preferably against all clonal stains. Preferred combinations include FnbB and betahemolysin, FnbB and Cna, FnbB and TSST-1, FnbB and mecA, FnbB and SdrD, FnbB and SdrF, FnbB and EbpS, FnbB and Efb, beta-haemolysin and Cna, beta-haemolysin and TSST-1, beta-haemolysin and mecA, beta-haemolysin and SdrD, beta-haemolysin and SdrF, beta-haemolysin and EbpS, beta-haemolysin and Efb, Cna and TSST-1, Cna and mecA, Cna and SdrD, Cna and SdrF, Cna and EbpS, Cna and Efb, TSST-1 and mecA, TSST-1 and SdrD, TSST-1 and SdrF, TSST-1 and EbpS, TssT-1 and Efb, MecA and SdrD, MecA and SdrF, MecA and EbpS, MecA and Efb, SdrD and SdrF, SdrD and EbpS, SdeD and Efb, SdrF and EbpS, SdrF and Efb, and, EbpS and Efb.

The preferred combinations described above may be combined with additional components described above.

Protection against *S.aureus* and *S. epidermidis*

In a preferred embodiment of the invention the immunogenic composition provides an effective immune response against more than one strain of staphylococci, preferably against strains from both *S.aureus* and *S. epidermidis*. More preferably, a protective immune response is generated against type 5 and 8 serotypes of *S. aureus*. More

preferably, a protective immune response is generated against serotypes I, II and III of *S. epidermidis*.

One use of the immunogenic composition of the invention is to prevent nosocomial infections, for instance in elective surgery patients, by inoculating prior to hospital treatment. At this stage, it is difficult to accurately predict which staphylococcal strains the patient will be exposed to. It is therefore advantageous to inoculate with a vaccine that is capable of generating an effective immune response against various strains of staphylococci.

An effective immune response is defined as an immune response that gives significant protection in a mouse challenge model or opsonophagocytosis assay as described in the examples. Significant protection in a mouse challenge model, for instance that of example 5, is defined as an increase in the LD50 in comparison with carrier inoculated mice of at least 10%, 20%, 50%, 100% or 200%. Significant protection in a cotton rat challenge model, for instance that of example 8, is defined as a decrease in the mean observed LogCFU/nose of at least 10%, 20%, 50%, 70% or 90%. The presence of opsonising antibodies is known to correlate with protection, therefore significant protection is indicated by a decrease in the bacterial count of at least 10%, 20%, 50%, 70% or 90% in an opsonophagocytosis assay, for instance that of example 7.

Several of the proteins including immunodominant ABC transporter, RNA III activating protein, Laminin receptors, SitC, IsaA/PisA, SsaA, EbhA/EbhB, EbpS and Aap are well conserved between *S.aureus* and *S. epidermidis* and example 8 shows that IsaA, ClfA, IsdB, SdrG, HarA, FnbpA and Sbi can generate a cross-reactive immune response (for example crossreactive between at least one *S. aureus* and at least one *S. epidermidis* strain). PIA is also well conserved between *S. aureus* and *S. epidermidis*.

Therefore in a preferred embodiment, the immunogenic composition of the invention will comprise PIA and type 5 and 8 polysaccharides and will further comprise one, two, three or four of the above proteins.

Vaccines

In a preferred embodiment, the immunogenic composition of the invention is mixed with a pharmaceutically acceptable excipient, more preferably with an adjuvant to form a vaccine.

The vaccines of the present invention are preferably adjuvanted. Suitable adjuvants include an aluminum salt such as aluminum hydroxide gel (alum) or aluminium phosphate, but may also be a salt of calcium, magnesium, iron or zinc, or may be an insoluble suspension of acylated tyrosine, or acylated sugars, cationically or anionically derivatized polysaccharides, or polyphosphazenes.

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

It is important to remember that the distinction of Th1 and Th2-type immune response is not absolute. In reality an individual will support an immune response which is described as being predominantly Th1 or predominantly Th2. However, it is often convenient to consider the families of cytokines in terms of that described in murine CD4 +ve T cell clones by Mosmann and Coffman (Mosmann, T.R. and Coffman, R.L. (1989) TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. Annual Review of Immunology, 7, p145-173). Traditionally, Th1-type responses are associated with the production of the INF-γ and IL-2 cytokines by T-lymphocytes. Other cytokines often directly associated with the induction of Th1-type immune responses are not produced by T-cells, such as IL-12. In contrast, Th2-type responses are associated with the secretion of Il-4, IL-5, IL-6, IL-10. Suitable adjuvant systems which promote a predominantly Th1 response include: Monophosphoryl lipid A or a derivative thereof, particularly 3-de-O-acylated monophosphoryl lipid A (3D-MPL) (for its preparation see GB 2220211 A); and a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A, together with either an aluminium salt (for instance aluminium phosphate or aluminium hydroxide) or an oil-in-water emulsion. In such combinations, antigen and 3D-MPL are contained in the same particulate structures, allowing for more efficient delivery of antigenic and immunostimulatory signals. Studies have shown that 3D-MPL is able to further enhance the immunogenicity of an alum-adsorbed antigen [Thoelen *et al.* Vaccine (1998) 16:708-14; EP 689454-B1].

An enhanced system involves the combination of a monophosphoryl lipid A and a saponin derivative, particularly the combination of QS21 and 3D-MPL as disclosed in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with

cholesterol as disclosed in WO 96/33739. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil in water emulsion is described in WO 95/17210, and is a preferred formulation. Preferably the vaccine additionally comprises a saponin, more preferably QS21. The formulation may also comprise an oil in water emulsion and tocopherol (WO 95/17210). The present invention also provides a method for producing a vaccine formulation comprising mixing a protein of the present invention together with a pharmaceutically acceptable excipient, such as 3D-MPL. Unmethylated CpG containing oligonucleotides (WO 96/02555) are also preferential inducers of a TH1 response and are suitable for use in the present invention.

Preferred compositions of the invention are those forming a liposome structure. Compositions where the sterol/immunologically active saponin fraction forms an ISCOM structure also form an aspect of the invention.

The ratio of QS21 : sterol will typically be in the order of 1 : 100 to 1 : 1 weight to weight. Preferably excess sterol is present, the ratio of QS21 : sterol being at least 1 : 2 w/w. Typically for human administration QS21 and sterol will be present in a vaccine in the range of about 1 μg to about 100 μg, preferably about 10 μg to about 50 μg per dose.

The liposomes preferably contain a neutral lipid, for example phosphatidylcholine, which is preferably non-crystalline at room temperature, for example eggyolk phosphatidylcholine, dioleoyl phosphatidylcholine or dilauryl phosphatidylcholine. The liposomes may also contain a charged lipid which increases the stability of the lipsome-QS21 structure for liposomes composed of saturated lipids. In these cases the amount of charged lipid is preferably 1-20% w/w, most preferably 5-10%. The ratio of sterol to phospholipid is 1-50% (mol/mol), most preferably 20-25%.

Preferably the compositions of the invention contain MPL (3-deacylated mono-phosphoryl lipid A, also known as 3D-MPL). 3D-MPL is known from GB 2 220 211 (Ribi) as a mixture of 3 types of De-O-acylated monophosphoryl lipid A with 4, 5 or 6 acylated chains and is manufactured by Ribi Immunochem, Montana. A preferred form is disclosed in International Patent Application 92/116556.

Suitable compositions of the invention are those wherein liposomes are initially prepared without MPL, and MPL is then added, preferably as 100 nm particles. The MPL is therefore not contained within the vesicle membrane (known as MPL out). Compositions where the MPL is contained within the vesicle membrane (known as MPL in) also form an aspect of the invention. The antigen can be contained within the vesicle membrane or contained outside the vesicle membrane. Preferably soluble antigens are outside and hydrophobic or lipidated antigens are either contained inside or outside the membrane.

The vaccine preparations of the present invention may be used to protect or treat a mammal susceptible to infection, by means of administering said vaccine via systemic or mucosal route. These administrations may include injection *via* the intramuscular, intraperitoneal, intradermal or subcutaneous routes; or *via* mucosal administration to the oral/alimentary, respiratory, genitourinary tracts. Intranasal administration of vaccines for the treatment of pneumonia or otitis media is preferred (as nasopharyngeal carriage of pneumococci can be more effectively prevented, thus attenuating infection at its earliest stage). Although the vaccine of the invention may be administered as a single dose, components thereof may also be co-administered together at the same time or at different times (for instance pneumococcal polysaccharides could be administered separately, at the same time or 1-2 weeks after the administration of any bacterial protein component of the vaccine for optimal coordination of the immune responses with respect to each other). For co-administration, the optional Th1 adjuvant may be present in any or all of the different administrations, however it is preferred if it is present in combination with the bacterial protein component of the vaccine. In addition to a single route of administration, 2 different routes of administration may be used. For example, polysaccharides may be administered IM (or ID) and bacterial proteins may be administered IN (or ID). In addition, the vaccines of the invention may be administered IM for priming doses and IN for booster doses.

The amount of conjugate antigen in each vaccine dose is selected as an amount which induces an immunoprotective response without significant, adverse side effects in typical vaccines. Such amount will vary depending upon which specific immunogen is employed and how it is presented. Generally, it is expected that each dose will comprise 0.1-100 μg of polysaccharide, preferably 0.1-50 μg for polysaccharide conjugates, preferably 0.1-10 μg, more preferably 1-10 μg, of which 1 to 5 μg is a more preferable range. However, for serotype 6B, the preferred dosage will comprise 3-10 μg of polysaccharide.

The content of protein antigens in the vaccine will typically be in the range 1-100μg, preferably 5-50μg, most typically in the range 5 - 25μg. Following an initial vaccination, subjects may receive one or several booster immunizations adequately spaced.

Vaccine preparation is generally described in Vaccine Design ("The subunit and adjuvant approach" (eds Powell M.F. & Newman M.J.) (1995) Plenum Press New York). Encapsulation within liposomes is described by Fullerton, US Patent 4,235,877.

The vaccines of the present invention may be stored in solution or lyophilized. Preferably the solution is lyophilized in the presence of a sugar such as sucrose, trehalose or lactose. It is still further preferable that they are lyophilized and extemporaneously reconstituted prior to use. Lyophilizing may result in a more stable composition (vaccine) and may possibly lead to higher antibody titers in the presence of 3D-MPL and in the absence of an aluminium based adjuvant.

Antibodies and passive immunisation

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

Inocula for polyclonal antibody production are typically prepared by dispersing the antigenic composition in a physiologically tolerable diluent such as saline or other adjuvants suitable for human use to form an aqueous composition. An immunostimulatory amount of inoculum is administered to a mammal and the inoculated mammal is then maintained for a time sufficient for the antigenic composition to induce protective antibodies.

The antibodies can be isolated to the extent desired by well known techniques such as affinity chromatography (Harlow and Lane Antibodies; a laboratory manual 1988).

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

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

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

An additional aspect of the invention is a pharmaceutical composition comprising two of more monoclonal antibodies (or fragments thereof; preferably human or humanised) reactive against at least two constituents of the immunogenic composition of the invention, which could be used to treat or prevent infection by Gram positive bacteria, preferably staphylococci, more preferably *S. aureus* or *S. epidermidis*.

Such pharmaceutical compositions comprise monoclonal antibodies that can be whole immunoglobulins of any class e.g. IgG, IgM, IgA, IgD or IgE, chimeric antibodies or hybrid

antibodies with specificity to two or more antigens of the invention. They may also be fragments e.g. F(ab')2, Fab', Fab, Fv and the like including hybrid fragments.

Methods of making monoclonal antibodies are well known in the art and can include the fusion of splenocytes with myeloma cells (Kohler and Milstein 1975 Nature 256; 495; Antibodies – a laboratory manual Harlow and Lane 1988). Alternatively, monoclonal Fv fragments can be obtained by screening a suitable phage display library (Vaughan TJ et al 1998 Nature Biotechnology 16; 535). Monoclonal antibodies may be humanised or part humanised by known methods.

Methods

The invention also encompasses method of making the immunogenic compositions and vaccines of the invention.

A preferred process of the invention, is a method to make a vaccine comprising the steps of mixing antigens to make the immunogenic composition of the invention and adding a pharmaceutically acceptable excipient.

Methods of treatment

The invention also encompasses method of treatment or staphylococcal infection, particularly hospital acquired nosocomial infections.

This immunogenic composition or vaccine of the invention is particularly advantageous to use in cases of elective surgery. Such patients will know the date of surgery in advance and could be inoculated in advance. Since it is not know whether the patient will be exposed to *S.aureus* or *S. epidermidis* infection, it is preferred to inoculate with a vaccine of the invention that protects against both, as described above. Preferably adults over 16 awaiting elective surgery are treated with the immunogenic compositions and vaccines of the invention.

It is also advantageous to inoculate health care workers with the vaccine of the invention.

The vaccine preparations of the present invention may be used to protect or treat a mammal susceptible to infection, by means of administering said vaccine via systemic or mucosal route. These administrations may include injection *via* the intramuscular,

intraperitoneal, intradermal or subcutaneous routes; or *via* mucosal administration to the oral/alimentary, respiratory, genitourinary tracts.

The amount of antigen in each vaccine dose is selected as an amount which induces an immunoprotective response without significant, adverse side effects in typical vaccines. Such amount will vary depending upon which specific immunogen is employed and how it is presented. The protein content of the vaccine will typically be in the range1 -100μg, preferably 5-50μg, most typically in the range 10 - 25μg. Generally, it is expected that each dose will comprise 0.1-100 μg of polysaccharide where present, preferably 0.1-50 μg, preferably 0.1-10 μg, of which 1 to 5 μg is the most preferable range. An optimal amount for a particular vaccine can be ascertained by standard studies involving observation of appropriate immune responses in subjects. Following an initial vaccination, subjects may receive one or several booster immunisations adequately spaced.

Although the vaccines of the present invention may be administered by any route, administration of the described vaccines into the skin (ID) forms one embodiment of the present invention. Human skin comprises an outer "horny" cuticle, called the stratum corneum, which overlays the epidermis. Underneath this epidermis is a layer called the dermis, which in turn overlays the subcutaneous tissue. Researchers have shown that injection of a vaccine into the skin, and in particular the dermis, stimulates an immune response, which may also be associated with a number of additional advantages. Intradermal vaccination with the vaccines described herein forms a preferred feature of the present invention.

The conventional technique of intradermal injection, the "mantoux procedure", comprises steps of cleaning the skin, and then stretching with one hand, and with the bevel of a narrow gauge needle (26-31 gauge) facing upwards the needle is inserted at an angle of between 10-15°. Once the bevel of the needle is inserted, the barrel of the needle is lowered and further advanced whilst providing a slight pressure to elevate it under the skin. The liquid is then injected very slowly thereby forming a bleb or bump on the skin surface, followed by slow withdrawal of the needle.

More recently, devices that are specifically designed to administer liquid agents into or across the skin have been described, for example the devices described in WO 99/34850

and EP 1092444, also the jet injection devices described for example in WO 01/13977; US 5,480,381, US 5,599,302, US 5,334,144, US 5,993,412, US 5,649,912, US 5,569,189, US 5,704,911, US 5,383,851, US 5,893,397, US 5,466,220, US 5,339,163, US 5,312,335, US 5,503,627, US 5,064,413, US 5,520, 639, US 4,596,556, US 4,790,824, US 4,941,880, US 4,940,460, WO 97/37705 and WO 97/13537. Alternative methods of intradermal administration of the vaccine preparations may include conventional syringes and needles, or devices designed for ballistic delivery of solid vaccines (WO 99/27961), or transdermal patches (WO 97/48440; WO 98/28037); or applied to the surface of the skin (transdermal or transcutaneous delivery WO 98/20734 ; WO 98/28037).

When the vaccines of the present invention are to be administered to the skin, or more specifically into the dermis, the vaccine is in a low liquid volume, particularly a volume of between about 0.05 ml and 0.2 ml.

The content of antigens in the skin or intradermal vaccines of the present invention may be similar to conventional doses as found in intramuscular vaccines (see above). However, it is a feature of skin or intradermal vaccines that the formulations may be "low dose". Accordingly the protein antigens in "low dose" vaccines are preferably present in as little as 0.1 to 10μg, preferably 0.1 to 5 μg per dose; and the polysaccharide (preferably conjugated) antigens may be present in the range of 0.01-1μg, and preferably between 0.01 to 0.5 μg of polysaccharide per dose.

As used herein, the term "intradermal delivery" means delivery of the vaccine to the region of the dermis in the skin. However, the vaccine will not necessarily be located exclusively in the dermis. The dermis is the layer in the skin located between about 1.0 and about 2.0 mm from the surface in human skin, but there is a certain amount of variation between individuals and in different parts of the body. In general, it can be expected to reach the dermis by going 1.5 mm below the surface of the skin. The dermis is located between the stratum corneum and the epidermis at the surface and the subcutaneous layer below. Depending on the mode of delivery, the vaccine may ultimately be located solely or primarily within the dermis, or it may ultimately be distributed within the epidermis and the dermis.

A preferred embodiment of the invention is a method of preventing or treating staphylococcal infection or disease comprising the step of administering the immunogenic composition or vaccine of the invention to a patient in need thereof.

In a preferred embodiment, the patient is awaiting elective surgery.

A further preferred embodiment of the invention is a use of the immunogenic composition of the invention in the manufacture of a vaccine for treatment or prevention of staphylococcal infection or disease, preferably post-surgery staphylococcal infection.

The term 'staphylococcal infection' encompasses infection caused by *S.aureus* and/or *S. epidermidis* and other staphylococcal strains capable of causing infection in a mammalina, preferably human host.

The terms "comprising", "comprise" and "comprises" herein are intended by the inventors to be optionally substitutable with the terms "consisting of", "consist of" and "consists of", respectively, in every instance.

All references or patent applications cited within this patent specification are incorporated by reference herein.

In order that this invention may be better understood, the following examples are set forth. These examples are for purposes of illustration only, and are not to be construed as limiting the scope of the invention in any manner.

Examples

Example 1 Construction of Plasmid to Express Recombinant proteins

A: Cloning.

Appropriate restriction sites engineered into oligonucleotides specific for the staphylococcal gene permitted directional cloning of the PCR product into the *E.coli* expression plasmid pET24d or pQE-30 such that a protein could be expressed as a fusion protein containing a (His)6 affinity chromatography tag at the N- or C-terminus.

The primers used were:

Alpha toxin – 5'-CGCGGATCCGCAGATTCTGATATTAATATTAAAAC-3' and 5'CCCAAGCTTTTAATTTGTCATTTCTTCTTTTTC-3'

EbpS – 5'-CGCGGATCCGCTGGGTCTAATAATTTTAAAGATG-3' and 5'CCCAAGCTTTTATGGAATAACGATTTGTTG-3'

ClfA – 5'-CGCGGATCCAGTGAAAATAGTGTTACGCAATC-3' and 5'CCCAAGCTTTTACTCTGGAATTGGTTCAATTTC-3'

FnbpA – 5'-CGCGGATCCACACAAACAACTGCAACTAACG-3' and 5'CCCAAGCTTTTATGCTTTGTGATTCTTTTTCAAAC3'

Sbi – 5'-CGCGGATCCAACACGCAACAAACTTC-3' and 5'GGAACTGCAGTTATTTCCAGAATGATAATAAATTAC-3'

SdrC – 5'-CGCGGATCCGCAGAACATACGAATGGAG-3' and 5'CCCAAGCTTTTATGTTTCTTCTTCGTAGTAGC-3'

SdrG – 5'-CGCGGATCCGAGGAGAATTCAGTACAAG-3' and 5'CCCAAGCTTTTATTCGTCATCATAGTATCCG-3'

Ebh – 5'-AAAAGTACTCACCACCACCACCACC-3' and 5'AAAAGTACTCACTTGATTCATCGCTTCAG-3'

Aaa – 5'-GCGCGCCATGGCACAAGCTTCTACACAACATAC-3' and 5'GCGCGCTCGAGATGGATGAATGCATAGCTAGA-3'

IsaA – 5'-GCATCCATGGCACCATCACCATCACCACGAAGTAAACGTTGATCAAGC-3' and 5'-AGCACTCGAGTTAGAATCCCCAAGCACCTAAACC-3'

HarA – 5'-GCACCCATGGCAGAAAATACAAATACTTC-3' and 5'TTTTCTCGAGCATTTTAGATTGACTAAGTTG-3'

Autolysin glucosaminidase – 5'-CAAGTCCCATGGCTGAGACGACACAAGATCAAC-3' and 5'-CAGTCTCGAGTTTTACAGCTGTTTTTGGTTG-3'

Autolysin amidase – 5'-AGCTCATATGGCTTATACTGTTACTAAACC-3' and 5'GCGCCTCGAGTTTATATTGTGGGATGTCG-3'

IsdA – 5'-CAAGTCCCATGGCAACAGAAGCTACGAACGCAAC-3' and 5'ACCAGTCTCGAGTAATTCTTTAGCTTTAGAGCTTG-3'

IsdB – 5'-TATTCTCGAGGCTTTGAGTGTGTCCATCATTTG-3' and 5' GAAGCCATGGCAGCAGCTGAAGAAACAGGTGG-3'

MRPII – 5'-GATTACACCATGGTTAAACCTCAAGCGAAA-3' and 5'AGGTGTCTCGAGTGCGATTGTAGCTTCATT-3'

The PCR products were first introduced into the pGEM-T cloning vector (Novagen) using Top10 bacterial cells, according to the manufacturer's instructions. This intermediate construct was made to facilitate further cloning into an expression vector. Transformants containing the DNA insert were selected by restriction enzyme analysis. Following digestion, a ~20µl aliquot of the reaction was analyzed by agarose gel electrophoresis (0.8 % agarose in a Tris-acetate-EDTA (TAE) buffer). DNA fragments were visualized by UV illumination after gel electrophoresis and ethidium bromide staining. A DNA molecular size standard (1 Kb ladder, Life Technologies) was electrophoresed in parallel with the test samples and was used to estimate the size of the DNA fragments. Plasmid purified from selected transformants for each cloning was then sequentially digested to completion with appropriate restriction enzymes as recommended by the manufacturer (Life Technologies). The digested DNA fragment was then purified using silica gel-based spin columns prior to ligation with the pET24d or pQE-30 plasmid. Cloning of Ebh (H2 fragment), AaA, IsdA, IsdB, HarA, Atl-amidase, Atl-glucosamine, MRP, IsaA was carried out using the pET24d plasmid and cloning of ClfA, SdrC, SdrE, FnbpA, SdrG/Fbe, alpha toxin and Sbi were carried out using the pQE-30 plasmid.

B: Production of expression vector.

To prepare the expression plasmid pET24d or pQE-30 for ligation, it was similarly digested to completion with appropriate restriction enzymes. An approximately 5-fold molar excess of the digested fragments to the prepared vector was used to program the ligation reaction. A standard ~20 µl ligation reaction (~16°C, ~16 hours), using methods well known in the art, was performed using T4 DNA ligase (~2.0 units / reaction, Life Technologies). An aliquot of the ligation (~5 µl) was used to transform M15(pREP4) or BT21::DE3 electro-competent cells according to methods well known in the art. Following a ~2-3 hour outgrowth period at 37°C in ~1.0 ml of LB broth, transformed cells were

plated on LB agar plates containing ampicillin (100 µg/ml) and/or kanamycin (30µg/ml). Antibiotics were included in the selection. Plates were incubated overnight at 37°C for ~16 hours. Individual ApR/KanR colonies were picked with sterile toothpicks and used to "patch" inoculate fresh LB ApR/KanR plates as well as a ~1.0 ml LB Ap/ Kan broth culture. Both the patch plates and the broth culture were incubated overnight at 37°C in either a standard incubator (plates) or a shaking water bath. A whole cell-based PCR analysis was employed to verify that transformants contained the DNA insert. Here, the ~1.0 ml overnight LB Ap/Kan broth culture was transferred to a 1.5 ml polypropylene tube and the cells collected by centrifugation in a Beckmann microcentrifuge (~3 min., room temperature, ~12,000 X g). The cell pellet was suspended in ~200µl of sterile water and a ~10µl aliquot used to program a ~50µl final volume PCR reaction containing both forward and reverse amplification primers. The initial 95°C denaturation step was increased to 3 minutes to ensure thermal disruption of the bacterial cells and liberation of plasmid DNA. An ABI Model 9700 thermal cycler and a 32 cycle, three-step thermal amplification profile, i.e. 95°C, 45sec; 55-58°C, 45sec, 72°C, 1min., were used to amplify the BASB203 fragment from the lysed transformant samples. Following thermal amplification, a ~20µl aliquot of the reaction was analyzed by agarose gel electrophoresis (0.8 % agarose in a Tris-acetate-EDTA (TAE) buffer). DNA fragments were visualised by UV illumination after gel electrophoresis and ethidium bromide staining. A DNA molecular size standard (1 Kb ladder, Life Technologies) was electrophoresed in parallel with the test samples and was used to estimate the size of the PCR products. Transformants that produced the expected size PCR product were identified as strains containing a protein expression construct. Expression plasmid containing strains were then analyzed for the inducible expression of recombinant protein.

C: Expression Analysis of PCR-Positive Transformants.

An aliquot of the overnight seed culture (~1.0 ml) was inoculated into a 125 ml erlenmeyer flask containing ~25 ml of LB Ap/Kan broth and was grown at 37 °C with shaking (~250 rpm) until the culture turbidity reached O.D.600 of ~0.5, i.e. mid-log phase (usually about 1.5 - 2.0 hours). At this time approximately half of the culture (~12.5 ml) was transferred to a second 125 ml flask and expression of recombinant protein induced by the addition of IPTG (1.0 M stock prepared in sterile water, Sigma) to a final concentration of 1.0 mM. Incubation of both the IPTG-induced and non-induced cultures continued for an additional ~4 hours at 37 °C with shaking. Samples (~1.0 ml) of both induced and non-induced

cultures were removed after the induction period and the cells collected by centrifugation in a microcentrifuge at room temperature for ~3 minutes. Individual cell pellets were suspended in ~50µl of sterile water, then mixed with an equal volume of 2X Laemelli SDS-PAGE sample buffer containing 2-mercaptoethanol, and placed in boiling water bath for ~3 min to denature protein. Equal volumes (~15µl) of both the crude IPTG-induced and the non-induced cell lysates were loaded onto duplicate 12% Tris/glycine polyacrylamide gel (1 mm thick Mini-gels, Novex). The induced and non-induced lysate samples were electrophoresed together with prestained molecular weight markers (SeeBlue, Novex) under conventional conditions using a standard SDS/Tris/glycine running buffer (BioRad). Following electrophoresis, one gel was stained with commassie brilliant blue R250 (BioRad) and then destained to visualize novel IPTG-inducible protein(s) .The second gel was electroblotted onto a PVDF membrane (0.45 micron pore size, Novex) for ~2 hrs at 4 °C using a BioRad Mini-Protean II blotting apparatus and Towbin's methanol (20 %) transfer buffer. Blocking of the membrane and antibody incubations were performed according to methods well known in the art. A monoclonal anti-RGS (His)3 antibody, followed by a second rabbit anti-mouse antibody conjugated to HRP (QiaGen), were used to confirm the expression and identity of the recombinant protein. Visualization of the anti-His antibody reactive pattern was achieved using either an ABT insoluble substrate or using Hyperfilm with the Amersham ECL chemiluminescence system.

Example 2: Production of Recombinant Protein

Bacterial strain

A recombinant expression strain of *E. coli* M15(pREP4) containing a plasmid (pQE30) or BL21::DE3 containing plasmid pET24d encoding staphylococcal protein was used to produce cell mass for purification of recombinant protein.

Media

The fermentation medium used for the production of recombinant protein consisted of 2X YT broth (Difco) containing 100µg/ml Ap and/or 30 µg/ml Km. Antifoam was added to medium for the fermentor at 0.25 ml/L (Antifoam 204, Sigma). To induce expression of the recombinant protein, IPTG (Isopropyl ß-D-Thiogalactopyranoside) was added to the fermentor (1 mM, final).

Production of recombinant proteins

Under native conditions

IPTG was added at a final concentration of 1mM and the culture was grown for 4 additional hours. The culture was then centrifuged at 6,000 rpm for 10 minutes and the pellet was resuspended in phosphate buffer (50mM K2HPO4, KH2PO4 pH 7) including a protease inhibior cocktail. This sample was subjected to French pressure lysis using 1500 bar pressure (2 runs). After centrifugation for 30 minutes at 15,000 rpm, the supernatant was reserved for further purification and NaCl was added to 0.5M. The sample was then loaded on a Ni-NTA resin (XK 16 column Pharmacia, Ni-NTA resin Qiagen) conditioned in 50mM K2HPO4, KH2PO4 pH 7. After loading the sample, the column was washed with Buffer A (0.2M NaH2PO4 pH7, 0.3M NaCl, 10% glycerol). To elute bound protein, a step gradient ws used where different proportions of buffer B (0.2M NaH2PO4 pH7, 0.3M NaCl, 10% glycerol and 200mM imidazole) were added to buffer A. The proportion of buffer B was gradually increased from 10% to 100%. After purification, eluted fraction containing the protein were pooled, concentrated and dialysed against 0.002M KH2PO4/K2HPO4 pH7, 0.15M NaCl.

This method was used to purify ClfA, SdrG, IsdA, IsaB, HarA, Atl-glucosamine and alpha toxin.

Under denaturing conditions

IPTG was added at a final concentration of 1mM and the culture was grown for 4 additional hours. The culture was then centrifuged at 6,000 rpm for 10 mintes and the pellet was resuspended in phosphate buffer (50mM K2HPO4, KH2PO4 pH 7) including a protease inhibior cocktail. This sample was subjected to French pressure lysis using 1500 bar pressure (2 runs). After centrifugation for 30 minutes at 15,000 rpm, the pellet was washed with phosphate buffer including 1M urea. The sample was centrifuged for 30 mins at 15000rpm and the pellet was resuspended in 8M urea, 0.1M NaH2PO4, 0.5M NaCl, 0.01M Tris-Hcl pH8 and kept overnight at room temperature. The sample was centrifuged fro 20 minutes at 15000rpm and the supernatant was collected for further purification. The sample was then loaded on a Ni-NTA resin (XK 16 column Pharmacia, Ni-NTA resin Qiagen) conditioned in 8M urea, 0.1M NaH2PO4, 0.5M NaCl, 0.01M Tris-Hcl pH8. After passsage of the flowthrough, the column was washed succesively with buffer A (8M Urea, 0.1MNaH2PO4, 0,5M NaCl, 0.01M Tris, pH 8.0), buffer C (8M Urea, 0.1MNaH2PO4, 0.5M

NaCl, 0.01M Tris, pH 6.3), buffer D (8M Urea, 0.1MNaH2PO4, 0.5M NaCl, 0.01M Tris, pH 5.9) and buffer E (8M Urea, 0.1MNaH2PO4, 0.5M NaCl, 0.01M Tris, pH 4.5). The recombinant protein was eluted from the column during washes with buffer D and E. The denatured, recombinant protein could be solubilized in a solution devoid of urea. For this purpose, denatured protein contained in 8M urea was successively dialyzed against 4M urea, 0.1MNa2PO4, 0.01M Tris-HCl, pH7.1, 2M urea, 0.1 M NaH2PO4, 0.01M Tris-HCl, pH 7.1, 0.5M arginine and 0.002M KH2PO4/K2HPO4 pH7.1, 0.15M NaCl, 0.5M arginine.

This method was used to purify Ebh (H2 fragment), AaA, SdrC, FnbpA, Sbi, Atl-amidase and IsaA.

The purified proteins were analysed by SDS-PAGE. The results for one protein purified under native conditions (alpha toxin) and one protein purified under denaturing conditions (SdrC) are shown in Figures 3 and 4.

Example 3 Preparation of Polysaccharides

PNAG is prepared as described in Joyce et al 2003, Carbohydrate Research 338; 903-922.

Type 5 and type 8 polysaccharides are extracted from *S.aureus* as described in Infection and Immunity (1990) 58(7); 2367.

LTA is extracted from staphylococci as described in Fischer W, et al Eur. J. Biochem. (1983) 133; 523 or as described in Morath et al J. Exp. Med. 2001; 193; 393-397.

Activation and coupling chemistry:

Native polysaccharide is dissolved in NaCl 2M or in water. The optimal polysaccharide concentration is evaluated for all the serotypes and is between 2mg/ml and 5mg/ml.

From a 100 mg/ml stock solution in acetonitrile ,CDAP (CDAP/PS ratio:0.75 mg/mg PS) is added to the polysaccharide solution.1.5 minute later, 0.2M triethylamine is added to obtain the specific activation pH (pH 8.5-10.0). The activation of the polysaccharide is performed at this pH during 2 minutes at 25°C. The carrier protein is added to the activated polysaccharide in an amount sufficient to give a 1/1 molar ratio and the coupling reaction is performed at the specific pH for 1 hour.

Then, the reaction is quenched with glycine for 30 minutes at 25°C and overnight at 4°C.

The conjugates are purified by gel filtration using a Sephacryl 500HR gel filtration column equilibrated with 0.2M NaCl.

The carbohydrate and protein contents of the eluted fractions are determined .The conjugates are pooled and sterile filtered on a 0.22µm sterilizing membrane. The PS/Protein ratios in the conjugate preparations are determined.

Characterisation:

Each conjugate is characterised for protein and polysaccharide content.

The polysaccharide content is measured by the Resorcinol test and the protein content by the Lowry test. The final PS/PD ratio(w/w) is determined by the ratio of the concentrations.

Residual DMAP content (ng/µg PS):

The activation of the polysaccharide with CDAP introduces a cyanate group in the polysaccharide and DMAP (4-dimethylamino-pyridin) is liberated. The residual DMAP content is determined by a specific assay developed and validated at GSK.

Free polysaccharide content (%):

The free polysaccharide content on conjugates kept at 4°C or stored 7 days at 37°C is determined on the supernatant obtained after incubation with α-carrier antibodies and saturated ammonium sulfate, followed by a centrifugation.

An α-PS/α-PS ELISA is used for the quantification of free polysaccharide in the supernatant . The absence of conjugate is also controlled by an α-carrier/α-PS ELISA.

Example 4 Formulation

Adjuvant compositions

Protein, either individually or together, from the above examples maybe formulated with the staphylococcal polysaccharide combination and as adjuvant, the formulation may comprise a mixture of 3 de -O-acylated monophosphoryl lipid A (3D-MPL) and aluminium

hydroxide, or of 3 de -O-acylated monophosphoryl lipid A (3D-MPL) and aluminium phosphate, or 3D-MPL and/or QS21 optionally in an oil/water emulsion, and optionally formulated with cholesterol, or aluminium salt alone, preferably aluminium phosphate.

3D-MPL: is a chemically detoxified form of the lipopolysaccharide (LPS) of the Gram-negative bacteria *Salmonella minnesota.*
Experiments performed at GSK Biologicals have shown that 3D-MPL combined with various vehicles strongly enhances both the humoral and a TH1 type of cellular immunity.

QS21: is one saponin purified from a crude extract of the bark of the Quillaja Saponaria Molina tree, which has a strong adjuvant activity: it activates both antigen-specific lymphoproliferation and CTLs to several antigens.

Vaccine containing an antigen of the invention containing 3D-MPL and alum may be prepared in analogous manner to that described in WO93/19780 or 92/16231.
Experiments performed at GSK Biologicals have demonstrated a clear synergistic effect of combinations of 3D-MPL and QS21 in the induction of both humoral and TH1 type cellular immune responses. Vaccines containing an antigen such antigens are described in US 5750110.

The oil/water emulsion is composed of 2 oils (a tocopherol and squalene), and of PBS containing Tween 80 as emulsifier. The emulsion comprised 5% squalene 5% tocopherol 0.4% Tween 80 and had an average particle size of 180 nm and is known as SB62 (see WO 95/17210).

Experiments performed at GSK Biologicals have proven that the adjunction of this O/W emulsion to MPL/QS21 further increases their immunostimulant properties.

Preparation of emulsion SB62 (2 fold concentrate)

Tween 80 is dissolved in phosphate buffered saline (PBS) to give a 2% solution in the PBS. To provide 100 ml two fold concentrate emulsion 5g of DL alpha tocopherol and 5ml of squalene are vortexed to mix thoroughly. 90ml of PBS/Tween solution is added and mixed thoroughly. The resulting emulsion is then passed through a syringe and finally microfluidised by using an M110S microfluidics machine. The resulting oil droplets have a size of approximately 180 nm.

Example 5

Animal experiments.

Female CD-1 mice, 8 to 10 weeks old, are obtained from Charles River Laboratories, Kingston, Mass. For lethality studies, five groups of 9 to 11 CD-1 mice are challenged intraperitoneally (i.p.) with serial dilutions of *S. aureus* grown on CSA plates. The inocular sizes range from ~10^{10} to 10^{8} CFU/mouse. Mortality is assessed on a daily basis for 3 days. The 50% lethal doses (LD_{50}s) is estimated by using a probit model of the dose-response relationship. The null hypothesis of common LD_{50}s was tested by the likelihood ratio test. Sublethal bacteremia is initiated by challenging groups of 8 to 20 mice by the intravenous (i.v.) route with ~ 2 x 10^{6} CFU/mouse or by the i.p. route with ~ 2 x 10^{7} CFU/mouse. After inoculation separate groups of animals are bled from the tail at specified times, and the bacteremia levels are estimated by quantitative plate counts performed in duplicate on tryptic soy agar plates with 5% sheep blood (Becton Dickinson Microbiology Systems). Statistical significance is determined with the Welch modification of the unpaired Stutent's *t* test.

Example 6

General Methodology of Determining Antibody Responses in Various Mammals

The sera were tested for IgG antibodies to the staphylococcal polysaccharides by an ELISA. Briefly, purified capsular polysaccharides from ATCC (Rockville, Md, 20852) are coated at 25 μg/ml in phosphate buffered saline (PBS) on high binding microtitre plates (Nunc Maxisorp) overnight at 4 C. The plates are blocked with 10% fetal calf serum (FCS), 1 hour at 37 C. Serum samples are pre-incubated with the 20 μg/ml cell-wall polysaccharide (Statens Serum Institute, Copenhagen) and 10% FCS at room temperature for 30 minutes to neutralize antibodies to this antigen. The samples are then diluted two-fold on the microplate in 10% FCS in PBS, and equilibrated at room temperature for 1 hour with agitation. After washing, the microplates are equilibrated with peroxidase labelled anti-human IgG Fc monoclonal antibody (HP6043-HRP, Stratech Scientific Ltd) diluted 1:4000 in 10% FCS in PBS for 1 hour at room temperature with agitation. The ELISA is performed to measure rat IgG using Jackson ImmunoLaboratories Inc. peroxidase-conjugated AffiniPure Goat anti-Rat IgG (H+L) (code 112-035-003) at 1:5000. The titration curves are referenced to standard sera for each serotype using

logistic log comparison by SoftMax Pro. The polysaccharide concentrations used to coat the ELISA plate are 10-20 μg/ml. The color is developed using 4 mg OPD (Sigma) per 10 ml pH 4.5 0.1M citrate buffer with 14 μl H2O2 for 15 minutes in the dark at room temperature. The reaction is stopped with 50 μl HCl, and the optical density is read at 490 nm relative to 650 nm. IgG concentrations are determined by reference of titration ıts to the calibration curve modeled using a 4-parameter logistic log equation calcul SoftMax Pro software.

The ELISA to measure the murine and rat IgG to the staphylococcal polysaccharides is similar with the following exceptions. Jackson ImmunoLaboratories Inc. peroxidase-conjugated affiniPure Goat Anti-mouse IgG (H+L) and AffiniPure Goat Anti-rat IgG (H+L) were employed to detect bound IgG.

HP6043-HRP reacts equally with human and Rhesus purified IgG, and so this reagent is used for Rhesus antiserum.

The protein ELISA is performed similarly to the polysaccharide ELISA with the following modifications. The protein is coated overnight at 2.0 μg/ml in PBS. The serum samples are diluted in PBS containing 10% foetal calf serum and 0.1 % polyvinyl alcohol. Bound human antibody is detected using Sigma Peroxidase-conjugated goat affinity purified antibody to Human IgG Fc (reference A-2290).

Example 7

Opsonophagocytosis assay.

The in vitro opsonophagocytosic killing of *S.aureus* by human polymorphonuclear leykocytes (PMNs) is performed as described in Xu et al 1992 Infect. Immun. 60; 1358. Human PMNs are prepared from heparinized blood by sedimentation in 3% dextran T-250. The opsonic reaction mixture (1 ml) contains ~ 10^6 PMNs in RPMI 1640 medium supplemented with 10% heat-inactivated fetal calf serum, ~ 10^8 CFU of S-aureus, and 0.1 ml of the test serum or IgG preparation. Hyperimmunized rabbit serum is used as a positive control, and 0.1 ml of nonimmune rabbit serum was used as a complete source for the IgG samples. The reaction mixtures are incubated at 37°C, and bacterial samples are transferred at 0, 60, and 120 min into water and subsequently diluted, spread on

tryptic soy agar plates, and incubated at 37°C for bacterial count after overnight incubation.

Example 8

Immunogenicity of staphylococcal proteins in mice and rabbits

Animals were immunized with purified staphylococcal proteins in order to generate hyper-immune sera. Mice were immunized three times (days 0, 14 and 28) with 10 µg of each proteins adjuvanted in Specol. Rabbits were immunized three times (days 0, 21 and 42) with 20 µg of each proteins adjuvanted in Specol. Immune sera were collected and evaluated in anti-protein and anti-killed whole cells ELISA.

Anti-Protein ELISA:

The purified protein was coated at 1 µg/ml in phosphate buffered saline (PBS) on high binding microtitre plates (Nunc Maxisorp) overnight at 4° C. The plates were blocked with PBS-BSA 1%, for 30 min at RT with agitation. The test samples were then diluted 1/1000 and incubated at room temperature for 1 hour with agitation. After washing, bound murine or rabbit antibody was detected using Jackson ImmunoLaboratories Inc. peroxidase-conjugated affiniPure Goat Anti-Mouse IgG (H+L) (ref: 115-035-003) or AffiniPure Goat Anti-Rabbit IgG (H+L) (ref: 11-035-003) diluted 1:5000 in PBS-tween 0.05%. The detection antibodies were incubated for 30 min. at room temperature with agitation. The color was developed using 4 mg OPD (Sigma) + 5 µl H2O2 per 10 ml pH 4.5 0.1M citrate buffer for 15 minutes in the dark at room temperature. The reaction was stopped with 50 µl HCl, and the optical density was read at 490 nm relative to 650 nm.
The O.D. for a 1/1000 dilution of Post III was compared to the O.D. obtained with the same dilution of Pre-immune sera.

Results generated with mice and rabbit sera are presented in Figure 5. A good seroconversion against each antigen was observed. Evaluation of sera directed against SBI was impaired due to the Ig binding activity of this protein.

Anti-killed whole cells ELISA:

Killed whole cells (heat or formaldehyde inactivated) from *S. aureus* type 5 and 8 or *S. epidermidis* strain Hay were coated at 20 µg/ml in phosphate buffered saline (PBS) on high binding microtitre plates (Nunc Maxisorp) overnight at 4° C with evaporation. The plates were blocked with PBS-BSA 1% 30 min at room temperature with agitation. Protein A was neutralised by addition of 10µg/ml of Affinity Purified Chickedn anti-ProteinA (ICL ref: CPA-65A-2) diluted in PBS-tween 0.05% followed by incubation for 1 hour at room temperature. The test samples were then diluted two-fold on the microplate in PBS-0.05% from a starting dilution at 1/10 and incubated 1 hour at room temperature with agitation. After washing, bound murine or rabbit antibody was detected using Jackson ImmunoLaboratories Inc. peroxidase-conjugated affiniPure Goat Anti-Mouse IgG (H+L) (ref: 115-035-003) or AffiniPure Goat Anti-Rabbit IgG (H+L) (ref: 11-035-003) diluted 1:5000 in PBS-tween 0.05%. This detection antibodies were incubated for 30 min. at room temperature with agitation. The color was developed using 4 mg OPD (Sigma) + 5 µl H2O2 per 10 ml pH 4.5 0.1M citrate buffer for 15 minutes in the dark, at room temperature. The reaction was stopped with 50 µl HCl, and the optical density was read at 490 nm relative to 650 nm.

It should be noted that expression levels of proteins in staphylococci will vary depending on culture conditions. Therefore a negative result may reflect the choice of incorrect culture conditions rather than a lack of immunogenicity.

The results using mice sera are shown in Table 5 and some of the graphs are shown in figure 6. A weak recognition of *S. aureus* strain 5 is observed with sera directed against SdrC, FnbpA, Ebh, Sbi and IsaA. Recognition of *S. aureus* strain 8 is only observed with the serum directed against Sbi. Weak recognition of *S. epidermidis* Hay is observed with sera directed against Atl amidase, MRP, IsdA, IsaA, Ebh, Aaa and Sbi.

A selection of results generated using rabbit sera are shown in figure 7 and summarized in Table 6. Very good recognition of the three strains was observed with IsaA and IsdB. A weak recognition of the three stains was observed with HarA although animals only received one injection rather than the three injections used for the other proteins.

Table 5

Protein name	React on SA5	React on SA8	React on SE Hay
IsaA	(+)	(+)	(+)
ClfA	-	(+)	(+)
Atl amidase	-	-	++
SdrG	-	-	-
Glucosamidase	-	-	-
IsdA	-	-	++
Alpha toxin	-	-	-
SrdC	++	(+)	-
Ebh	+	-	+
AaA	-	-	++
MRP	-	-	++
Sbi	++	++	+++
FnbpA	+	+	(+)

Table 6

Protein name	React on SA5	React on SA8	React on SE Hay
IsaA	+++	+++	+++
ClfA	+	++	++
Atl amidase	-	++	+
IsdB	+++	+++	+++
SdrG	+	+	+
Glucosamidase	-	-	-
HarA (1 inject.)	+	+	+
IsdA	-	-	-
Alpha toxin	-	-	+
SrdC	-	-	-
Ebh	-	+	-
AaA	-	-	-
MRP	-	-	++
Sbi	-	+++	-
FnbpA	-	++	++

Example 8

Efficacy of combinations of staphylococcal proteins in a nasal colonization model.

Fifteen groups of three cotton rats were inoculated with combinations of eight staphylococcal antigens and five cotton rats which acted as controls were treated with no antigen. These sixteen groups are as follows:

Group 1 – Atl-glucosamine, Atl-amidase, AAA, alpha toxin, SdrC, SdrG, Ebh, Sbi
Group 2 - Atl-glucosamine, Atl-amidase , IsdA, IsdB, ClfA, SdrC, Ebh, FnbpA
Group 3 - Atl-glucosamine, Atl-amidase, HarA, IsdA, MRP, IsdB, AAA, alpha toxin
Group 4 - Atl-glucosamine, HarA, IsdA, AAA, ClfA, IsaA, Ebh, Sbi
Group 5 – HarA, MRP, AAA, alpha toxin, ClfA, SdrC, Ebh, FnbpA
Group 6 – IsdA, IsdB, AAA, alpha toxin, ClfA, SdrG, Sbi, FnbpA
Group 7 – Atl-aminidase, IsdA, MRP, AAA, IsaA, SdrG, Ebh, FnbpA
Group 8 – Control
Group 9 – Atl-glucosamine, IsdA, MRP, alpha toxin, IsaA, SdrC, Sbi, FnbpA
Group 10 – Atl-glucosamine, MRP, IsdB, AAA, ClfA, IsaA, SdrC, SdrG
Group 11- Atl-amindase, MRP, IsdB, alpha toxin, ClfA, IsaA, Ebh, Sbi
Group 12 – Atl-glucosamine, HarA, IsdB, alpha toxin, IsaA, SdrG, Ebh, FnbpA
Group 13 – Atl-amidase, HarA, IsdB, AAA, IsaA, SdrC, Sbi, FnbpA
Group 14 – Atl-glucosamine, Atl-amidase, HarA, MRP, ClfA, SdrG, Sbi, FnbpA
Group 15 – Atl-amidase, HarA, IsdA, alpha toxin, ClfA, IsaA, SdfC, SdrG
Group 16 – HarA, IsdA, MRP, IsdB, SdrC, SdrG, Ebh, Sbi

Each mix of antigens contained 3μg of each antigen mixed with an adjuvant made of liposomes containing MPL and QS21. The cotton rats were inoculated three times on days 1, 14 and 28 of the experiment. Two weeks after inoculation, the efficacy of the immunisations were assessed using a nasal colonisation assay as described in Kokai-Kun et al (2003) Antimicrob.Agents.Chemother. 47; 1589-1597.

Classical multiple linear regression analysis was carried out on the data using "Design Expert 6" software. The presence of an antigen was coded as +1 and the absence of an antigen by -1. Using the equation of the model it was possible to determine which antigens were the key antigens which produced a large decrease in the number of colonies per nose.

Results

The results of the nasal colonisation assay are shown in Table 7. The control group had a mean logCFU/nose of 3.51335 and a decrease in nasal colonisation could be see for all the groups of cotton rats inoculated with staphylococcal proteins. Groups 4, 9 and 13 showed the greatest decrease in nasal colonisation with a decrease of over 2 logs in CFU/nose. Groups 12 and 16 also gave good results, showing a decease of about 2 logs in CFU/nose.

Table 7

Group	Mean observed LogCFU/nose	Predicted LogCFU/nose
1	1.77527	2.03560
2	2.90435	2.52684
3	1.96556	2.23033
4	1.27748	1.21872
5	1.67304	1.93128
6	2.79745	2.98193
7	2.21481	2.30705
8	3.51355	3.47317
9	1.22480	1.44080
10	2.03085	1.93204
11	2.02522	1.81581
12	1.53402	1.70996
13	1.36063	1.49100
14	2.31201	1.73909
15	2.22979	1.98223
16	1.58109	1.44004

The contribution of specific antigens within the antigen mix was calculated using multiple regression analysis of the nasal colonisation data. The final mdel contains the seven best antigens. Results for these antigens are shown in Table 8. Within the context of the protein mix, the inclusion of HarA gave the greatest decrease in nasal colonisation, followed by IsaA, Sbi, SdrC, autolysin-glucosamine, MRP and Ebh.

Table 8 Effects in difference of logCFU/nose and ratio of CFU/nose for the seven best antigens in the model and corresponding p-values.

antigen	prob >F	Effect estimate	Reduction ratio	Cumulative effect	Cumulative ratio
HarA	0.033	-0.596	3.9	-0.596	3.9

IsaA	0.046	-0.558	3.6	-1.154	14.3
Sbi	0.077	-0.491	3.1	-1.645	44.2
SdrC	0.22	-0.337	2.2	-1.982	96.0
Atl-glucos	0.238	-0.324	2.1	-2.306	202.2
MRP	0.239	-0.323	2.1	-2.629	425.3
Ebh	0.297	-0.286	1.9	-2.914	821.0

CLAIMS

1. An immunogenic composition comprising staphylococcal PNAG and Type 5 and/or 8 capular polysaccharide or oligosaccharide from *S. aureus.*

2. The immunogenic composition of claim 1 further comprising Type I, and/or Type II and/or Type III capsular polysaccharide or oligosaccharide from *S. epidermidis.*

3. The immunogenic composition of claims 1 or 2 wherein the PNAG is derived from a staphylococcal bacterium.

4. The immunogenic composition of any one of claims 1-3 further comprising a staphylococcal protein or fragment thereof.

5. The immunogenic composition of claim 4 wherein the staphylococcal protein or fragment thereof is an extracellular component binding protein selected form the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrG, SdrH, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig and MAP.

6. The immunogenic composition of claim 4 wherein the staphylococcal protein or fragment thereof is a transporter protein selected from the group consisting of Immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC and Ni ABC transporter.

7. The immunogenic composition of claim 4 wherein the staphylococcal protein or fragment thereof is a toxin or regulator of virulence selected from the group consisting of alpha toxin (Hla), alpha toxin H35R mutant, RNA III activating protein (RAP).

8. The immunogenic composition of any one of claims 4-7 comprising 2 or more staphylococcal proteins selected from at least 2 different groups selected from;

   a) at least one staphylococcal extracellular component binding protein or fragment thereof selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrG, SdrH, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig and MAP;

b) at least one staphylococcal transporter protein or fragment thereof selected from the group consisting of Immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC and Ni ABC transporter;

c) at least one staphylococcal regulator of virulence, toxin or fragment thereof selected from the group consisting of alpha toxin (Hla), alpha toxin H35R mutant, RNA III activating protein (RAP).

9. The immunogenic composition of any one of claims 1-8 wherein a staphylococcal polysaccharide is conjugated to a protein carrier.

10. The immunogenic composition of any one of claims 1-9 wherein the PNAG is conjugated to a protein carrier.

11. The immunogenic composition of claim 9 or 10 wherein the protein carrier comprises a staphylococcal protein or fragment thereof selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrG, SdrH, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, Immunodominant ABC transporter, IsdA, IsdB, Mg2+ transporter, SitC and Ni ABC transporter, alpha toxin (Hla), alpha toxin H35R mutant and RNA III activating protein (RAP).

12. The immunogenic composition of claim 9 or 10 wherein the protein carrier is selected from the group consisting of tetanus toxoid, diphtheria toxoid, CRM197, *Haemophilus influenzae* protein D, *Pseudomonas aeruginosa* exoprotein A, pneumococcal pneumolysin and alpha toxoid.

13. The immunogenic composition of claims 1-12 wherein an effective immune response is generated against both *S.aureus* and *S. epidermidis*.

14. A vaccine comprising the immunogenic composition of claims 1-13 and a pharmaceutically acceptable excipient.

15. A method of making a vaccine comprising the steps of mixing antigens to make the immunogenic composition of claims 1-13 and adding a pharmaceutically acceptable excipient.

16. A method of preventing or treating staphylococcal infection comprising the step of administering the vaccine of claim 14 to a patient in need thereof.

17. A use of the immunogenic composition of claims 1-13 in the manufacture of a vaccine for treatment or prevention of staphylococcal infection.

Figure 1

SEQ ID NO:1 polypeptide sequence

MLQVTDVSLRFGDRKLFEDVNIKFTEGNCYGLIGANGAGKSTFLKILSGELDSQTGHVSLGKNERLAVLKQDHYAYEDER
VLDVVIKGHERLYEVMKEKDEIYMKPDFSDEDGIRAAELEGEFAEMNGWNAEADAANLLSGLGIDPTLHDKKMAELENNQ
KIKVLLAQSLFGEPDVLLLDEPTNGLDIPAISWLEDFLINFDNTVIVVSHDRHFLNNVCTHIADLDFGKIKVYVGNYDFW
YQSSQLAQKMAQEQNKKKEEKMKELQDFIARFSANASKSKQATSRKKQLEKIELDDIQPSSRRYPFVKFTPEREIGNDLL
IVQNLSKTIDGEKVLDNVSFTMNPNDKAILIGDSEIAKTTLLKILAGEMEPDEGSFKWGVTTSLSYFPKDNSEFFEGVNM
NLVDWLRQYAPEDEQTETFLRGFLGRMLFSGEEVKKKASVLSGGEKVRCMLSKMMLSSANVLLLDEPTNHLDLESITAVN
DGLKSFKGSIIFTSYDFEFINTIANRVIDLNKQGGVSKEIPYEEYLQEIGVLK

SEQ ID NO:2 polypeptide sequence

MLQVTDVSLRFGDRKLFEDVNIKFTEGNCYGLIGANGAGKSTFLKILSGEIDSQTGHVSLGKDERLAVLKQDHFAYEDER
VLDVVIKGHERLYQVMKEKDEIYMKPDFSDEDGIRAAELEGEFAEMNGWNAEADAANLLSGLGIEPDLHDKNMSELENNQ
KVKVLLAQSLFGDPDVLLLDEPTNGLDIPAISWLEDFLINFENTVIVVSHDRHFLNNVCTHIADLDFGKIKLYVGNYDFW
YQSSQLAQKMAQEQNKKKEEKMKELQDFIARFSANASKSKQATSRKKQLEKIELDDIQPSSRRYPYVKFTPEREIGNDLL
TVENLSKTIDGEKVLDNVSFTMNPNDKAILVGDSEIAKTTLLKILAGEMEPDEGTFKWGVTTSLSYFPKDNSEFFDGVDM
NLVEWLRQYAPEDEQTETFLRGFLGRMLFSGEEVKKKASVLSGGEKVRCMLSKMMLSSANVLLLDEPTNHLDLESITAVN
DGLKSFKGSIIFTSYDFEFINTIANRVIDLNQAGALSKEVPYEEYLQEIGVLQNN

SEQ ID NO:3 polypeptide sequence

MPIITDVYAREVLDSRGNPTVEVEVLTESGAFGRALVPSGASTGEHEAVELRDGDKSRYLGKGVTKAVENVNEIIAPEII
EGEFSVLDQVSIDKMMIALDGTPNKGKLGANAILGVSIAVARAAADLLGQPLYKYLGGFNGKQLPVPMMNIVNGGSHSDA
PIAFQEFMILPVGATTFKESLRWGTEIFHNLKSILSKRGLETAVGDEGGFAPKFEGTEDAVETIIQAIEAAGYKPGEEVF
LGFDCASSEFYENGVYDYSKFEGEHGAKRTAAEQVDYLEQLVDKYPIITIEDGMDENDWDGWKQLTERIGDRVQLVGDDL
FVTNTEILAKGIENGIGNSILIKVNQIGTLTETFDAIEMAQKAGYTAVVSHRSGETEDTTIADIAVATNAGQIKTGSLSR
TDRIAKYNQLLRIEDELFET
AKYDGIKSFYNLDK

SEQ ID NO:4 polypeptide sequence

MPIITDVYAREVLDSRGNPTVEVEVLTESGAFGRALVPSGASTGEHEAVELRDGDKSRYLGKGVTKAVENVNEMIAPEIV
EGEFSVLDQVSIDKMMIQLDGTHNKGKLGANAILGVSIAVARAAADLLGQPLYKYLGGFNGKQLPVPMMNIVNGGSHSDA
PIAFQEFMILPVGAESFKESLRWGAEIFHNLKSILSERGLETAVGDEGGFAPRFEGTEDAVETIIKAIEKAGYKPGEDVF
LGFDCASSEFYENGVYDYTKFEGEHGAKRSAAEQVDYLEELIGKYPIITIEDGMDENDWEGWKQLTDRIGDKVQLVGDDL
FVTNTEILSKGIEQGIGNSILIKVNQIGTLTETFDAIEMAQKAGYTAVVSHRSGETEDTTIADIAVATNAGQIKTGSLSR
TDRIAKYNQLLRIEDELYETAKFEGIKSFYNLDK

SEQ ID NO:5 polypeptide sequence

MKKIVTATIATAGLATIAFAGHDAQAAEQNNNGYNSNDAQSYSYTYTIDAQGNYHYTWTGNWNPSQLTQNNTYYYNNYNT
YSYNNASYNNYYNHSYQYNNYTNNSQTATNNYYTGGSGASYSTTSNNVHVTTTAAPSSNGRSISNGYASGSNLYTSGQCT
YYVFDRVGGKIGSTWGNASNWANAAASSGYTVNNTPKVGAIMQTTQGYYGHVAYVEGVNSNGSVRVSEMNYGHGAGVVTS
RTISANQAGSYNFIH

SEQ ID NO:6 polypeptide sequence

MKKIATATIATAGFATIAIASGNQAHASEQDNYGYNPNDPTSYSYTYTIDAQGNYHYTWKGNWHPSQLNQDNGYYSYYYY
NGYNNYNNYNNGYSYNNYSRYNNYSNNNQSYNYNNYNSYNTNSYRTGGLGASYSTSSNNVQVTTTMAPSSNGRSISSGYT
SGRNLYTSGQCTYYVFDRVGGKIGSTWGNASNWANAAARAGYTVNNTPKAGAIMQTTQGAYGHVAYVESVNSNGSVRVSE
MNYGYGPGVVTSRTISASQAAGYNFIH

SEQ ID NO:7 polypeptide sequence

MKKIATATIATAGIATFAFAHHDAQAAEQNNDGYNPNDPYSYSYTYTIDAEGNYHYTWKGNWSPDRVNTSYNYNNYNNYN
YYGYNNYSNYNNYSNYNNYNNYQSNNTQSQRTTQPTGGLGASYSTSSSNVHVTTTSAPSSNGVSLSNARSASGNLYTSGQ
CTYYVFDRVGGKIGSTWGNANNWANAAARSGYTVNNSPAKGAILQTSQGAYGHVAYVEGVNSNGSIRVSEMNYGHGAGVV

TSRTISASQAASYNYIH

SEQ ID NO:8 polypeptide sequence

MKKLVPLLLALLLLVAACGTGGKQSSDKSNGKLKVVTTNSILYDMAKNVGGDNVDIHSIVPVGQDPHEYEVKPKDIKKLT
DADVILYNGLNLETGNGWFEKALEQAGKSLKDKKVIAVSKDVKPIYLNGEEGNKDKQDPHAWLSLDNGIKYVKTIQQTFI
DNDKKHKADYEKQGNKYIAQLEKLNNDSKDKFNDIPKEQRAMITSEGAFKYFSKQYGITPGYIWEINTEKQGTPEQMRQA
IEFVKKHKLKHLLVETSVDKKAMESLSEETKKDIFGEVYTDSIGKEGTKGDSYYKMMKSNIETVHGSMK

SEQ ID NO:9 polypeptide sequence

MKKILALAIAFLIILAACGNHSNHEHHSHEGKLKVVTTNSILYDMVKRVGGNKVDVHSIVPVGQDPHEYEVKPKDIKALT
DADVVFYNGLNLETGNGWFEKALDQAGKSTKDKNVIAASNNVKPIYLNGEEGNKNKQDPHAWLSLENGIKYVKTIQKSLE
HHDKKDKSTYEKQGNAYISKLEELNKDSKNKFDDIPKNQRAMMTSEGAFKYFAQQFDVKPGYIWEINTEKQGTPGQMKQA
IKFVKDNHLKHLLVETSVDKKAMQSLSEETKKDIYGEVFTDSIGKEGTKGDSYYKMMKSNIDTIHGSMK

SEQ ID NO:10 polypeptide sequence

MKKTIMASSLAVALGVTGYAAGTGHQAHAAEVNVDQAHLVDLAHNHQDQLNAAPIKDGAYDIHFVKDGFQYNFTSNGTTW
SWSYEAANGQTAGFSNVAGADYTTSYNQGSDVQSVSYNAQSSNSNVEAVSAPTYHNYSTSTTSSSVRLSNGNTAGATGSS
AAQIMAQRTGVSASTWAAIIARESNGQVNAYNPSGASGLFQTMPGWGPTNTVDQQINAAVKAYKAQGLGAWGF

SEQ ID NO:11 polypeptide sequence

MKKTVIASTLAVSLGIAGYGLSGHEAHASETTNVDKAHLVDLAQHNPEELNAKPVQAGAYDIHFVDNGYQYNFTSNGSEW
SWSYAVAGSDADYTESSSNQEVSANTQSSNTNVQAVSAPTSSESRSYSTSTTSYSAPSHNYSSHSSSVRLSNGNTAGSVG
SYAAAQMAARTGVSASTWEHIIARESNGQLHARNASGAAGLFQTMPGWGSTGSVNDQINAAYKAYKAQGLSAWGM

SEQ ID NO:12 polypeptide sequence

MNYRDKIQKFSIRKYTVGTFSTVIATLVFLGFNTSQAHAAETNQPASVVKQKQQSNNEQTENRESQVQNSQNSQNSQSLS
ATHENEQPNNSQANLVNQKVAQSSTTNDEQPASQNVNTKKDSATAATTQPDKEESKHKQNESQSANKNGNDNRAAHVENH
EANVVTASDSSDNGNVQHDRNELQAFFDANYHDYRFIDRENADSGTFNYVKGIFDKINTLLGSNDPINNKDLQLAYKELE
QAVALIRTMPQRQQTSRRSNRIQTRSVESRAAEPRSVSDYQNANSSYYVENANDGSGYPVGTYINASSKGAPYNLPTTPW
NTLKASDSKEIALMTAKQTGDGYQWVIKFNKGHAPHQNMIFWFALPADQVPVGRTDFVTVNSDGTNVQWSHGAGAGANKP
LQQMWEYGVNDPDRSHDFKIRNRSGQVIYSWPTVHVYSLEDLSRASDYFSEAGATPATKAFGRQNFEYINGQKPAESPGV
PKVYTFIGQGDASYTISFKTQGPTVNKLYYAAGGRALEYNQLFMYSQLYVESTQDHQQRLNGLRQVVNRTYRIGTTKRVE
VSQGNVQTKKVLESTNLNIDDFVDDPLSYVKTPSNKVLGFYPTNANTNAFRPGGVQELNEYQLSQLFTDQKLQEAARTRN
PIRLMIGFDYPDGYGNSETLVPVNLTVLPEIQHNIKFFKNDDTQNIAEKPFSKQAGHPVFYVYAGNQGNASVNLGGSVTS
IQPLRINLTSNENFTDKDWQITGIPRTLHIENSTNRTNNARERNIELVGNLLPGDYFGTIRFGRKEQLFEIRVKPHTPTI
TTTAEQLRGTALQKVPVNISGIPLDPSALVYLVAPTNQTTNGGSEADQIPSGYTILATGTPDGVHNTITIRPQDYVVFIP
PVGKQIRAVVYYNKVVASNMSNAVTILPDDIPPTINNPVGINAKYYRGDEVNFTMGVSDRHSGIKNTTITTLPSGWTSNL
TKSDNKNGSLAITGRVSMNQAFNSDITFKVSATDNVNNTTNDSQSKHVSIHVGKISEDAHPIVLGNTEKVVVVNPTAVSN
DEKQSIITAFMNKNQNIRGYLASTDPVTVDNNGNVTLHYRDGSSTTLDATNVMTYEPVVKSEYQTANAAKTATVTIAKGQ
SFNIGDIKQYFTLSNGQAIPNGTFTNITSDRTIPTAQEVSQMNAGTQLYHIVASNAYHKDTEDFYISLKIVDVKQPEGDQ
RVYRTSTYDLTTDEISKVKQAFINANRDVITLAEGDISVTNTPNGANVSTITVNINKGRLTKSFASNLANMNFLRWVNFP
QDYTVTWTNAKIANRPTDGGLSWSDDHKSLIYRYDATLGTQITTNDILTMLKATTTVPGLRNNITGNEKAQAEAGGRPNY
RTTGYSQSNATTDGQRQFTLNGQVIQILDIINPSNGYGGQPVTNSNTRANHSNSTVVNVNEPAANGAGAFTIDHVVKSNS
THNASDAVYKAQLYLTPYGPKQYVEHLNQNTGNTTDAINIYFVPSDLVNPTISVGNYTNHQVFSGETFTNTITANDNFGV
QSVTVPNTSQITGTVDNNHQHVSATAPNVTSATSKTINLLATDTSGNTATTSFNVTVKPLRDKYRVGTSSTAANPVRIAN
ISNNATVSQADQTTIINSLTFTSNAPNRNYATASANEITSKTVSNVSRTGNNANVTVTVTHQDGTTSTVTVPVKHVIPEI
VAHSHYTVQGQDFPAGNGSSAADYFKLSNGSAIPDATITWVSGQAPNKDNTRIGEDITVTAHILIDGETTPITKTATYKV
VRTVPKHVFETARGVLYPGVSDMYDAKQYVKPVNNSWSTNAQHMNFQFVGTYGPNKDVVGISTRLIRVTYDNRQTEDLTI
LSKVKPDPPRIDANSVTYKAGLTNQEIKVNNVLNNSSVKLFKADNTPLNVTNITHGSGFSSVVTVSDALPNGGIKAKSSI
SMNNVTYTTQDEHGQVVTVTRNESVDSNDSASVTVTPQLQATTEGAVFIKGGDGFDFGHVERFIQNPPHGATVAWHDSPD
TWKNTVGNTHKTAVVTLPSGQGTRNVEVPVKVYPVANAKAPSRDVKGQNLTHGTNAIDYITFDPNTNTNGITAAWANRQQ
PNNQQAGVQHLNVDVTYPGISAAKRVPVTVNVYQFEFPQTTYTTTVGGTLASGTQASGYAHMQNASGLPTDGFTYKWNRD
TTGTNDANWAAMNKPNTAQVVNAKYDVIYNGHTFATSLPAKFVVKDVQPAKPTVTETAAGAITIAPGANQTVNTHAGNVT
TYADKLVIKRNGNVVTTFTRRNNTSPWVKEASADNVTGIVGTNNGITVAAGTFNPADTIQVVATQGSGETISDEQRSDDF
TVVAPQPNQATTKIWQNGHIDITPNNPSGHLINPTQAMDIAYTEKVGNGAEHSKTINVVRGQNNQWTIANKPDYVTLDAQ
TGKVTFNANTIKPNSSITITPKAGTGHSVSSNPSTLTAPAAHTVNTTEIVKDYGSNVTAAEINNAVQVANKRTATIKNGT
AMPTNLAGGSTTTIPVTVTYNDGSTEEVQESIFTKADKRELITAKNHLDDPVSTEGKKPGTITQYNNAMHNAQQQINTAK
TEAQQVINNERATPQQVSDALTKVRAAQTKIDQAKALLQNKEDNSQLVTSKNNLQSSVNQVPSTAGMTQQSIDNYNAKKR
EAETEITAAQRVIDNGDATAQQISDEKHRVDNALTALNQAKHDLTADTHALEQAVQQLNRTGTTTGKKPASITAYNNSIR

ALQSDLTSAKNSANAIIQKPIRTVQEVQSALTNVNRVNERLTQAINQLVPLADNSALRTAKTKLDEEINKSVTTDGMTQS
SIQAYENAKRAGQTETTNAQNVINNGDATDQQIAAEKTKVEEKYNSLKQAIAGLTPDLAPLQTAKTQLQNDIDQPTSTTG
MTSASVAAFNDKLSAARTKIQEIDRVLASHPDVATIRQNVTAANAAKTALDQARNGLTVDKAPLENAKNQLQHSIDTQTS
TTGMTQDSINAYNAKLTAARNKVQQINQVLAGSPTVDQINTNTSAANQAKSDLDHARQALTPDKAPLQNAKTQLEQSINQ
PTDTTGMTTASLNAYNQKLQAARQKLTEINQVLNGNPTVQNINDKVAEANQAKDQLNTARQGLTLDRQPALTTLHGASNL
NQAQQNNFTQQINAAQNHAALETIKSNITALNTAMTKLKDSVADNNTIKSGQNYTDATPANKQAYDNAVNAAKGVIGETT
NPTMDVNTVNQKAASVKSTKDALDGQQNLQRAKTEATNAITHASDLNQAQKNALTQQVNSAQNVQAVNDIKQTTQSLNTA
MTGLKRGVANHNQVVQSDNYVNADTNKKNDYNNAYNHANDIINGNAQHPVITPSDVNNALSNVTSKEHALNGEAKLNAAK
QEANTALGHLNNLNNVQRQNLQSQINGAHQIDAVNTIKQNATNLNSAMGNLRQAVADKDQVKRTEDYADADTAKQNAYNS
AVSSAETIINQTANPTMSVDDVNRATSAVTTNKNALNGDEKLVQSKTDAARAIDALPHLNNAQKADVKSKINAASNIAGV
NTVKQQGTDLNTAMGNLQGAINDEQTTLNSQNYQDATPSKKTAYTNAVQAAKDILNKSNGQNKTKDQVTEAMNQVNSAKN
NLDGTRLLDQAKQTAKQQLNNMTHLTTAQKTNLTNQINSGTTVAGVHTVQSNANTLDQAMNTLRQSIANNDATKASEDYV
DANNDKQTAYNNAVAAAETIINANSNPEMNPSTITQKAEQVNSSKTALNGDENLATAKQNAKTYLNTLTSITDAQKNNLI
SQISSATRVSGVDTVKQNAQHLDQAMANLQNGINNESQVKSSEKYRDADTNKQQEYDNAITAAKAILNKSTGPNTAQNAV
EAALQRVNTAKDALNGDAKLIAAQNAAKQHLGTLTHITTAQRNDLTNQIS

SEQ ID NO:13 polypeptide sequence

MGNLQTAINDKSGTLASQNFLDADEQKRNAYNQAISAAETILNKQTGPNTAKTAVEQALNNVNSAKHALNGTQNLNNAKQ
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VTNAEHIISGTPTVVTTPSEVTAAANQVNSAKQELNGDERLRVAKQNANTAIDALTQLNTPQKAKLKEQVGQANRLEDVQ
SVQTNGQSLNNAMKGLRDSIANETTVKASQNYTDASPNNQSTYNSAVSNAKGIINQTNNPTMDTSAITQATTQVNNAKNG
LNGAENLRNAQNTAKQNLNTLSHLTNNQKSAISSQIDRAGHVSEVTAAKNAATELNAQMGNLEQAIHDQNTVKQGVNFTD
ADKAKRDAYTNAVSRAETILNKTQGANTSKQDVEAAIQNVTSAKNALNGDQNVTNAKNAAKNALNNLTSINNAQKRDLTT
KIDQATTVAGVEAVSNTGTQLNTAMANLQNGINDKANTLASENYHDADSDKKTAYTQAVTNAENILNKNSGSNLDKAAVE
NALSQVTNAKGALNGNHNLEQAKSNANTTINGLQHLTTAQKDKLKQQVQQAQNVAGVDTVKSSANTLNGAMGTLRNSIQD
NTATKNGQNYLDATERNKTNYNNAVDSANGVINATSNPNMDANAINQIATQVTSTKNALDGTHNLTQAKQTATNAIDGAT
NLNKAQKDALKAQVTSAQRVANVTSIQQTANELNTAMGQLQHGIDDENATKQTQKYRDAEQSKKTAYDQAVAAAKAILNK
QTGSNSDKAAVDRALQQVTSTKDALNGDAKLAEAKAAARQNLGTLNHITNAQRTALEGQINQATTVDGVNTVKTNANTLD
GAMNSLQGAINDKDATLRNQNYLDADESKRNAYTQAVTAAEGILNKQTGGNTSKADVDNALNAVTRAKAALNGAENLRNA
KTSATNTINGLPNLTQLQKDNLKHQVEQAQNVVGVNGVKDKGNTLNTAMGALRTSIQNDNTTKTSQNYLDASDSNKNNYN
TAVNNANGVINATNNPNMDANAINDMANQVNTTKAALNGAQNLAQAKTNATNTINNAQDLNQKQKDALKTQVNNAQRVSD
ANNVQHTATELNGAMTALKAAIADKERTKASGNYVNADQEKRQAYDSKVTNAENIINGTPNATLTVNDVNSAASQVNAAK
TALNGDNNLRVAKEHANNTIDGLAQLNNVQKAKLKEQVQSATTLDGVQTVKNSSQTLNTAMKGLRDSIANEATIKAGQNY
TDASPNNRNEYDSAVTAAKAIINQTSNPTMEPNTITQATSQVTTKEHALNGAQNLAQAKTTAKNNLNNLTSINNAQKDAL
TRNIDGATTVAGVNQETAKATELNNAMHSLQNGINDETQTKQTQKYLDAEPSKKSAYDQAVNAAKAILTKASGQNVDKAA
VEQALQNVNSTKTALNGDAKLNEAKAAAKQTLGTLTHINNAQRNALDNEITQATNVEGVNTVKAKAQQLDGAMGQLETSI
RDKDTTLQSQNYQDADDAKRTAYSQAVNAAATILNKTAGGNTPKADVERAMQAVTQANTALNGIQNLERAKQAANTAITN
ASDLNTKQKEALKAQVTSAGRVSAANGVEHTATELNTAMTALKRAIADKADTKASGNYVNADANKRQAYDEKVTAAEHIV
SGTPTPTLTPSDVTNAATQVTNAKTQLNGNHNLEVAKQNANTAIDGLTSLNGPQKAKLKEQVGQATTLPNVQTVRDNAQT
LNTAMKGLRDSIANEATIKAGQNYTDASQNKQNDYNNAVTAAKAIIGQTTSPSMIAQEINQAKDQVTAKQQALNGQENLR
TAQTNAKQHLNGLSDLTNAQKDAAKRQIEGATHVNEVTQAQNNADALNTAMTNLKNGIQDQNTIKQGVNFTDADEAKRNA
YTNAVTQAEQILNKAQGPNTAKDGVETALQNVQRAKNELNGNQNVANAKTTAKNALNNLTSINNAQKAALKSQIEGATTV
AGVNQVSTMASELNTAMSNLQRGINDEAATKAAQKYTEADRDKQTAYNDAVTAAKTLLDKTAGSNDNKVAVEQALQRVNT
AKTALNGDARLNEAKNTAKQQLATMSHLTNAQKANLTEQIERGTTVAGVQGIQANAGTLNQAMNQLRQSIASKDATKSSE
DYQDANADLQNAYNDAVTNAEGIISATNNPEMNPDTINQKASQVNSAKSALNGDEKLAAVKQTAKSDIGRLTDLNNAQRT
AANAEVDQAPNLAAVTAAKNKATSLNTAMGNLKHALAEKDNTKRSVNYTDADQPKQQAYDTAVTQAEAITNANGSNANET
QVQAALNQLNQAKNDLNGDNKVAQAKETAKRALASYSNLNNAQSTAATSQIDNATTVADVTAAQNTANELNTAMGQLQNG
INDQNTVKQQVNFTDADQGKKDAYTNAVTNAQGILDKANGQNMTKAQVEAALNQVTTAKNALNGDANVRQAKSDAKANLG
TLTHLNNAQKQDLTSQIEGATTVNGVNSVKTKAQDLDGAMQRLESAIANKDQTKASENYIDADPTKKTAFDNAITQAESY
LNKDHGTNKDKQAVEQAIQSVTSTENALNGDANLQCAKTEATQAIDNLTQLNTPQKTALKQQVNAAQRVSGVTDLKNSAT
SLNNAMDQLKQAIGDHDTIVAGGNYTNASPDKQGAYTDAYNAAKNIVNGSPNVITNAADVTAATQRVNNAETSLNGDTNL
ATAKQQAKDALRQMTHLSDAQKQSITGQIDSATQVTGVQSVKDNATNLDNAMNQLRNSIANKDEVKASQPYVDADTDKQN
AYNTAVTSAENIINATSQPTLDPSAVTQAANQVNTNKTALNGAQNLANKKQETTANINRLSHLNNAQKQDLNTQVTNAPN
ISTVNQVKTKAEQLDQAMERLINGIQDKDQVKQSVNFTDADPEKQTAYNNAVTAAENIINQANGTNANQSQVEAALSTVT
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QNFADADPEKKNAYNEAVRNAENILNKSTGTNVPKDQVEAAMNQVNTTKAALNGTQNLEKAKQHANTAIDGLSHLTNAQK
EALKQLVQQSTTVAEAQGNEQKANNVDAAMDKLRQSIADNATTKQNQNYTDASPNKKDAYNNAVTTAQGIIDQTTNPSLD
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INNSNDLNQAQKDALKQQVQNATTVAGVNNVKQTAQELNNAMTQLKQGIADKEQTKADGNFVNADSDKQNAYNQAVAKAE
ALISGTPDVVVTPSEITAALNKVTQAKNDLNGNTNLATAKQNVQHAIDQLPNLNQAQRDEYSKQITQATLVPNVNAIQQA

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KDDYTNAVSHAEGILSKANGSNASQTEVEQAMQRVNEAKQALNGNDNVQRAKDAAKQVITNANDLNQAQKDALKQQVDAA
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VNQAKGDLNGNHNLQVAKDNANTAIDQLPNLNQPQKTALKDQVSHAELVTGVNAIKQNADALNNAMGTLKQQIQANSQVP
QSVDFTQADQDKQQAYNNAANQAQQIANGTPTPVLAPDTVTKAVTTMNQAKDALNGDEKLAQAKQDALANLDTLRDLNQP
QRDALRNQINQAQALATVEQTKQNAQNVNTAMGNLKQGIANKDTVKASENYHDADVDKQTAYTNAVSQAEGIINQTTNPT
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LSQAINDKDQILADGNYLNADPDKQNAYKQAVAKAEALLNKQSGTNEVQAQVESITNEVNAAKQALNGNDNLANAKQQAK
QQLANLTHLNDAQKQSFESQITQAPLVTDVTTINQKAQTLDHAMELLRNSVADNQTTLASEDYHDATAQRQNDYNKAVTA
ANNIINQTTSPTMNPDDVNGATTQVNNTKVALDGDENLAAAKQQANNRLDQLDHLNNAQKQQLQSQITQSSDIAAVNGHK
QTAESLNTAMGNLINAIADHQAVEQRGNFINADTDKQTAYNTAVNEAAAMINKQTGQNANQTEVEQAITKVQTTLQALNG
DHNLQVAKTNATQAIDVLTSLNDPQKTALKDQVTAATLVTAVHQIEQNANTLNQAMHGLRQSIQDNAATKANSKYINEDQ
PEQQNYDQAVQAANNIINEQTATLDNNAINQVAATVNTTKAALHGDVKLQNDKDHAKQTVSQLAHLNNAQKHMEDTLIDS
ETTRTAVKQDLTEVQALDQLMDALQQSIADKDATRASSAYVNAEPNKKQAYDEAVQNAESIIAGLNNPTINKGNVSSATQ
AVISSKNALDGVERLAQDKQTAGNSLNHLDQLTPAQQQALENQINNATTCDKVAEIIAQAQALNEAMKALKESIKDQPQT
EASSKFINEDQAQKDAYTQAVQHAKDLINKTTDPTLAKSIIDQATQAVTDAKNNLHGDQKLAQDKQRATETLNNLSNLNT
PQRQALENQINNAATRGEVAQKLTEAQALNQAMEALRNSIQDQQQTESGSKFINEDKPQKDAYQAAVQNAKDLINQTGNP
TLDKAQVEQLTHAFKQAKDNLHGDQKLADDKQHAVTDLNQLNGLNNPQRQALESQINNAATRGEVAQKLAEAKALDQAMQ
ALRNSIQDQQQTEAGSKFINEDKPQKDAYQAAVQNAKDLINQTGNPTLDKSQVEQLTQAVTTAKDNLHGDQKLARDQQQA
VTTVNALPNLNHAQQQTLTDAINAAPTRTEVAQHVQTATELDHAMETLKNKVDQVNTDKAQPNYTEASTDKKEAVDQALQ
AAQSITDPTNGSNANKDAVEQALTKLQEKVNELNGNERVAEAKTQAKQTIDQLTHLNADQIATAKQNIDQATKLQPIAEL
VDQATQLNQSMDQLQQAVNEHANVEQTIDYTQADSDKQKAYKQAIADAENVLKQNANKQQVDQALQNILNAKQALNGDER
VALAKTNGKHDIDQLNALNNAQQDGFKGRIDQSNDLNQIQQIVDEAKALNRAMDQLSQEITGNEGRTKGSTNYVNADTQV
KQVYDEAVDKAKQALDKSSGQNLTAEQVIKLNDAVTAAKKALNGEERLNNRKAEALQRLDQLTHLNNAQRQLAIQQINNA
ETLNKASRAINRATKLDNAMGAVQQYIDEQHLGVISSTNYINADDNLKANYDNAIANAAHELDKVQGNAIAKAEAEQLKQ
NIIDAQNALNGDQNLANAKDKANAFVNSLNGLNQQQQDLAHKAINNADTVSDVTDIVNNQIDLNDAMETLKHLVDNEIPN
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DKEKQALKDRINQILQQGHNDINNAMTKEEIEQAKAQLAQALQDIKDLVKAKEDAKNAIKALANAKRDQINSNPDLTPEQ
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QDILAHINLIDQLSAEVIDTPSTATISDSLTAKVEVTLLDGSKVIVNVPVKVVEKELSVVKQQAIESIENAAQQKIDEIN
NSVTLTLEQKEAAIAEVNKLKQQAIDHVNNAPDVHSVEEIQQQEQAYIEQFNPEQFTIEQAKSNAIKSIEDAIQHMIDEI
KARTDLTDKEKQEAIAKLNQLKEQAIQAIQRAQSISEITEQLEQFKAQMKAANPTAKELAKRKQEAISRIKDFSNEKINS
IRNSEIGTADEKQAAMNQINEIVLETIRDINNAHTLQQVEAALNNGIARISAVQIVISDRAKQSSSTGNESNSHLTIGYG
TANHPFNSSTIGHKKKLDEDDDIDPLHMRHFSNNFGNVIKNAIGVVGISGLLASFWFFIAKRRRKEDEEEELEIRDNNKD
SIKETLDDTKHLPLLFAKRRRKEDEEDVTVEEKDSLNNGESLDKVKHTPFFLPKRRRKEDEEDVEVTNENTDEKVLKDNE
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SEQ ID NO:14 polypeptide sequence

MNNRDKLQKFSIRKYAIGTFSTVIATLVFMGINTNHASADELNQNQKLIKQLNQTDDDDSNTHSQEIENNKQNSSGQTES
LRSSTSQNQANARLSDQFKDTNETSQQLPTNVSDDSINQSHSEANMNNEPLKVDNSTMQAHSKIVSDSDGNASENKHHKL
TENVLAESRASKNDKEKENLQEKDKSQQVHPPLDKNALQAFFDASYHNYRMIDRDRADATEYQKVKSTFDYVNDLLGNNQ
NIPSEQLVSAYQQLEKALELARTLPQQSTTEKRGRRSTRSVVENRSSRSDYLDARTEYYVSKDDDDSGFPPGTFFHASNR
RWPYNLPRSRNILRASDVQGNAYITTKRLKDGYQWDILFNSNHKGHEYMYYWFGLPSDQTPTGPVTFTIINRDGSSTSTG
GVGFGSGAPLPQFWRSAGAINSSVANDFKHGSATNYAFYDGVNNFSDFARGGELYFDREGATQTNKYYGDENFALLNSEK
PDQIRGLDTIYSFKGSGDVSYRISFKTQGAPTARLYYAAGARSGEYKQATNYNQLYVEPYKNYRNRVQSNVQVKNRTLHL
KRTIRQFDPTLQRTTDVPILDSDGSGSIDSVYDPLSYVKNVTGTVLGIYPSYLPYNQERWQGANAMNAYQIEELFSQENL
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SEQ ID NO:15 polypeptide sequence

MSGTLHNTVGSGILPYQQEIRIKLTSNEPIKDSEWSITGYPNTLTLQNAVGRTNNATEKNLALVGHIDPGNYFITVKFGD
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DPSKNGVLTFRSSDYLKDLPLSGELKAIVYYNQYVQSNFSKSVPFSSDTTPPTINEPAGLVHKYYRGDHVEITLPVTDNT
GGSGLRDVNVNLPQGWTKTFTINPNNNTEGTLKLIGNIPSNEAYNTTYHFNITATDNSGNTTNPAKTFILNVGKLADDLN
PVGLSRDQLQLVTDPSSLSNSEREEVKRKISEANANIRSYLLQNNPILAGVNGDVTFYYRDGSVDVIDAENVITYEPERK
SIFSENGNTNKKEAVITIARGQNYTIGPNLRKYFSLSNGSDLPNRDFTSISAIGSLPSSSEISRLNVGNYNYRVNAKNAY
HKTQQELNLKLKIVEVNAPTGNNRVYYRVSTYNLTNDEINKIKQAFKAANSGLNLNDNDITVSNNFDHRNVSSVTVTIRKG

DLIKEFSSNLNNMNFLRWVNIRDDYTISWTSSKIQGRNTDGGLEWSPDHKSLIYKYDATLGRQINTNDVLTLLQATAKNS
NLRSNINSNEKQLAERGSNGYSKSIIRDDGEKSYLLNSNPIQVLDLVEPDNGYGGRQVSHSNVIYNEKNSSIVNGQVPEA
NGASAFNIDKVVKANAANNGIMGVIYKAQLYLAPYSPKGYIEKLGQNLSNTNNVINVYFVPSDKVNPSITVGNYDHHTVY
SGETFKNTINVNDNYGLNTVASTSDSAITMTRNNNELVGQAPNVTNSINKIVKVKATDKSGNESIVSFTVNIKPLNEKYR
ITTSSSNQTPVRISNIQNNANLSIEDQNRVKSSLSMTKILGTRNYVNESNNDVRSQVVSKVNRSGNNATVNVTTTFSDGT
TNTITVPVKHVLLEVVPTTRTTVRGQQFPTGKGTSPNDFFSLRTGGPVDARIVWVNNQGPDINSNQIGRDLTLHAEIFFD
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YQNGQTENVNVLFKVKPNKPVIDSNSVISKGQLNGQQILVRNVPQNAQVTLYQSNGTVIPNTNTTIDSNGIATVTIQGTL
PTGNITAKTSMTNNVTYTKQNSSGIASNTTEDISVFSENSDQVNVTAGMQAKNDGIKIIKGTNYNFNDFNSFISNIPAHS
TLTWNEEPNSWKNNIGTTTKTVTVTLPNHQGTRTVDIPITIYPTVTAKNPVRDQKGRNLTNGTDVYNYIIFENNNRLGGT
ASWKDNRQPDKNIAGVQNLIALVNYPGISTPLEVPVKVWVYNFDFTQPIYKIQVGDTFPKGTWAGYYKHLENGEGLPIDG
WKFYWNQQSTGTTSDQWQSLAYTRTPFVKTGTYDVVNPSNWGVWQTSQSAKFIVTNAKPNQPTITQSKTGDVTVTPGAVR
NILISGTNDYIQASADKIVINKNGNKLTTFVKNNDGRWTVETGSPDINGIGPTNNGTAISLSRLAVRPGDSIEAIATEGS
GETISTSATSEIYIVKAPQPEQVATHTYDNGTFDILPDNSRNSLNPTERVEINYTEKLNGNETQKSFTITKNNNGKWTIN
NKPNYVEFNQDNGKVVFSANTIKPNSQITITPKAGQGNTENTNPTVIQAPAQHTLTINEIVKEQGQNVTNDDINNAVQVP
NKNRVAIKQGNALPTNLAGGSTSHIPVVIYYSDGSSEEATETVRTKVNKTELINARRRLDEEISKENKTPSSIRNFDQAM
NRAQSQINTAKSDADQVIGTEFATPQQVNSALSKVQAAQNKINEAKALLQNKADNSQLVRAKEQLQQSIQPAASTDGMTQ
DSTRNYNNKRQAAEQAIQHANSVINNGDATSQQINDAKNTVEQAQRDYVEAKSNLRADKSQLQSAYDTLNRDVLTNDKKP
ASVRRYNEAISNIRKELDTAKADASSTLRNTNPSVEQVRDALNKINTVQPKVNQAIALLQPKENNSELVQAKKRLQDAVN
DIPQTQGMTQQTINNYNDKQREAERALTSAQRVIDNGDATTQEITSEKSKVEQAMQALTNAKSNLRADKNELQTAYNKLI
ENVSTNGKKPASIRQYETAKARIQNQINDAKNEAERILGNDNPQVSQVTQALNKIKAIQPKLTEAINMLQNKENNTELVN
AKNRLENAVNDTDPTHGMTQETINNYNAKKREAQNEIQKANMIINNGDATAQDISSEKSKVEQVLQALQNAKNDLRADKR
ELQTAYNKLIQNVNTNGKKPSSIQNYKSARRNIENQYNTAKNEAHNVLENTNPTVNAVEDALRKINAIQPEVTKAINILQ
DKEDNSELVRAKEKLDQAINSQPSLNGMTQESINNYTTKRREAQNIASSADTIINNGDASIEQITENKIRVEEATNALNE
AKQHLTADTTSLKTEVRKLSRRGDTNNKKPSSVSAYNNTIHSLQSEITQTENRANTIINKPIRSVEEVNNALHEVNQLNQ
RLTDTINLLQPLANKESLKEARNRLESKINETVQTDGMTQQSVENYKQAKIKAQNESSIAQTLINNGDASDQEVSTEIEK
LNQKLSELTNSINHLTVNKEPLETAKNQLQANIDQKPSTDGMTQQSVQSYERKLQEAKDKINSINNVLANNPDVNAIRTN
KVETEQINNELTQAKQGLTVDKQPLINAKTALQQSLDNQPSTTGMTEATIQNYNAKRQKAEQVIQNANKIIENAQPSVQQ
VSDEKSKVEQALSELNNAKSALRADKQELQQAYNQLIQPTDLNNKKPASITAYNQRYQQFSNELNSTKTNTDRILKEQNP
SVADVNNALNKVREVQQKLNEARALLQNKEDNSALVRAKEQLQQAVDQVPSTEGMTQQTKDDYNSKQQAAQQEISKAQQV
IDNGDATTQQISNAKTNVERALEALNNAKTGLRADKEELQNAYNQLTQNIDTSGKTPASIRKYNEAKSRIQTQIDSAKNE
ANSILTNDNPQVSQVTAALNKIKAVQPELDKAIAMLKNKENNNALVQAKQQLQQIVNEVDPTQGMTTDTANNYKSKKREA
EDEIQKAQQIINNGDATEQQITNETNRVNQAINAINKAKNDLRADKSQLENAYNQLIQNVDTNGKKPASIQQYQAARQAI
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NNYEAKRNEAQSAIRNAEAVINNGDATAKQISDEKSKVEQALAHLNDAKQQLTADTTELQTAVQQLNRRGDTNNKKPRSI
NAYNKAIQSLETQITSAKDNANAVIQKPIRTVQEVNNALQQVNQLNQQLTEAINQLQPLSNNDALKAARLNLENKINQTV
QTDGMTQQSIEAYQNAKRVAQNESNTALALINNGDADEQQITTETDRVNQQTTNLTQAINGLTVNKEPLETAKTALQNNI
DQVPSTDGMTQQSVANYNQKLQIAKNEINTINNVLANNPDVNAIKTNKAEAERISNDLTQAKNNLQVDTQPLEKIKRQLQ
DEIDQGTNTDGMTQDSVDNYNDSLSAAIIEKGKVNKLLKRNPTVEQVKESVANAQQVIQDLQNARTSLVPDKTQLQEAKN
RLENSINQQTDTDGMTQDSLNNYNDKLAKARQNLEKISKVLGGQPTVAEIRQNTDEANAHKQALDTARSQLTLNREPYIN
HINNESHLNNAQKDNFKAQVNSAPNHNTLETIKNKADTLNQSMTALSESIADYENQKQQENYLDASNNKRQDYDNAVNAA
KGILNQTQSPTMSADVIDQKAEDVKRTKTALDGNQRLEVAKQQALNHLNTLNDLNDAQRQTLTDTINHSPNINSVNQAKE
KANTVNTAMTQLKQTIANYDDELHDGNYINADKDKKDAYNNAVNNAKQLINQSDANQAQLDPAEINKVTQRVNTTKNDLN
GNDKLAEAKRDANTTIDGLTYLNEAQRNKAKENVGKASTKTNITSQLQDYNQLNIAMQALRNSVNDVNNVKANSNYINED
NGPKEAYNQAVTHAQTLINAQSNPEMSRDVVNQKTQAVNTAHQNLHGQQKLEQAQSSANTEIGNLPNLTNTQKAKEKELV
NSKQTRTEVQEQLNQAKSLDSSMGTLKSLVAKQPTVQKTSVYINEDQPEQSAYNDSITMGQTIINKTADPVLDKTLVDNA
ISNISTKENALHGEQKLTTAKTEAINALNTLADLNTPQKEAIKTAINTAHTRTDVTAEQSKANQINSAMHTLRQNISDNE
SVTNESNYINAEPEKQHAFTEALNNAKEIVNEQQATLDANSINQKAQAILTTKNALDGEEQLRRAKENADQEINTLNQLT
DAQRNSEKGLVNSSQTRTEVASQLAKAKELNKVMEQLNHLINGKNQMINSSKFINEDANQQQAYSNAIASAEALKNKSQN
PELDKVTIEQAINNINSAINNLNGEAKLTKAKEDAVASINNLSGLTNEQKTKENQAVNGAQTRDQVANKLRDAEALDQSM
QTLRDLVNNQNAIHSTSNYFNEDSTQKNTYDNAIDNGSTYITGQHNPELNKSTIDQTISRINTAKNDLHGVEKLQRDKGT
ANQEIGQLGYLNDPQKSGEESLVNGSNTRSEVEEHLNEAKSLNNAMKQLRDKVAEKTNVKQSSDYINDSTEHQRGYDQAL
QEAENIINEIGNPTLNKSEIEQKLQQLTDAQNALQGSHLLEEAKNNAITGINKLTALNDAQRQKAIENVQAQQTIPAVNQ
QLTLDREINTAMQALRDKVGQQNNVHQQSNYFNEDEQPKHNYDNSVQAGQTIIDKLQDPIMNKNEIEQAINQINTTQTAL
SGENKLHTDQESTNRQIEGLSSLNTAQINAEKDLVNQAKTRTDVAQKLAAAKEINSAMSNLRDGIQNKEDIKRSSAYINA
DPTKVTAYDQALQNAENIINATPNVELNKATIEQALSRVQQAQQDLDGVQQLANAKQQATQTVNGLNSLNDGQKRELNLL
INSANTRTKVQEELNKATELNHAMEALRNSVQNVDQVKQSSNYVNEDQPEQHNYDNAVNEAQATINNNAQPVLDKLAIER
LTQTVNTTKDALHGAQKLTQDQQAAETGIRGLTSLNEPQKNAEVAKVTAATTRDEVRNIRQEATTLDTAMLGLRKSIKDK
NDTKNSSKYINEDHDQQQAYDNAVNNAQQVIDETQATLSSDTINQLANAVTQAKSNLHGDTKLQHDKDSAKQTIAQLQNL
NSAQKHMEDSLIDNESTRTQVQHDLTEAQALDGLMGALKESIKDYTNIVSNGNYINAEPSKKQAYDAAVQNAQNIINGTN
QPTINKGNVTTATQTVKNTKDALDGDHRLEEAKNNANQTIRNLSNLNNAQKDAEKNLVNSASTLEQVQQNLQTAQQLDNA

MGELRQSIAKKDQVKADSKYLNEDPQIKQNYDDAVQRVETIINETQNPELLKANIDQATQSVQNAEQALHGAEKLNQDKQ
TSSTELDGLTDLTDAQREKLREQINTSNSRDDIKQKIEQAKALNDAMKKLKEQVAQKDGVHANSDYTNEDSAQKDAYNNA
LKQAEDIINNSSNPNLNAQDITNALNNIKQAQDNLHGAQKLQQDKNTTNQAIGNLNHLNQPQKDALIQAINGATSRDQVA
EKLKEAEALDEAMKQLEDQVNQDDQISNSSPFINEDSDKQKTYNDKIQAAKEIINQTSNPTLDKQKIADTLQNIKDAVNN
LHGDQKLAQSKQDANNQLNHLDDLTEEQKNHFKPLINNADTRDEVNKQLEIAKQLNGDMSTLHKVINDKDQIQHLSNYIN
ADNDKKQNYDNAIKEAEDLIHNHPDTLDHKALQDLLNKIDQAHNELNGESRFKQALDNALNDIDSLNSLNVPQRQTVKDN
INHVTTLESLAQELQKAKELNDAMKAMRDSIMNQEQIRKNSNYTNEDLAQQNAYNHAVDKINNIIGEDNATMDPQIIKQA
TQDINTAINGLNGDQKLQDAKTDAKQQITNFTGLTEPQKQALENIINQQTSRANVAKQLSHAKFLNGKMEELKVAVAKAS
LVRQNSNYINEDVSEKEAYEQAIAKGQEIINSENNPTISSTDINRTIQEINDAEQNLHGDNKLRQAQEIAKNEIQNLDGL
NSAQITKLIQDIGRTTTKPAVTQKLEEAKAINQAMQQLKQSIADKDATLNSSNYLNEDSEKKLAYDNAVSQAEQLINQLN
DPTMDISNIQAITQKVIQAKDSLHGANKLAQNQADSNLIINQSTNLNDKQKQALNDLINHAQTKQQVAEIIAQANKLNNE
MGTLKTLVEEQSNVHQQSKYINEDPQVQNIYNDSIQKGREILNGTTDDVLNNNKIADAIQNIHLTKNDLHGDQKLQKAQQ
DATNELNYLTNLNNSQRQSEHDEINSAPSRTEVSNDLNHAKALNEAMRQLENEVALENSVKKLSDFINEDEAAQNEYSNA
LQKAKDIINGVPSSTLDKATIEDALLELQNARESLHGEQKLQEAKNQAVAEIDNLQALNPGQVLAEKTLVNQASTKPEVQ
EALQKAKELNEAMKALKTEINKKEQIKADSRYVNADSGLQANYNSALNYGSQIIATTQPPELNKDVINRATQTIKTAENN
LNGQSKLAEAKSDGNQSIEHLQGLTQSQKDKQHDLINQAQTKQQVDDIVNNSKQLDNSMNQLQQIVNNDNTVKQNSDFIN
EDSSQQDAYNHAIQAAKDLITAHPTIMDKNQIDQAIENIKQALNDLHGSNKLSEDKKEASEQLQNLNSLTNGQKDTILNH
IFSAPTRSQVGEKIASAKQLNNTMKALRDSIADNNEILQSSKYFNEDSEQQNAYNQAVNKAKNIINDQPTPVMANDEIQS
VLNEVKQTKDNLHGDQKLANDKTDAQATLNALNYLNQAQRGNLETKVQNSNSRPEVQKVVQLANQLNDAMKKLDDALTGN
DAIKQTSNYINEDTSQQVNFDEYTDRGKNIVAEQTNPNMSPTNINTIADKITEAKNDLHGVQKLKQAQQQSINTINQMTG
LNQAQKEQLNQEIQQTQTRSEVHQVINKAQALNDSMNTLRQSITDEHEVKQTSNYINETVGNQTAYNNAVDRVKQIINQT
SNPTMNPLEVERATSNVKISKDALHGERELNDNKNSKTFAVNHLDNLNQAQKEALTHEIEQATIVSQVNNIYNKAKALNN
DMKKLKDIVAQQDNVRQSNNYINEDSTPQNMYNDTINHAQSIIDQVANPTMSHDEIENAINNIKHAINALDGEHKLQQAK
ENANLLINSLNDLNAPQRDAINRLVNEAQTREKVAEQLQSAQALNDAMKHLRNSIQNQSSVRQESKYINASDAKKEQYNH
AVREVENIINEQHPTLDKEIIKQLTDGVNQANNDLNGVELLDADKQNAHQSIPTLMHLNQAQQNALNEKINNAVTRTEVA
AIIGQAKLLDHAMENLEESIKDKEQVKQSSNYINEDSDVQETYDNAVDHVTEILNQTVNPTLSIEDIEHAINEVNQAKKQ
LRGKQKLYQTIDLADKELSKLDDLTSQQSSSISNQIYTAKTRTEVAQAIEKAKSLNHAMKALNKVYKNADKVLDSSRFIN
EDQPEKKAYQQAINHVDSIIHRQTNPEMDPTVINSITHELETAQNNLHGDQKLAHAQQDAANVINGLIHLNVAQREVMIN
TNTNATTREKVAKNLDNAQALDKAMETLQQVVAHKNNILNDSKYLNEDSKYQQQYDRVIADAEQLLNQTTNPTLEPYKVD
IVKDNVLANEKILFGAEKLSYDKSNANDEIKHMNYLNNAQKQSIKDMISHAALRTEVKQLLQQAKILDEAMKSLEDKTQV
VITDTTLPNYTEASEDKKEKVDQTVSHAQAIIDKINGSNVSLDQVRQALEQLTQASENLDGDQRVEEAKVHANQTIDQLT
HLNSLQQQTAKESVKNATKLEEIATVSNNAQALNKVMGKLEQFINHADSVENSDNYRQADDDKIIAYDEALEHGQDIQKT
NATQNETKQALQQLIYAETSLNGFERLNHARPRALEYIKSLEKINNAQKSALEDKVTQSHDLLELEHIVNEGTNLNDIMG
ELANAIVNNYAPTKASINYINADNLRKDNFTQAINNARDALNKTQGQNLDFNAIDTFKDDIFKTKDALNGIERLTAAKSK
AEKLIDSLKFINKAQFTHANDEIMNTNSIAQLSRIVNQAFDLNDAMKSLRDELNNQAFPVQASSNYINSDEDLKQQFDHA
LSNARKVLAKENGKNLDEKQIQGLKQVIEDTKDALNGIQRLSKAKAKAIQYVQSLSYINDAQRHIAENNIHNSDDLSSLA
NTLSKASDLDNAMKDLRDTIESNSTSVPNSVNYINADKNLQIEFDEALQQASATSSKTSENPATIEEVLGLSQAIYDTKN
ALNGEQRLATEKSKDLKLIKGLKDLNKAQLEDVTNKVNSANTLTELSQLTQSTLELNDKMKLLRDKLKTLVNPVKASLNY
RNADYNLKRQFNKALKEAKGVLNKNSGTNVNINDIQHLLTQIDNAKDQLNGERRLKEHQQKSEVFIIKELDILNNAQKAA
IINQIRASKDIKIINQIVDNAIELNDAMQGLKEHVAQLTATTKDNIEYLNADEDHKLQYDYAINLANNVLDKENGTNKDA
NIIIGMIQNMDDARALLNGIERLKDAQTKAHNDIKDTLKRQLDEIEHANATSNSKAQAKQMVNEEARKALSNINDATSND
LVNQAKDEGQSAIEHIHADELPKAKLDANQMIDQKVEDINHLISQNPNLSNEEKNKLISQINKLVNGIKNEIQQAINKQQ
IENATTKLDEVIETTKKLIIAKAEAKQMIKELSQKKRDAINNNTDLTPSQKAHALADIDKTEKDALQHIENSNSIDDINN
NKEHAFNTLAHIIIWDTDQQPLVFELPELSLQNALVTSEVVVHRDETISLESIIGAMTLTDELKVNIVSLPNTDKVADHL
TAKVKVILADGSYVTVNVPVKVVEKELQIAKKDAIKTIDVLVKQKIKDIDSNNELTSTQREDAKAEIERLKKQAIDKVNH
SKSIKDIETVKRTDFEEIDQFDPKRFTLNKAKKDIITDVNTQIQNGFKEIETIKGLTSNEKTQFDKQLTALQKEFLEKVE
HAHNLVELNQLQQEFNNRYKHILNQAHLLGEKHIAEHKLGYVVVNKTQQILNNQSASYFIKQWALDRIKQIQLETMNSIR
GAHTVQDVHKALLQGIEQILKVNVSIINQSFNDSLHNFNYLHSKFDARLREKDVANHIVQTETFKEVLKGTGVEPGKINK
ETQQPKLHKNDNDSLFKHLVDNFGKTVGVITLTGLLSSFWLVLAKRRKKEEEEKQSIKNHHKDIRLSDTDKIDPIVITKR
KIDKEEQIQNDDKHSIPVAKHKKSKEKQLSEEDIHSIPVVKRKQNSDNKDTKQKKVTSKKKKTPQSTKKVVKTKKRSKK

SEQ ID NO:16 polypeptide sequence

MRDKKGPVNKRVDFLSNKLNKYSIRKFTVGTASILIGSLMYLGTQQEAEAAENNIENPTTLKDNVQSKEVKIEEVTNKDT
APQGVEAKSEVTSNKDTIEHEASVKAEDISKKEDTPKEVANVAEVQPKSSVTHNAEAPKVRKARSVDEGSFDITRDSKNV
VESTPITIQGKEHFEGYGSVDIQKNPTDLGVSEVTRFNVGNESNGLIGALQLKNKIDFSKDFNFKVRVANNHQSNTTGAD
GWGFLFSKGNAEEYLTNGGILGDKGLVNSGGFKIDTGYIYTSSMDKTEKQAGQGYRGYGAFVKNDSSGNSQMVGENIDKS
KTNFLNYADNSTNTSDGKFHGQRLNDVILTYVASTGKMRAEYAGKTWETSITDLGLSKNQAYNFLITSSQRWGLNQGINA
NGWMRTDLKGSEFTFTPEAPKTITELEKKVEEIPFKKERKFNPDLAPGTEKVTREGQKGEKTITTPTLKNPLTGEIISKG
ESKEEITKDPINELTEYGPETIAPGHRDEFDPKLPTGEKEEVPGKPGIKNPETGDVVRPPVDSVTKYGPVKGDSIVEKEE
IPFEKERKFNPDLAPGTEKVTREGQKGEKTITTPTLKNPLTGEIISKGESKEEITKDPINELTEYGPETIAPGHRDEFDP
KLPTGEKEEVPGKPGIKNPETGDVVRPPVDSVTKYGPVKGDSIVEKEEIPFKKERKFNPDLAPGTEKVTREGQKGEKTIT

TPTLKNPLTGEIISKGESKEEITKDPINELTEYGPETITPGHRDEFDPKLPTGEKEEVPGKPGIKNPETGDVVRPPVDSV
TKYGPVKGDSIVEKEEIPFEKERKFNPDLAPGTEKVTREGQKGEKTITTPTLKNPLTGEIISKGESKEEITKDPVNELTE
FGGEKIPQGHKDIFDPNLPTDQTEKVPGKPGIKNPDTGKVIEEPVDDVIKHGPKTGTPETKTVEIPFETKREFNPKLQPG
EERVKQEGQPGSKTITTPITVNPLTGEKVGEGQPTEEITKQPVDKIVEFGGEKPKDPKGPENPEKPSRPTHPSGPVNPNN
PGLSKDRAKPNGPVHSMDKNDKVKKSKIAKESVANQEKKRAELPKTGLESTQKGLIFSSIIGIAGLMLLARRRKN

SEQ ID NO:17 polypeptide sequence

MGKRRQGPINKKVDFLPNKLNKYSIRKFTVGTASILLGSTLIFGSSSHEAKAAEEKQVDPITQANQNDSSERSLENTNQP
TVNNEAPQMSSTLQAEEGSNAEAPNVPTIKANSDNDTQTQFSEAPTRNDLARKEDIPAVSKNEELQSSQPNTDSKIEPTT
SEPVNLNYSSPFMSLLSMPADSSSNNTKNTIDIPPTTVKGRDNYDFYGRVDIQSNPTDLNATNLTRYNYGQPPGTTTAGA
VQFKNQVSFDKDFDFNIRVANNRQSNTTGADGWGFMFSKKDGDDFLKNGGILREKGTPSAAGFRIDTGYYNNDPLDKIQK
QAGQGYRGYGTFVKNDSQGNTSKVGSGTPSTDFLNYADNTTNDLDGKFHGQKLNNVNLKYNASNQTFTATYAGKTWTATL
SELGLSPTDSYNFLVTSSQYGNGNSGTYADGVMRADLDGATLTYTPKAVDGDPITSTKEIPFNKKREFDPNLAPGTEKVV
QKGEPGIETTTTPTYVNPNTGEKVGEGTPTTKITKQPVDEIVHYGGEEIKPGHKDEFDPNAPKGSQTTQPGKPGVKNPDT
GEVVTPPVDDVTKYGPVDGDPITSTEEIPFDKKREFNPDLKPGEERVKQKGEPGTKTITTPTTKNPLTGEKVGEGEPTEK
ITKQPVDEITEYGGEEIKPGHKDEFDPNAPKGSQEDVPGKPGVKNPDTGEVVTPPVDDVTKYGPVDGDPITSTEEIPFDK
KREFDPNLAPGTEKVVQKGEPGTKTITTPTTKNPLTGEKVGEGEPTEKITKQPVDEIVHYGGEEIKPGHKDEFDPNAPKG
SQEDVPGKPGVKNPDTGEVVTPPVDDVTKYGPVDGDPITSTEEIPFDKKREFNPDLKPGEERVKQKGEPGTKTITTPTTK
NPLTGEKVGEGEPTEKVTKQPVDEIVHYGGEEIKPGHKDEFDPNAPKGSQEDVPGKPGVKNPDTGEVVTPPVDDVTKYGP
VDGDPITSTEEIPFDKKREFDPNLAPGTEKVVQKGEPGTKTITTPTTKNPLTGEKVGEGEPTEKITKQPVDEIVHYGGEE
IKPGHKDEFDPNAPKGSQTTQPGKPGVKNPDTGEVVTPPVDDVTKYGPVDGDPITSTEEIPFDKKREFDPNLAPGTEKVV
QKGEPGTKTITTPTTKNPLTGEKVGEGEPTEKITKQPVDEIVHYGGEQIPQGHKDEFDPNAPVDSKTEVPGKPGVKNPDT
GEVVTPPVDDVTKYGPKVGNPITSTEEIPFDKKRVFNPDLKPGEERVKQKGEPGTKTITTPILVNPITGEKVGEGKSTEK
VTKQPVDEIVEYGPTKAEPGKPAEPGKPAEPGKPAEPGKPAEPGKPAEPGTPAEPGKPAEPGKPAEPGKPAEPGKPAEPG
TPAEPGKPAEPGKPAEPGKPAEPGTPAEPGKPAEPGTPAEPGKPAEPGTPTQSGAPEQPNRSMHSTDNKNQLPDTGENRQ
ANEGTLVGSLLAIVGSLFIFGRRKKGNEK

SEQ ID NO:18 polypeptide sequence

MKKLYTSYGTYGFLHQIKINNPTHQLFQFSASDTSVIFEETDGETVLKSPSIYEVIKEIGEFSEHHFYCAIFIPSTEDHA
YQLEKKLISVDDNFRNFGGFKSYRLLRPAKGTTYKIYFGFADRHAYEDFKQSDAFNDHFSKDALSHYFGSSGQHSSYFER
YLYPIKE

SEQ ID NO:19 polypeptide sequence

MYLYTSYGTYQFLNQIKLNHQERSLFQFSTNDSSIILEESEGKSILKHPSAYQVIDSTGEFNEHHFYSAIFVPTSEDHRQ
QLEKKLLLVDVPLRNFGGFKSYRLLKPTEGSTYKIYFGFANRTAYEDFKASDIFNENFSKDALSQYFGASGQHSSYFERY
LYPIEDH

SEQ ID NO:20 polypeptide sequence

MINRDNKKAITKKGMISNRLNKFSIRKYTVGTASILVGTTLIFGLGNQEAKAAENTSTENAKQDDATTSDNKEVVSETEN
NSTTENDSTNPIKKETNTDSQPEAKEESTTSSTQQQQNNVTATTETKPQNIEKENVKPSTDKTATEDTSVILEEKKAPNY
TNNDVTTKPSTSEIQTKPTTPQESTNIENSQPQPTPSKVDNQVTDATNPKEPVNVSKEELKNNPEKLKELVRNDNNTDRS
TKPVATAPTSVAPKRLNAKMRFAVAQPAAVASNNVNDLITVTKQTIKVGDGKDNVAAAHDGKDIEYDTEFTIDNKVKKGD
TMTINYDKNVIPSDLTDKNDPIDITDPSGEVIAKGTFDKATKQITYTFTDYVDKYEDIKARLTLYSYIDKQAVPNETSLN
LTFATAGKETSQNVSVDYQDPMVHGDSNIQSIFTKLDENKQTIEQQIYVNPLKKTATNTKVDIAGSQVDDYGNIKLGNGS
TIIDQNTEIKVYKVNPNQQLPQSNRIYDFSQYEDVTSQFDNKKSFSNNVATLDFGDINSAYIIKVVSKYTPTSDGELDIA
QGTSMRTTDKYGYYNYAGYSNFIVTSNDTGGGDGTVKPEEKLYKIGDYVWEDVDKDGVQGTDSKEKPMANVLVTLTYPDG
TTKSVRTDANGHYEFGGLKDGETYTVKFETPAGYLPTKVNGTTDGEKDSNGSSITVKINGKDDMSLDTGFYKEPKYNLGD
YVWEDTNKDGIQDANEPGIKDVKVTLKDSTGKVIGTTTTDASGKYKFTDLDNGNYTVEFETPAGYTPTVKNTTAEDKDSN
GLTTTGVIKDADNMTLDSGFYKTPKYSLGDYVWYDSNKDGKQDSTEKGIKDVKVTLLNEKGEVIGTTKTDENGKYRFDNL
DSGKYKVIFEKPAGLTQTVTNTTEDDKDADGGEVDVTITDHDDFILDNGYFEEDTSDSDSDSDSDSDSDSDSDSDSDSDS
DSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDS
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GGLFAALGSLLLFGRRKKQNK

SEQ ID NO:21 polypeptide sequence

MINKKNNLLTKKKPIANKSNKYAIRKFTVGTASIVIGATLLFGLGHNEAKAEENSVQDVKDSNTDDELSDSNDQSSDEEK
NDVINNNQSINTDDNNQIIKKEETNNYDGIEKRSEDRTESTTNVDENEATFLQKTPQDNTHLTEEEVKESSSVESSNSSI
DTAQQPSHTTINREESVQTSDNVEDSHVSDFANSKIKESNTESGKEENTIEQPNKVKEDSTTSQPSGYTNIDEKISNQDE
LLNLPINEYENKARPLSTTSAQPSIKRVTVNQLAAEQGSNVNHLIKVTDQSITEGYDDSEGVIKAHDAENLIYDVTFEVD

DKVKSGDTMTVDIDKNTVPSDLTDSFTIPKIKDNSGEIIATGTYDNKNKQITYTFTDYVDKYENIKAHLKLTSYIDKSKV
PNNNTKLDVEYKTALSSVNKTITVEYQRPNENRTANLQSMFTNIDTKNHTVEQTIYINPLRYSAKETNVNISGNGDEGST
IIDDSTIIKVYKVGDNQNLPDSNRIYDYSEYEDVTNDDYAQLGNNNDVNINFGNIDSPYIIKVISKYDPNKDDYTTIQQT
VTMQTTINEYTGEFRTASYDNTIAFSTSSGQGQGDLPPEKTYKIGDYVWEDVDKDGIQNTNDNEKPLSNVLVTLTYPDGT
SKSVRTDEDGKYQFDGLKNGLTYKITFETPEGYTPTLKHSGTNPALDSEGNSVWVTINGQDDMTIDSGFYQTPKYSLGNY
VWYDTNKDGIQGDDEKGISGVKVTLKDENGNIISTTTTDENGKYQFDNLNSGNYIVHFDKPSGMTQTTTDSGDDDEQDAD
GEEVHVTITDHDDFSIDNGYYDDESDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSD
SDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSD
SDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDNDSDLGNSSDKSTKDKLPDTGANEDYGSKGTLLGTLFAGL
GALLLGKRRKNRKNKN

SEQ ID NO:22 polypeptide sequence

MSNNFKDDFEKNRQSIDTNSHQDHTEDVEKDQSELEHQDTIENTEQQFPPRNAQRRKRRRDLATNHNKQVHNESQTSEDN
VQNEAGTIDDRQVESSHSTESQEPSHQDSTPQHEEEYYNKNAFAMDKSHPEPIEDNDKHETIKDAENNTEHSTVSDKSIA
EQSQQPKPYFATGANQANTSKDKHDDVTVKQDKDESKDHHSGKKGAAIGAGTAGVAGAAGAMGVSKAKKHSNDAQNKSNS
DKSNNSTEDKASQDKSKDHHNGKKGAAIGAGTAGLAGGAASKSASAASKPHASNNASQNHDEHDNHDRDKERKKGGMAKV
LLPLIAAVLIIGALAIFGGMALNNHNNGTKENKIANTNKNNADESKDKDTSKDASKDKSKSTDSDKSKEDQDKATKDESD
NDQNNANQANNQAQNNQNQQQANQNQQQQQQQRQGGGQRHTVNGQENLYRIAIQYYGSGSPENVEKIRRANGLSGNNIRNG
QQIVIP

SEQ ID NO:23 polypeptide sequence

MIELIKMEGMIVVSNNNFKDDFEKNRQSINPDEQQTELKEDDKTNENKKEADSQNSLSNNSNQQFPPRNAQRRKRRRETA
TNQSKQQDDKHQKNSDAKTTEGSLDDRYDEAQLQQQHDKSQQQNKTEKQSQDNRMKDGKDAAIVNGTSESPEHKSKSTQN
RPGPKAQQQKRKSESTQSKPSTNKDKKAATGAGIAGAAGVAGAAETSKRHHNKKDKQDSKHSNHENDEKSVKNDDQKQSK
KGKKAAVGAGAAAGVGAAGVAHHNNQNKHHNEEKNSNQNNQYNDQSEGKKKGGFMKILLPLIAAILILGAIAIFGGMALN
NHNDSKSDDQKIANQSKKDSDKKDGAQSEDNKDKKSDSNKDKKSDSDKNADDDSDNSSSNPNATSTNNNDNVANNNSNYT
NQNQQDNANQNSNNQQATQGQQSHTVYGQENLYRIAIQYYGEGTQANVDKIKRANGLSSNNIHNGQTLVIPQ

SEQ ID NO:24 polypeptide sequence

MKNKLIAKSLLTIAAIGITTTTIASTADASEGYGPREKKPVSINHNIVEYNDGTFKYQSRPKFNSTPKYIKFKHDYNILE
FNDGTFEYGARPQFNKPAAKTDATIKKEQKLIQAQNLVREFEKTHTVSAHRKAQKAVNLVSFEYKVKKMVLQERIDNVLK
QGLVR

SEQ ID NO:25 polypeptide sequence

MKTRIVSSVTTTLLLGSILMNPVANAADSDINIKTGTTDIGSNTTVKTGDLVTYDKENGMHKKVFYSFIDDKNHNKKLLV
IRTKGTIAGQYRVYSEEGANKSGLAWPSAFKVQLQLPDNEVAQISDYYPRNSIDTKEYMSTLTYGFNGNVTGDDTGKIGG
LIGANVSIGHTLKYVQPDFKTILESPTDKKVGWKVIFNNMVNQNWGPYDRDSWNPVYGNQLFMKTRNGSMKAAENFLDPN
KASSLLSSGFSPDFATVITMDRKASKQQTNIDVIYERVRDDYQLHWTSTNWKGTNTKDKWTDRSSERYKIDWEKEEMTN

SEQ ID NO:26 polypeptide sequence

MHMKNKYISKLLVGAATITLATMISNGEAKASENTQQTSTKHQTTQNNYVTDQQKAFYQVLHLKGITEEQRNQYIKTLRE
HPERAQEVFSESLKDSKNPDRRVAQQNAFYNVLKNDNLTEQEKNNYIAQIKENPDRSQQVWVESVQSSKAKERQNIENAD
KAIKDFQDNKAPHDKSAAYEANSKLPKDLRDKNNRFVEKVSIEKAIVRHDERVKSANDAISKLNEKDSIENRRLAQREVN
KAPMDVKEHLQKQLDALVAQKDAEKKVAPKVEAPQIQSPQIEKPKAESPKVEVPQSKLLGYYQSLKDSFNYGYKYLTDTY
KSYKEKYDTAKYYYNTYYKYKGAIDQTVLTVLGSGSKSYIQPLKVDDKNGYLAKSYAQVRNYVTESINTGKVLYTFYQNP
TLVKTAIKAQETASSIKNTLSNLLSFWK

SEQ ID NO:27 polypeptide sequence

MTKHYLNSKYQSEQRSSAMKKITMGTASIILGSLVYIGADSQQVNAATEATNATNNQSTQVSQATSQPINFQVQKDGSSE
KSHMDDYMQHPGKVIKQNNKYYFQTVLNNASFWKEYKFYNANNQELATTVVNDNKKADTRTINVAVEPGYKSLTTKVHIV
VPQINYNHRYTTHLEFEKAIPTLADAAKPNNVKPVQPKPAQPKTPTEQTKPVQPKVEKVKPTVTTTSKVEDNHSTKVVST
DTTKDQTKTQTAHTVKTAQTAQEQNKVQTPVKDVATAKSESNNQAVSDNKSQQTNKVTKHNETPKQASKAKELPKTGLTS
VDNFISTVAFATLALLGSLSLLLFKRKESK

SEQ ID NO:28 polypeptide sequence

MNKQQKEFKSFYSIRKSSLGVASVAISTLLLLMSNGEAQAAAEETGGTNTEAQPKTEAVASPTTTSEKAPETKPVANAVS
VSNKEVEAPTSETKEAKEVKEVKAPKETKAVKPAAKATNNTYPILNQELREAIKNPAIKDKDHSAPNSRPIDFEMKKENG
EQQFYHYASSVKPARVIFTDSKPEIELGLQSGQFWRKFEVYEGDKKLPIKLVSYDTVKDYAYIRFSVSNGTKAVKIVSST

HFNNKEEKYDYTLMEFAQPIYNSADKFKTEEDYKAEKLLAPYKKAKTLERQVYELNKIQDKLPEKLKAEYKKKLEDTKKA
LDEQVKSAITEFQNVQPTNEKMTDLQDTKYVVYESVENNESMMDTFVKHPIKTGMLNGKKYMVMETTNDDYWKDFMVEGQ
RVRTISKDAKNNTRTIIFPYVEGKTLYDAIVKVHVKTIDYDGQYHVRIVDKEAFTKANTDKSNKKEQQDNSAKKEATPAT
PSKPTPSPVEKESQKQDSQKDDNKQLPSVEKENDASSESGKDKTPATKPTKGEVESSSTTPTKVVSTTQNVAKPTTASSK
TTKDVVQTSAGSSEAKDSAPLQKANIKNTNDGHTQSQNNKNTQENKAKSLPQTGEESNKDMTLPLMALLALSSIVAFVLP
RKRKN

SEQ ID NO:29 polypeptide sequence

MNNKKTATNRKGMIPNRLNKFSIRKYSVGTASILVGTTLIFGLSGHEAKAAEHTNGELNQSKNETTAPSENKTTEKVDSR
QLKDNTQTATADQPKVTMSDSATVKETSSNMQSPQNATASQSTTQTSNVTTNDKSSTTYSNETDKSNLTQAKNVSTTPKT
TTIKQRALNRMAVNTVAAPQQGTNVNDKVHFTNIDIAIDKGHVNKTTGNTEFWATSSDVLKLKANYTIDDSVKEGDTFTF
KYGQYFRPGSVRLPSQTQNLYNAQGNIIAKGIYDSKTNTTTYTFTNYVDQYTNVSGSFEQVAFAKRENATTDKTAYKMEV
TLGNDTYSKDVIVDYGNQKGQQLISSTNYINNEDLSRNMTVYVNQPKKTYTKETFVTNLTGYKFNPDAKNFKIYEVTDQN
QFVDSFTPDTSKLKDVTGQFDVIYSNDNKTATVDLLNGQSSSDKQYIIQQVAYPDNSSTDNGKIDYTLETQNGKSSWSNS
YSNVNGSSTANGDQKKYNLGDYVWEDTNKDGKQDANEKGIKGVYVILKDSNGKELDRTTTDENGKYQFTGLSNGTYSVEF
STPAGYTPTTANAGTDDAVDSDGLTTTGVIKDADNMTLDSGFYKTPKYSLGDYVWYDSNKDGKQDSTEKGIKGVKVTLQN
EKGEVIGTTETDENGKYRFDNLDSGKYKVIFEKPAGLTQTGTNTTEDDKDADGGEVDVTITDHDDFTLDNGYYEEETSDS
DSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSESDSDSDSDSDSDSDSDSDSDSDSDSDSDS
DSDSDSDSDSDSDSDSDSDSDSDNDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDS
DSDSDSDSDSDSDAGKHTPTKPMSTVKDQHKTAKALPETGSENNNSNNGTLFGGLFAALGSLLLFGRRKKQNK

SEQ ID NO:30 polypeptide sequence

MNMKKKEKHAIRKKSIGVASVLVGTLIGFGLLSSKEADASENSVTQSDSASNESKSNDSSSVSAAPKTDDTNVSDTKTSS
NTNNGETSVAQNPAQQETTQSSSTNATTEETPVTGEATTTTTNQANTPATTQSSNTNAEELVNQTSNETTSNDTNTVSSV
NSPQNSTNAENVSTTQDTSTEATPSNNESAPQNTDASNKDVVSQAVNPSTPRMRAFSLAAVAADAPAAGTDITNQLTDVK
VTIDSGTTVYPHQAGYVKLNYGFSVPNSAVKGDTFKITVPKELNLNGVTSTAKVPPIMAGDQVLANGVIDSDGNVIYTFT
DYVDNKENVTANITMPAYIDPENVTKTGNVTLTTGIGTNTASKTVLIDYEKYGQFHNLSIKGTIDQIDKTNNTYRQTIYV
NPSGDNVVLPALTGNLIPNTKSNALIDAKNTDIKVYRVDNANDLSESYYVNPSDFEDVTNQVRISFPNANQYKVEFPTDD
DQITTPYIVVVNGHIDPASTGDLALRSTFYGYDSNFIWRSMSWDNEVAFNNGSGSGDGIDKPVVPEQPDEPGEIEPIPED
SDSDPGSDSGSDSNSDSGSDSGSDSTSDSGSDSASDSDSASDSDSASDSDSASDSDSASDSDSASDSDSASDSDSASDSD
SASDSDSASDSDSASDSDSASDSDSASDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSD
SDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSD
SESDSDSDSDSDSESDSDSDSDSDSASDSDSGSDSDSSSDSDSDSTSDTGSDNDSDSDSNSDSESGSNNNVVPPNSPK
NGTNASNKNEAKDSKEPLPDTGSEDEANTSLIWGLLASLGSLLLFRRKKENKDKK

SEQ ID NO:31 polypeptide sequence

MKNNLRYGIRKHKLGAASVFLGTMIVVGMGQDKEAAASEQKTTTVEENGNSATDNKTSETQTTATNVNHIEETQSYNATV
TEQPSNATQVTTEEAPKAVQAPQTAQPANVETVKEEEKPQVKETTQPQDNSGNQRQVDLTPKKVTQNQGTETQVEVAQPR
TASESKPRVTRSADVAEAKEASDVSEVKGTDVTSKVTVESGSIEAPQGNKVEPHAGQRVVLKYKLKFADGLKRGDYFDFT
LSNNVNTYGVSTARKVPEIKNGSVVMATGEILGNGNIRYTFTNEIEHKVEVTANLEINLFIDPKTVQSNGEQKITSKLNG
EETEKTIPVVYNPGVSNSYTNVNGSIETFNKESNKFTHIAYIKPMNGNQSNTVSVTGTLTEGSNLAGGQPTVKVYEYLGK
KDELPQSVYANTSDTNKFKDVTKEMNGKLSVQDNGSYSLNLDKLDKTYVIHYTGEYLQGSDQVNFRTELYGYPERAYKSY
YVYGGYRLTWDNGLVLYSNKADGNGKNGQIIQDNDFEYKEDTAKGTMSGQYDAKQIIETEENQDNTPLDIDYHTAIDGEG
GYVDGYIETIEETDSSAIDIDYHTAVDSEVGHVGGYTESSEESNPIDFEESTHENSKHHADVVEYEEDTNPGGGQVTTES
NLVEFDEESTKGIVTGAVSDHTTIEDTKEYTTESNLIELVDELPEEHGQAQGPIEEITENNHHISHSGLGTENGHGNYGV
IEEIEENSHVDIKSELGYEGGQNSGNQSFEEDTEEDKPKYEQGGNIVDIDFDSVPQIHGQNKGDQSFEEDTEKDKPKYEH
GGNIIDIDFDSVPQIHGFNKHNEIIEEDTNKDKPNYQFGGHNSVDFEEDTLPKVSGQNEGQQTIEEDTTPPTPPTPEVPS
EPETPMPPTPEVPSEPETPTPPTPEVPSEPETPTPPTPEVPSEPETPTPPTPEVPSEPETPTPPTPEVPAEPGKPVPPAK
EEPKKPSKPVEQGKVVTPVIEINEKVKAVAPTKKAQSKKSELPETGGEESTNKGMLFGGLFSILGLALLRRNKKNNKA

SEQ ID NO:32 polypeptide sequence

MKKRIDYLSNKQNKYSIRRFTVGTTSVIVGATILFGIGNHQAQASEQSNDTTQSSKNNASADSEKNNMIETPQLNTTAND
TSDISANTNSANVDSTTKPMSTQTSNTTTTEPASTNETPQPTAIKNQATAAKMQDQTVPQEANSQVDNKTTNDANSIATN
SELKNSQTLDLPQSSPQTISNAQGTSKPSVRTRAVRSLAVAEPVVNAADAKGTNVNDKVTASNFKLEKTTFDPNQSGNTF
MAANFTVTDKVKSGDYFTAKLPDSLTGNGDVDYSNSNNTMPIADIKSTNGDVVAKATYDILTKTYTFVFTDYVNNKENIN
GQFSLPLFTDRAKAPKSGTYDANINIADEMFNNKITYNYSSPIAGIDKPNGANISSQIIGVDTASGQNTYKQTVFVNPKQ
RVLGNTWVYIKGYQDKIEESSGKVSATDTKLRIFEVNDTSKLSDSYYADPNDSNLKEVTDQFKNRIYYEHPNVASIKFGD
ITKTYVVLVEGHYDNTGKNLKTQVIQENVDPVTNRDYSIFGWNNENVVRYGGGSADGDSAVNPKDPTPGPPVDPEPSPDP
EPEPTPDPEPSPDPEPEPSPDPDPDSDSDSDSGSDSDSGSDSDSESDSDSDSDSDSDSDSDSESDSDSESDSDSDSDSDS
DSDSDSESDSDSDSDSDSDSDSDSESDSDSESDSESDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSESDSDSDS

DSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDS
DSDSRVTPPNNEQKAPSNPKGEVNHSNKVSKQHKTDALPETGDKSENTNATLFGAMMALLGSLLLFRKRKQDHKEKA

SEQ ID NO:33 polypeptide sequence

MKKQIISLGALAVASSLFTWDNKADAIVTKDYSKESRVNEKSKKGATVSDYYYWKIIDSLEAQFTGAIDLLEDYKYGDPI
YKEAKDRLMTRVLGEDQYLLKKKIDEYELYKKWYKSSNKNTNMLTFHKYNLYNLTMNEYNDIFNSLKDAVYQFNKEVKEI
EHKNVDLKQFDKDGEDKATKEVYDLVSEIDTLVVTYYADKDYGEHAKELRAKLDLILGDTDNPHKITNERIKKEMIDDLN
SIIDDFFMETKQNRPNSITKYDPTKHNFKEKSENKPNFDKLVEETKKAVKEADESWKNKTVKKYEETVTKSPVVKEEKKV
EEPQLPKVGNQQEVKTTAGKAEETTQPVAQPLVKIPQETIYGETVKGPEYPTMENKTLQGEIVQGPDFLTMEQNRPSLSD
NYTQPTTPNPILEGLEGSSSKLEIKPQGTESTLKGIQGESSDIEVKPQATETTEASQYGPRPQFNKTPKYVKYRDAGTGI
REYNDGTFGYEARPRFNKPSETNAYNVTTNQDGTVSYGARPTQNKPSETNAYNVTTHANGQVSYGARPTQKKPSKTNAYN
VTTHANGQVSYGARPTQKKPSKTNAYNVTTHANGQVSYGARPTYKKPSETNAYNVTTHANGQVSYGARPTQKKPSETNAY
NVTTHADGTATYGPRVTK

SEQ ID NO:67 polypeptide sequence

MKSNLRYGIRKHKLGAASVFLGTMIVVGMGQEKEAAASEQNNTTVEESGSSATESKASETQTTTNNVNT
IDETQSYSATSTEQPSKSTQVTTEEAPTTVQAPKVETEMKSQEDLPSEKVADKETTGTQVDIAQPSNVS
EIKPRMKRSADVTAVSEKEVAEEAKATGTDVTNKVEVTESSLEGHNKDSNIVNPHNAQRVTLKYKWKFG
EGIKAGDYFDFTLSDNVETHGISTLRKVPEIKS
STEDKVMANGQVINERTIRYTFTDYINNKKDLTAELNLNLFIDPTTVTKQGSQKVEVTLGQNKVSKEFD
IKYLDGVKDRMGVTVNGRIDTLNKEEGKFSHFAYVKPNNQSLTSVTVTGQVTSGYKQSANNPTVKVYKH
IGSDELAESVYAKLDDTSKFEDVTEKVNLSYTSNGGYTLNLGDLDNSKDYVIKYEGEYDQNAKDLNFRT
HLSGYHKYYPYYPYYPYYPVQLTWNNGVAFYSN
NAKGDGKDKPNDPIIEKSEPIDLDIKSEPPVEKHELTGTIEESNDSKPIDFEYHTAVEGAEGHAEGIIE
TEEDSIHVDFEESTHENSKHHADVVEYEEDTNPGGGQVTTESNLVEFDEESTKGIVTGAVSDHTTVEDT
KEYTTESNLIELVDELPEEHGQAQGPIEEITENNHHISHSGLGTENGHGNYGVIDEIEENSHVDIKSEL
GYEGGQNSGNQSFEEDTEEDKPKYEQGGNIVDI
DFDSVPQIHGQNNGNQSFEEDTEEDKPKYEQGGNIIDIDFDSVPQIHGFNKHNEIIEEDTNKDKPNYQF
GGHNSVDFEEDTLPKVSGQNEGQQTIEEDTTPPTPPTPEVPSEPETPTPPTPEVPSEPGEPTPPKPEVP
SEPETPVPPTPEVPSEPGKPVPPAKEEPKKPSKPVEQGKVVTPVIEINEKVKAVAPTKQKQSKKSELPE
TGGEESTNKGMLFGGLFSILGLVLLRRNKKNNK
A

SEQ ID NO:68 polypeptide sequence

MKFKSLITTTLALGVIASTGANFNTNEASAAAKPLDKSSSTLHHGHSNIQIPYTITVNGTSQNILSSLT
FNKNQNISYKD
IENKVKSVLYFNRGISDIDLRLSKQAEYTVHFKNGTKRVIDLKSGIYTADLINTSDIKAISVNVDTKKQ
PKDKAKANVQV
PYTITVNGTSQNILSNLTFNKNQNISYKDLEGKVKSVLESNRGITDVDLRLSKQAKYTVNFKNGTKKVI
DLKSGIYTANL
INSSDIKSININVDTKKHIENKAKRNYQVPYSINLNGTSTNILSNLSFSNKPWTNYKNLTSQIKSVLKH
DRGISEQDLKY
AKKAYYTVYFKNGGKRILQLNSKNYTANLVHAKDVKRIEITVKTGTKAKADRYVPYTIAVNGTSTPILS
KLKISNKQLIS
YKYLNDKVKSVLKSERGISDLDLKFAKQAKYTVYFKNGKKQVVNLKSDIFTPNLFSAKDIKKIDIDVKQ
YTKSKKKINKS
NNVKFPVTINKFENIVSNEFVFYNASKITINDLSIKLKSAMANDQGITKHDIGLAERAVYKVYFKNGSS
KYVDLKTEYKD
ERVFKATDIKKVDIELKF

SEQ ID NO: 69 polypeptide sequence

MNNKKTATNRKGMIPNRLNKFSIRKYSVGTASILVGTTLIFGLSGHEAKAAEHTNGELNQ
SKNETTAPSENKTTKKVDSRQLKDNTQTATADQPKVTMSDSATVKETSSNMQSPQNATAN
QSTTKTSNVTTNDKSSTTYSNETDKSNLTQAKDVSTTPKTTTIKPRTLNRMAVNTVAAPQ
QGTNVNDKVHFSNIDIAIDKGHVNQTTGKTEFWATSSDVLKLKANYTIDDSVKEGDTFTF
KYGQYFRPGSVRLPSQTQNLYNAQGNIIAKGIYDSTTNTTTYTFTNYVDQYTNVRGSFEQ
VAFAKRKNATTDKTAYKMEVTLGNDTYSEEIIVDYGNKKAQPLISSTNYINNEDLSRNMT
AYVNQPKNTYTKQTFVTNLTGYKFNPNAKNFKIYEVTDQNQFVDSFTPDTSKLKDVTDQF

DVIYSNDNKTATVDLMKGQTSSNKQYIIQQVAYPDNSSTDNGKIDYTLDTDKTKYSWSNS
YSNVNGSSTANGDQKKYNLGDYVWEDTNKDGKQDANEKGIKGVYVILKDSNGKELDRTTT
DENGKYQFTGLSNGTYSVEFSTPAGYTPTTANVGTDDAVDSDGLTTTGVIKDADNMTLDS
GFYKTPKYSLGDYVWYDSNKDGKQDSTEKGIKGVKVTLQNEKGEVIGTTETDENGKYRFD
NLDSGKYKVIFEKPAGLTQTGTNTTEDDKDADGGEVDVTITDHDDFTLDNGYYEEETSDS
DSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDS
DSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDS
DSDSDSDSDSDSDSDSDNDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDS
DSDSDSDSDSDSDSDSDSDSDSDNDSDSDSDSDSDAGKHTPAKPMSTVKDQHKTAKALPE
TGSENNNSNNGTLFGGLFAALGSLLLFGRRKKQNK

SEQ ID NO: 70 polypeptide sequence

EENSVQDVKDSNTDDELSDSNDQSSDEEKNDVINNNQSINTDDNNQIIKKEETNNYDGIE
KRSEDRTESTTNVDENEATFLQKTPQDNTHLTEEEVKESSSVESSNSSIDTAQQPSHTTI
NREESVQTSDNVEDSHVSDFANSKIKESNTESGKEENTIEQPNKVKEDSTTSQPSGYTNI
DEKISNQDELLNLPINEYENKARPLSTTSAQPSIKRVTVNQLAAEQGSNVNHLIKVTDQS
ITEGYDDSEGVIKAHDAENLIYDVTFEVDDKVKSGDTMTVDIDKNTVPSDLTDSFTIPKI
KDNSGEIIATGTYDNKNKQITYTFTDYVDKYENIKAHLKLTSYIDKSKVPNNNTKLDVEY
KTALSSVNKTITVEYQRPNENRTANLQSMFTNIDTKNHTVEQTIYINPLRYSAKETNVNI
SGNGDEGSTIIDDSTIIKVYKVGDNQNLPDSNRIYDYSEYEDVTNDDYAQLGNNNDVNIN
FGNIDSPYIIKVISKYDPNKDDYTTIQQTVTMQTTINEYTGEFRTASYDNTIAFSTSSGQ
GQGDLPPEKTYKIGDYVWEDVDKDGIQNTNDNEKPLSNVLVTLTYPDGTSKSVRTDEDGK
YQFDGLKNGLTYKITFETPEGYTPTLKHSGTNPALDSEGNSVWVTINGQDDMTIDSGFYQ
TPKYSLGNYVWYDTNKDGIQGDDEKGISGVKVTLKDENGNIISTTTTDENGKYQFDNLNS
GNYIVHFDKPSGMTQTTTDSGDDDEQDADGEEVHVTITDHDDFSIDNGYYDDE

Figure 2

SEQ ID NO:34 polynucleotide sequence

ATGTTACAAGTAACTGATGTGAGTTTACGTTTTGGAGATCGTAAACTATTTGAAGATGTAAATATTAAATTTACAGAAGG
TAATTGTTATGGATTAATTGGTGCGAATGGTGCAGGTAAATCAACATTCTTAAAAATATTATCTGGTGAATTAGATTCTC
AAACAGGACATGTTTCATTAGGTAAAAATGAACGTCTAGCTGTTTTAAAACAGGACCACTATGCTTATGAAGATGAACGC
GTGCTTGATGTTGTAATTAAAGGTCACGAACGTCTTTATGAGGTTATGAAAGAAAAAGATGAAATCTATATGAAGCCAGA
TTTCAGTGATGAAGATGGTATCCGTGCTGCTGAACTTGAAGGTGAATTTGCAGAAATGAATGGTTGGAATGCTGAAGCTG
ATGCTGCTAACCTTTTATCTGGTTTAGGTATCGATCCAACTTTACACGATAAAAAAATGGCTGAATTAGAAAACAACCAA
AAAATTAAAGTATTATTAGCGCAAAGTTTATTCGGTGAACCAGACGTACTATTACTGGATGAGCCTACTAACGGTCTCGA
TATTCCAGCAATCAGTTGGTTAGAAGATTTCTTAATTAACTTTGATAATACTGTTATCGTAGTATCGCATGACCGTCATT
TCTTAAATAATGTATGTACTCATATCGCTGATTTAGACTTCGGTAAAATTAAAGTTTATGTTGGTAACTATGATTTTTGG
TATCAATCTAGTCAGTTAGCTCAAAAGATGGCTCAAGAACAAAACAAGAAAAAAGAAGAAAAAATGAAAGAGTTACAGGA
CTTTATTGCACGTTTCTCAGCTAACGCTTCTAAATCTAAACAAGCAACAAGTCGTAAAAAACAACTTGAGAAAATTGAAT
TAGATGATATTCAACCATCATCAAGAAGATATCCTTTCGTTAAATTCACGCCTGAGCGTGAGATTGGTAACGACTTATTA
ATCGTTCAAAATCTTTCTAAAACAATTGACGGCGAAAAAGTATTAGATAATGTATCATTCACAATGAATCCAAATGATAA
AGCGATTTTAATTGGAGATAGTGAAATTGCAAAAACAACATTACTTAAAATATTAGCTGGCGAAATGGAACCAGACGAAG
GTTCATTTAAATGGGGTGTTACTACATCATTAAGTTACTTCCCTAAAGATAACTCAGAGTTCTTTGAGGGTGTAAATATG
AATCTCGTTGATTGGTTAAGACAATATGCTCCTGAAGATGAACAAACAGAAACATTTTTACGTGGTTTCTTAGGTCGTAT
GTTATTTAGTGGTGAAGAAGTTAAGAAAAAAGCTAGTGTGCTTTCAGGTGGAGAAAAAGTACGTTGTATGCTAAGTAAAA
TGATGTTATCAAGTGCGAATGTACTTTTACTTGACGAACCTACTAACCACTTAGACTTAGAAAGTATTACTGCTGTCAAT
GATGGTCTTAAATCATTTAAAGGTTCTATCATCTTTACTTCTTATGACTTCGAATTTATCAACACGATTGCAAACCGTGT
TATCGATTTAAATAAACAAGGCGGCGTTTCAAAAGAAATTCCATATGAAGAATACTTGCAAGAAATCGGCGTTTTAAAAT
AA

SEQ ID NO:35 polynucleotide sequence

ATGTTACAAGTAACTGATGTAAGTTTACGTTTTGGTGATCGTAAACTATTTGAAGATGTAAATATAAAATTTACAGAGGG
TAATTGTTATGGATTAATTGGTGCAAATGGTGCTGGGAAATCTACATTCTTGAAGATTTTATCAGGCGAAATTGATTCAC
AGACTGGTCATGTATCTCTAGGTAAAGATGAGCGTTTGGCTGTGTTAAAACAAGATCATTTTGCTTATGAAGATGAACGT
GTTTTAGATGTTGTGATTAAAGGACATGAACGTTTGTATCAAGTGATGAAAGAGAAAGATGAAATTTATATGAAACCTGA
TTTCAGCGATGAGGACGGTATTCGCGCTGCAGAACTTGAAGGAGAATTTGCAGAAATGAACGGTTGGAATGCTGAAGCTG
ATGCTGCTAACTTATTATCAGGATTAGGCATAGAACCTGACTTACATGATAAAAATATGTCTGAACTTGAAAATAATCAA
AAAGTTAAGGTATTGTTAGCTCAAAGTTTATTTGGTGATCCTGACGTTCTTTTACTAGATGAGCCTACCAATGGTTTAGA
TATACCAGCAATAAGTTGGTTAGAAGACTTTTTAATTAATTTTGAAAATACTGTCATTGTCGTTTCGCATGACCGTCACT
TCTTAAATAATGTTTGTACTCATATTGCTGATTTAGACTTTGGCAAAATTAAACTTTATGTTGGTAACTATGATTTTTGG
TATCAATCAAGTCAATTAGCACAAAAAATGGCACAAGAACAAAATAAGAAAAAAGAAGAAAAAATGAAAGAGTTACAGGA
TTTCATCGCACGCTTCTCAGCAAATGCTTCTAAATCTAAACAGGCAACAAGTCGTAAGAAACAATTAGAAAAAATTGAAT
TAGATGATATCCAGCCATCATCTCGTAGATACCCTTACGTGAAATTTACTCCTGAACGTGAAATTGGAAATGATTTACTT
ACAGTAGAAAATCTTTCTAAAACAATTGACGGCGAAAAAGTACTAGACAATGTTTCATTCACTATGAATCCTAATGATAA
AGCTATTTTAGTTGGTGATAGCGAAATTGCTAAAACAACATTGTTAAAAATTTTAGCTGGAGAAATGGAACCAGATGAAG
GTACATTTAAATGGGGTGTAACGACATCTTTAAGTTACTTCCCTAAAGATAACTCTGAGTTCTTTGATGGTGTCGATATG
AATTTAGTTGAATGGTTACGTCAATACGCTCCAGAAGATGAACAAACTGAAACATTTTTACGTGGTTTCTTAGGTCGCAT
GTTATTTAGTGGTGAGGAAGTTAAGAAAAAAGCAAGCGTGCTTTCAGGTGGAGAAAAAGTACGTTGCATGTTAAGTAAAA
TGATGTTATCAAGTGCTAACGTACTTTTACTTGATGAGCCAACAAACCATTTAGATTTGGAAAGTATCACTGCTGTAAAT
GACGGATTAAAATCATTTAAAGGTTCTATCATCTTCACTTCTTATGATTTTGAATTTATTAATACAATCGCAAATCGAGT
GATTGACTTGAATCAAGCTGGTGCCCTTTCTAAAGAAGTACCTTATGAGGAATACTTACAAGAAATTGGTGTATTACAAA
ATAATTAA

SEQ ID NO:36 polynucleotide sequence

ATGCCAATTATTACAGATGTTTACGCTCGCGAAGTCTTAGACTCTCGTGGTAACCCAACTGTTGAAGTAGAAGTATTAAC
TGAAAGTGGCGCATTTGGTCGTGCATTAGTACCATCAGGTGCTTCAACTGGTGAACACGAAGCTGTTGAATTACGTGATG
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GTGAAACAGAAGATACAACAATTGCTGATATTGCTGTTGCTACAAACGCTGGTCAAATTAAAACTGGTTCATTATCACGT
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SEQ ID NO:37 polynucleotide sequence

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SEQ ID NO:38 polynucleotide sequence

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ACGTTGAAGGCGTTAACAGCAACGGTTCTGTTCGTGTTTCAGAAATGAACTATGGACATGGTGCTGGTGTGGTTACGTCT
CGTACAATTTCAGCAAACCAAGCAGGTTCATATAATTTCATTCATTAA

SEQ ID NO:39 polynucleotide sequence

ATGAAGAAAATCGCTACAGCTACTATCGCAACTGCAGGATTCGCTACAATCGCAATTGCATCAGGAAATCAAGCTCATGC
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TGCAAACAACTCAAGGTGCATACGGTCACGTTGCATACGTTGAAAGTGTTAACAGCAATGGTTCAGTAAGAGTTTCAGAA
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CTAA

SEQ ID NO:40 polynucleotide sequence

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ACCACTACACTTGGAAAGGTAACTGGAGTCCAGATCGTGTAAATACTTCATATAACTATAATAATTATAATAACTACAAC
TACTATGGTTACAATAACTATAGCAACTACAATAACTACAGTAATTACAACAATTACAACAACTATCAATCAAACAACAC
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TAGCATACGTTGAAGGTGTAAACAGCAATGGTTCAATCAGAGTTTCAGAAATGAACTACGGTCACGGTGCAGGTGTTGTC
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SEQ ID NO:41 polynucleotide sequence

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ATTGAGTTTGTTAAAAAGCACAAATTAAAACACTTATTAGTAGAAACAAGTGTTGATAAGAAAGCAATGGAAAGTTTATC
TGAAGAAACGAAGAAAGATATCTTTGGTGAAGTGTACACAGATTCAATCGGTAAAGAAGGCACTAAAGGTGACTCTTACT
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SEQ ID NO:42 polynucleotide sequence

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ATAAAATGATGAAATCTAATATTGATACAATACATGGTAGTATGAAATAA

SEQ ID NO:43 polynucleotide sequence

ATGAAAAAGACAATTATGGCATCATCATTAGCAGTGGCATTAGGTGTAACAGGTTACGCAGCAGGTACAGGACATCAAGC
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CCAAGGTTCAGATGTACAATCAGTAAGCTACAATGCACAATCAAGTAACTCAAACGTTGAAGCTGTTTCAGCTCCAACTT
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GCAGCTCAAATCATGGCTCAACGTACTGGTGTTTCAGCTTCTACATGGGCTGCAATCATCGCTCGTGAATCAAATGGTCA
AGTAAATGCTTACAACCCATCAGGTGCTTCAGGTTTATTCCAAACTATGCCAGGTTGGGGTCCGACAAACACTGTTGACC
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SEQ ID NO:44 polynucleotide sequence

ATGAAAAAAACAGTTATCGCTTCTACATTAGCAGTATCTTTAGGAATTGCAGGTTACGGTTTATCAGGACATGAAGCACA
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CAGTTCAAGCTGGTGCTTACGATATTCATTTCGTAGACAATGGATACCAATACAACTTCACTTCAAATGGTTCTGAATGG
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TGGTCAATTACATGCACGTAATGCTTCAGGTGCTGCTGGATTATTCCAAACTATGCCAGGTTGGGGTTCAACTGGTTCAG
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SEQ ID NO:45 polynucleotide sequence

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SEQ ID NO:46 polynucleotide sequence

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SEQ ID NO:47 polynucleotide sequence

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SEQ ID NO:48 polynucleotide sequence

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SEQ ID NO:49 polynucleotide sequence

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SEQ ID NO:50 polynucleotide sequence

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SEQ ID NO:51 polynucleotide sequence

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SEQ ID NO:52 polynucleotide sequence

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SEQ ID NO:53 polynucleotide sequence

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SEQ ID NO:54 polynucleotide sequence

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SEQ ID NO:55 polynucleotide sequence

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SEQ ID NO:56 polynucleotide sequence

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SEQ ID NO:57 polynucleotide sequence

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SEQ ID NO:58 polynucleotide sequence

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SEQ ID NO:59 polynucleotide sequence

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SEQ ID NO:60 polynucleotide sequence

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SEQ ID NO:61 polynucleotide sequence

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SEQ ID NO:62 polynucleotide sequence

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SEQ ID NO:63 polynucleotide sequence

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SEQ ID NO:64 polynucleotide sequence

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SEQ ID NO:65 polynucleotide sequence

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SEQ ID NO:66 polynucleotide sequence

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SEQ ID NO:71 polynucleotide sequence

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SEQ ID NO:72 polynucleotide sequence

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SEQ ID NO:73 polynucleotide sequence

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SEQ ID NO: 74 polynucleotide sequence

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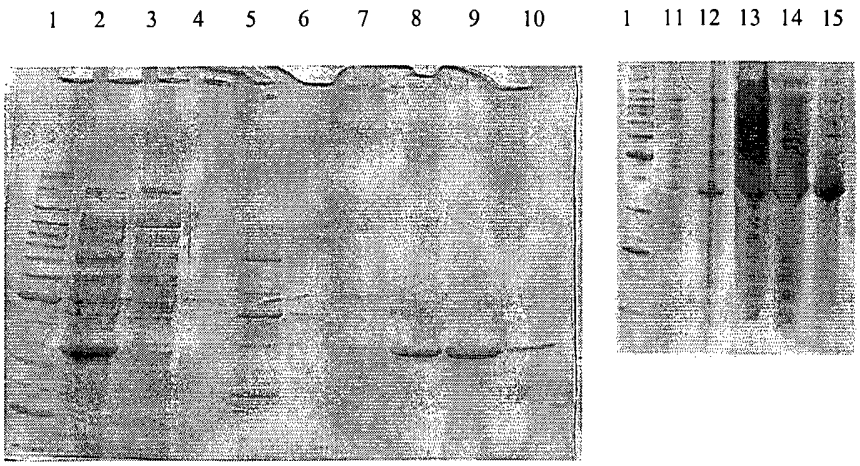
GTAACTTTGACGTATCCTGATGGAACTTCAAAATCAGTCAGAACAGATGAAGATGGGAAA
TATCAATTTGATGGATTGAAAAACGGATTGACTTATAAAATTACATTCGAAACACCTGAA
GGATATACGCCGACGCTTAAACATTCAGGAACAAATCCTGCACTAGACTCAGAAGGTAAT
TCTGTATGGGTAACTATTAATGGACAAGACGATATGACGATTGATAGTGGATTTTATCAA
ACACCTAAATACAGCTTAGGGAACTATGTATGGTATGACACTAATAAAGATGGTATTCAA
GGTGATGATGAAAAAGGAATCTCTGGAGTTAAAGTGACGTTAAAAGATGAAAACGGAAAT
ATCATTAGTACAACTACAACCGATGAAAATGGAAAGTATCAATTTGATAATTTAAATAGT
GGTAATTATATTGTTCATTTTGATAAACCTTCAGGTATGACTCAAACAACAACAGATTCT
GGTGATGATGACGAACAGGATGCTGATGGGGAAGAAGTTCATGTAACAATTACTGATCAT
GATGACTTTAGTATAGATAACGGATACTATGATGACGAA

Figure 3

Purification of alpha toxin

A



B

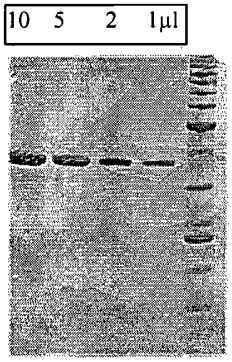
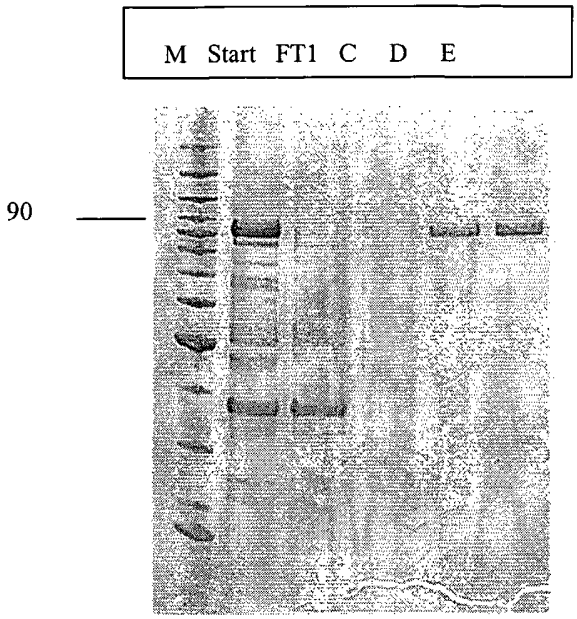


Figure 4

Purification of SdrC

A



B

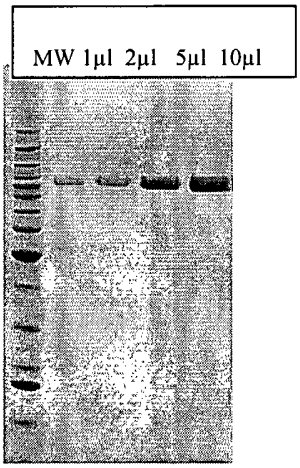
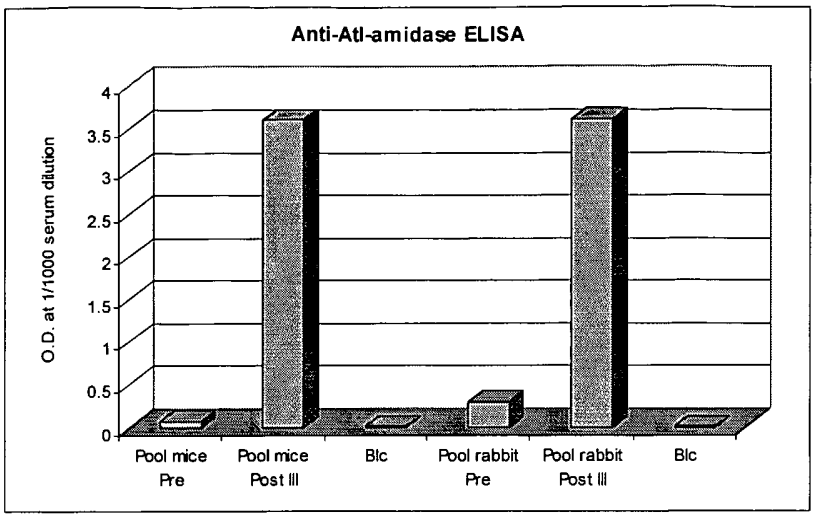
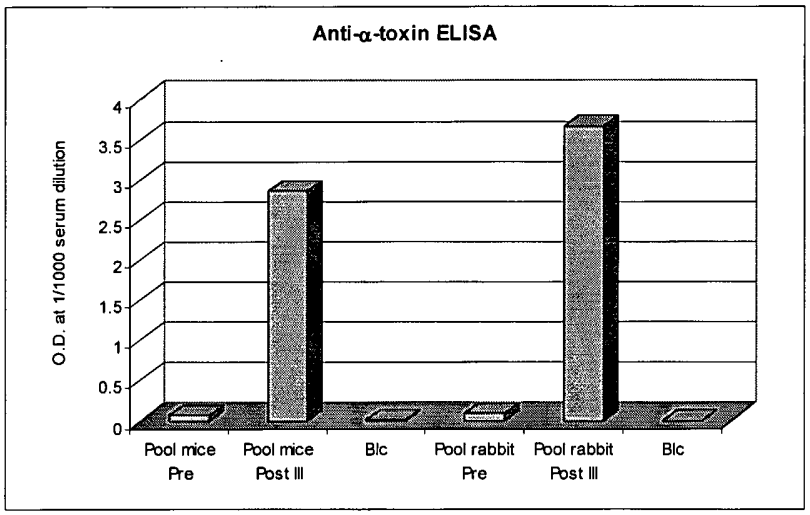


Figure 5


Anti-Atl-amidase ELISA
O.D. at 1/1000 serum dilution
0
0.5
1
1.5
2
2.5
3
3.5
4
Pool mice Pre
Pool mice Post III
Blc
Pool rabbit Pre
Pool rabbit Post III
Blc


Anti-α-toxin ELISA
O.D. at 1/1000 serum dilution
0
0.5
1
1.5
2
2.5
3
3.5
4
Pool mice Pre
Pool mice Post III
Blc
Pool rabbit Pre
Pool rabbit Post III
Blc

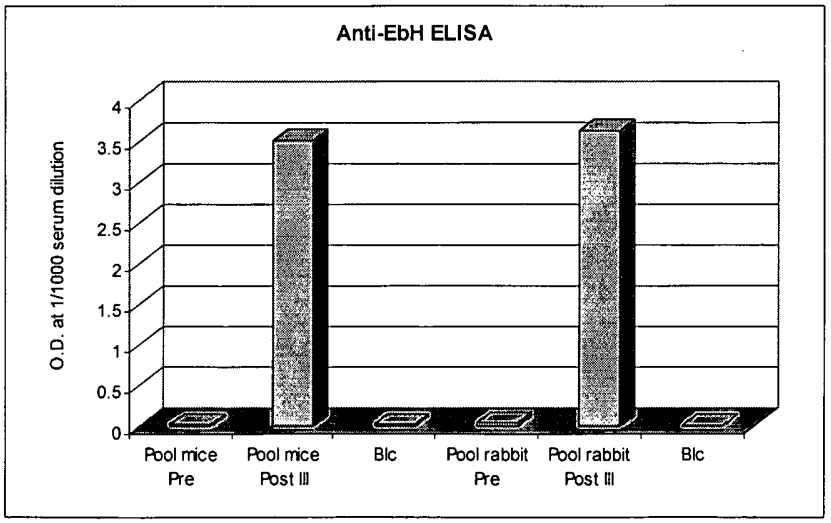
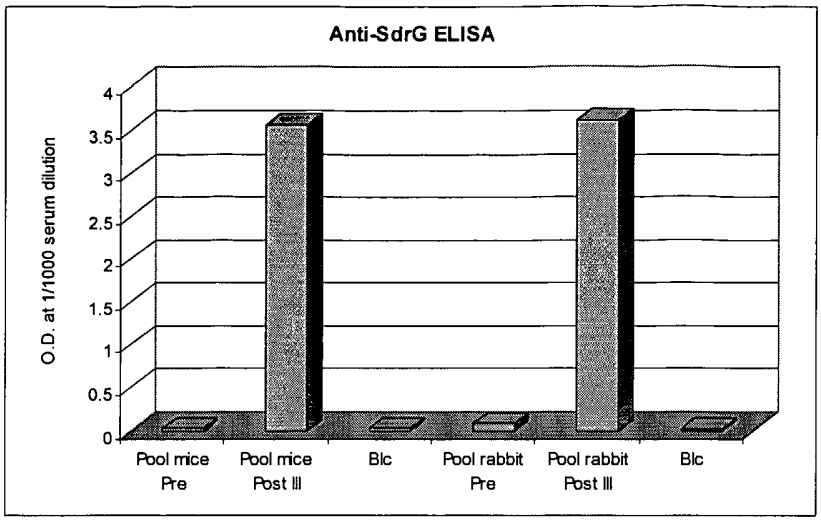
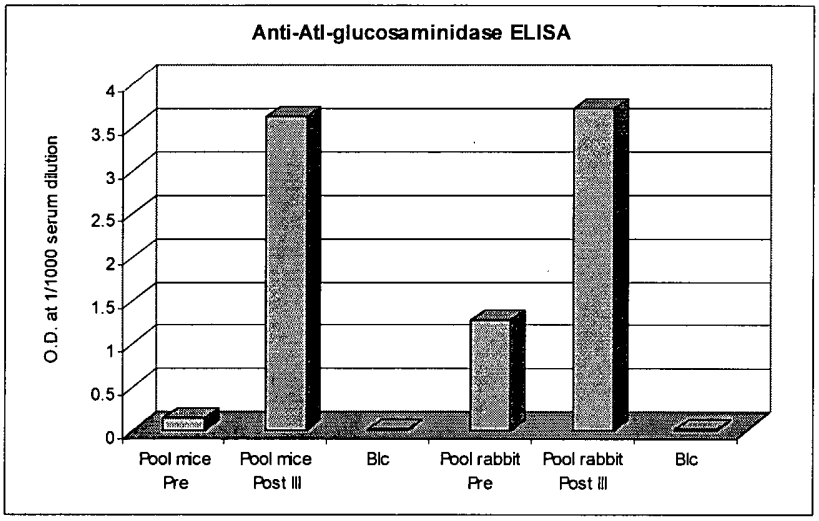

Anti-EbH ELISA
O.D. at 1/1000 serum dilution
0
0.5
1
1.5
2
2.5
3
3.5
4
Pool mice Pre
Pool mice Post III
Blc
Pool rabbit Pre
Pool rabbit Post III
Blc

Figure 5


Anti-SdrG ELISA
O.D. at 1/1000 serum dilution
4
3.5
3
2.5
2
1.5
1
0.5
0
Pool mice Pre
Pool mice Post III
Blc
Pool rabbit Pre
Pool rabbit Post III
Blc


Anti-Atl-glucosaminidase ELISA
O.D. at 1/1000 serum dilution
4
3.5
3
2.5
2
1.5
1
0.5
0
Pool mice Pre
Pool mice Post III
Blc
Pool rabbit Pre
Pool rabbit Post III
Blc

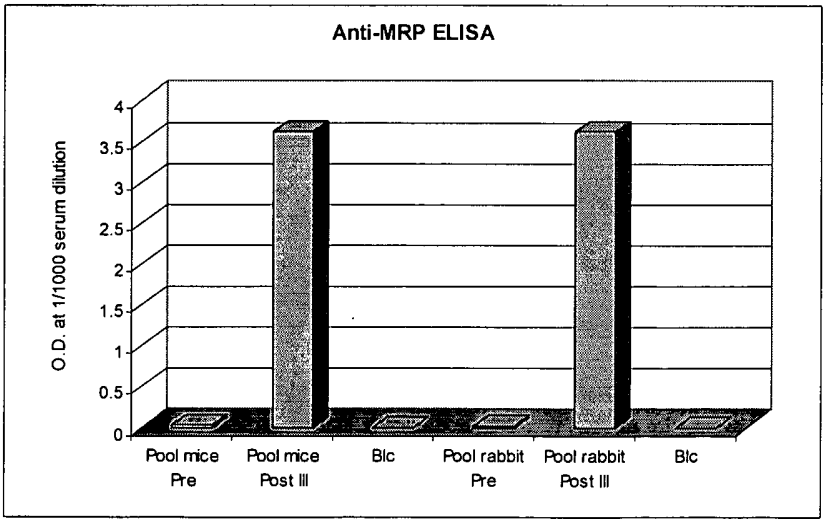
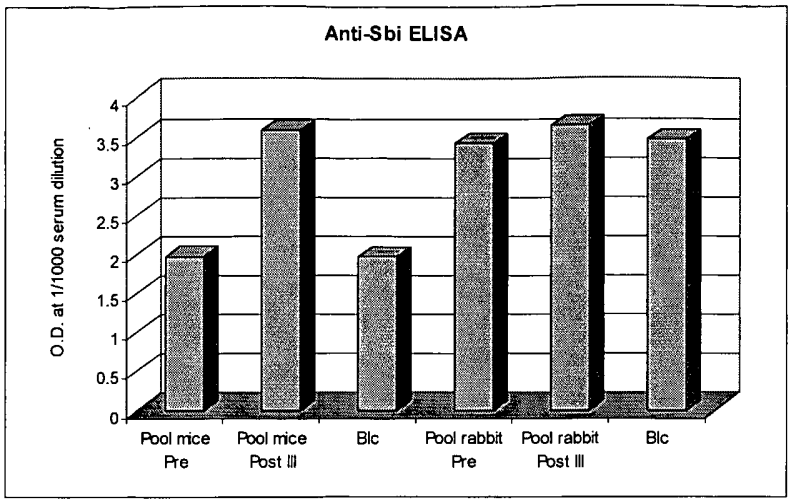
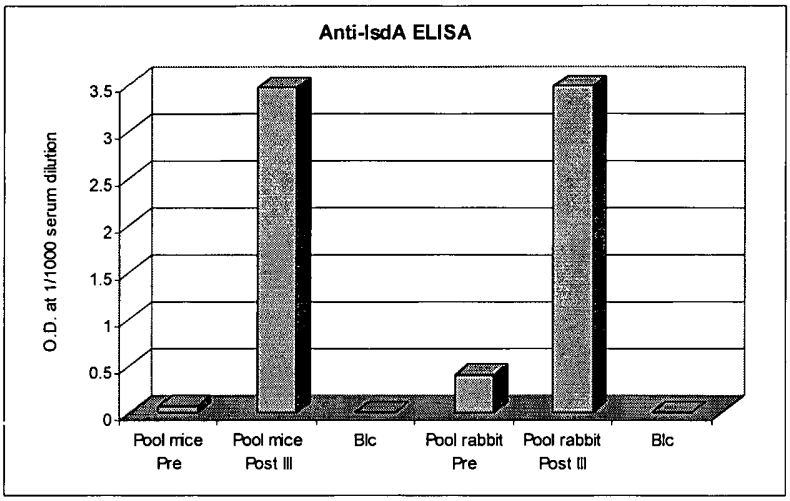

Anti-MRP ELISA
O.D. at 1/1000 serum dilution
4
3.5
3
2.5
2
1.5
1
0.5
0
Pool mice Pre
Pool mice Post III
Blc
Pool rabbit Pre
Pool rabbit Post III
Blc

Figure 5


Anti-Sbi ELISA
O.D. at 1/1000 serum dilution
0
0.5
1
1.5
2
2.5
3
3.5
4
Pool mice Pre
Pool mice Post III
Blc
Pool rabbit Pre
Pool rabbit Post III
Blc


Anti-IsdA ELISA
O.D. at 1/1000 serum dilution
0
0.5
1
1.5
2
2.5
3
3.5
Pool mice Pre
Pool mice Post III
Blc
Pool rabbit Pre
Pool rabbit Post III
Blc

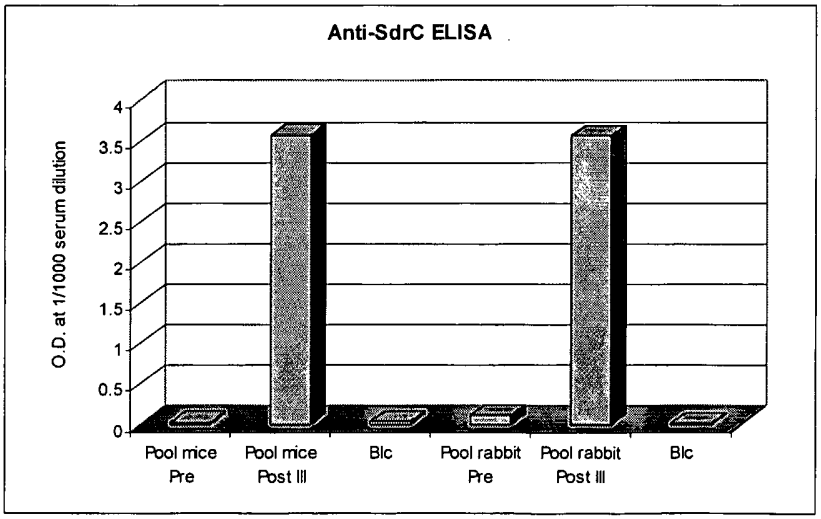
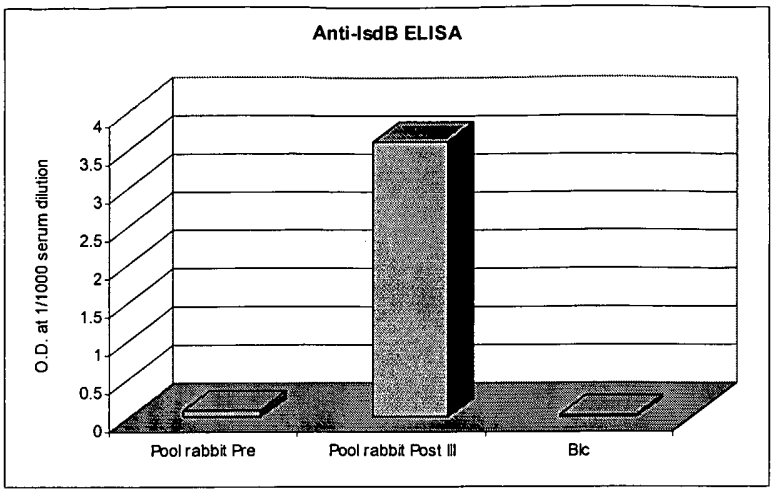
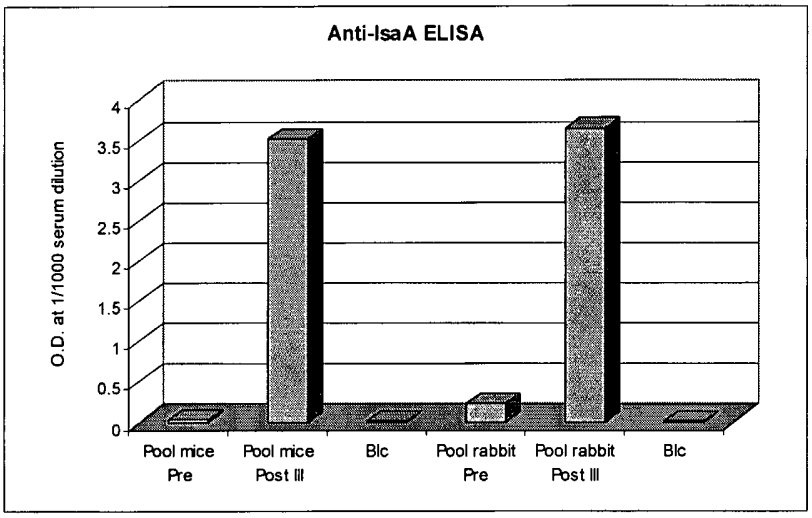

Anti-SdrC ELISA
O.D. at 1/1000 serum dilution
0
0.5
1
1.5
2
2.5
3
3.5
4
Pool mice Pre
Pool mice Post III
Blc
Pool rabbit Pre
Pool rabbit Post III
Blc

Figure 5


Anti-IsdB ELISA
O.D. at 1/1000 serum dilution
0
0.5
1
1.5
2
2.5
3
3.5
4
Pool rabbit Pre
Pool rabbit Post III
Blc


Anti-IsaA ELISA
O.D. at 1/1000 serum dilution
0
0.5
1
1.5
2
2.5
3
3.5
4
Pool mice Pre
Pool mice Post III
Blc
Pool rabbit Pre
Pool rabbit Post III
Blc

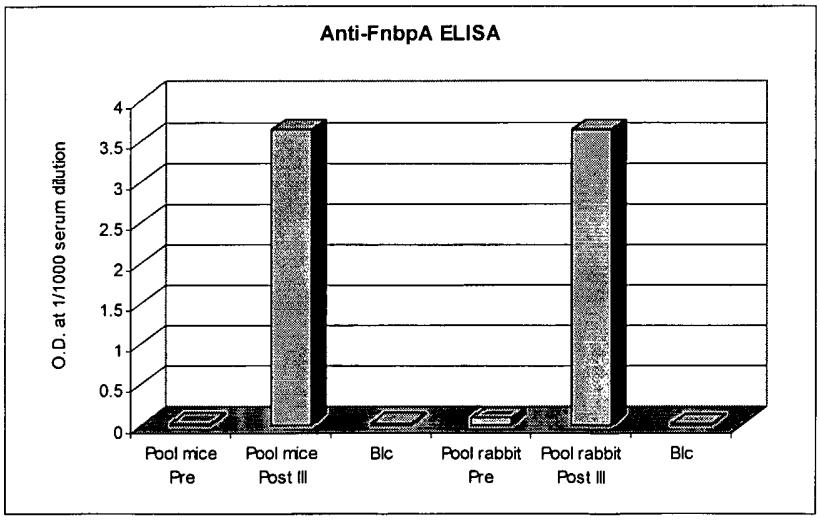
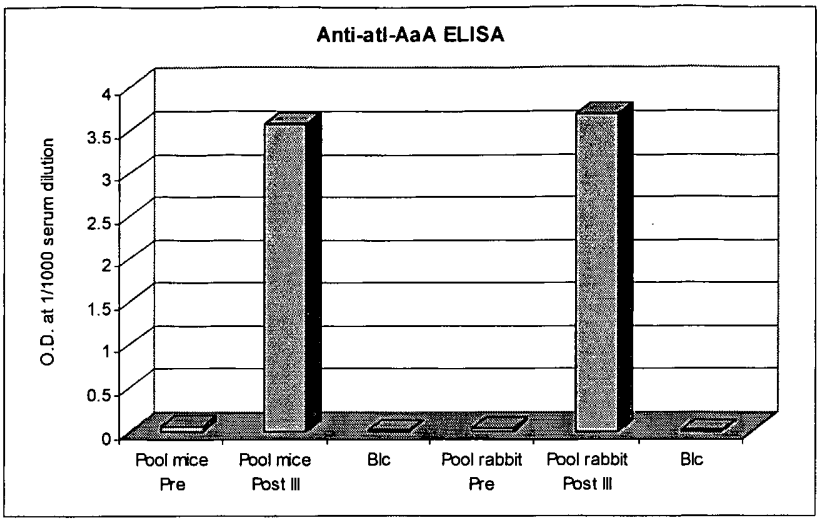
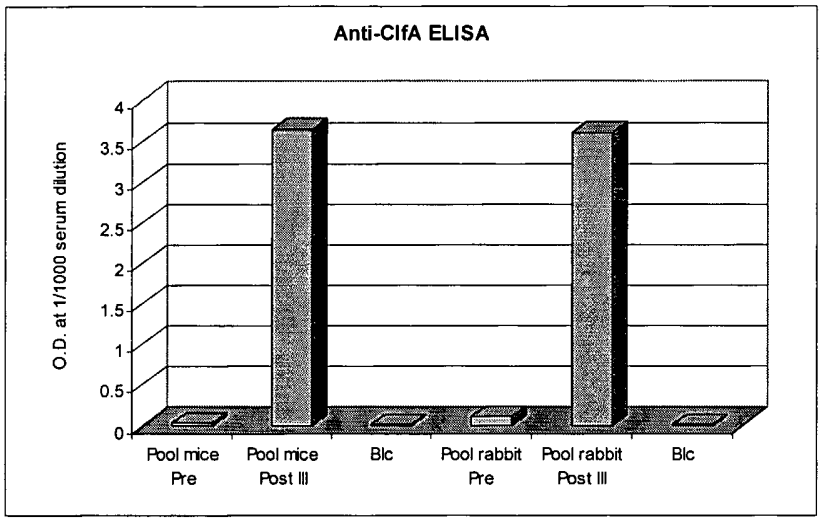

Anti-FnbpA ELISA
O.D. at 1/1000 serum dilution
0
0.5
1
1.5
2
2.5
3
3.5
4
Pool mice Pre
Pool mice Post III
Blc
Pool rabbit Pre
Pool rabbit Post III
Blc

Figure 5


Anti-atl-AaA ELISA
O.D. at 1/1000 serum dilution
0
0.5
1
1.5
2
2.5
3
3.5
4
Pool mice Pre
Pool mice Post III
Blc
Pool rabbit Pre
Pool rabbit Post III
Blc


Anti-ClfA ELISA
O.D. at 1/1000 serum dilution
0
0.5
1
1.5
2
2.5
3
3.5
4
Pool mice Pre
Pool mice Post III
Blc
Pool rabbit Pre
Pool rabbit Post III
Blc

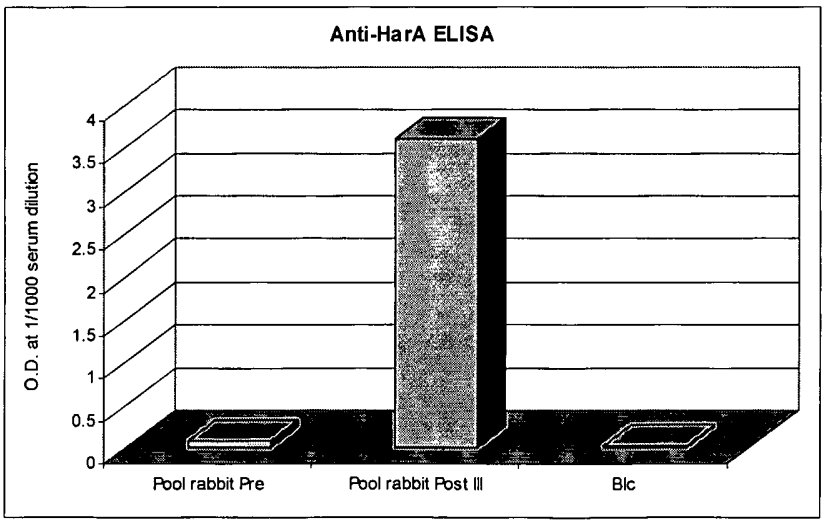
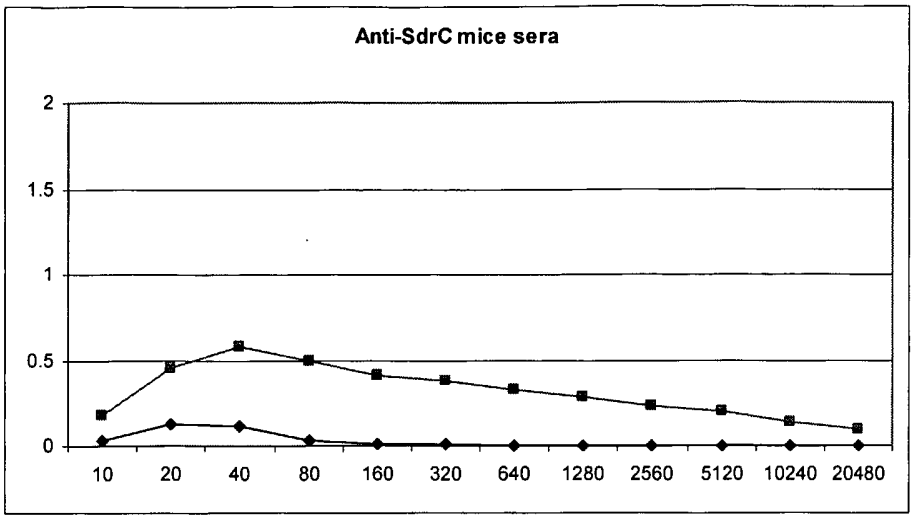
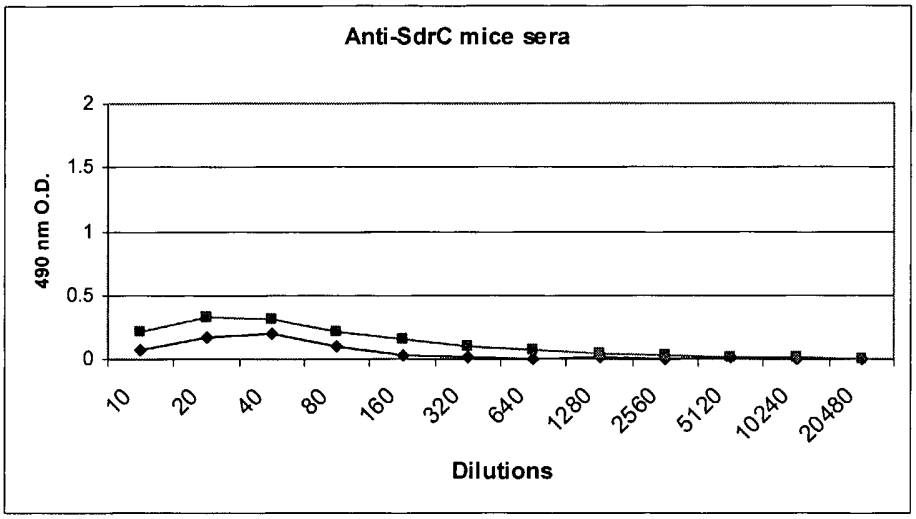

Anti-HarA ELISA
O.D. at 1/1000 serum dilution
0
0.5
1
1.5
2
2.5
3
3.5
4
Pool rabbit Pre
Pool rabbit Post III
Blc

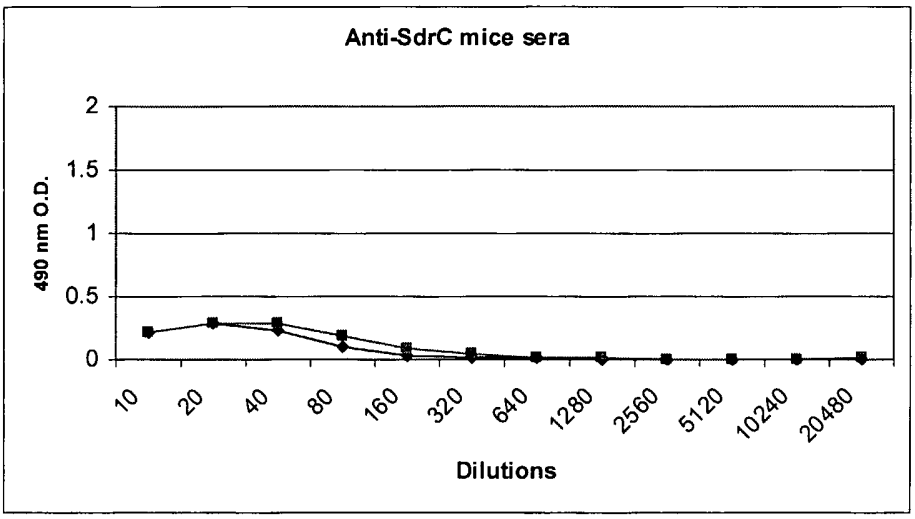
Figure 6


Anti-SdrC mice sera
2
1.5
1
0.5
0
10 20 40 80 160 320 640 1280 2560 5120 10240 20480

A

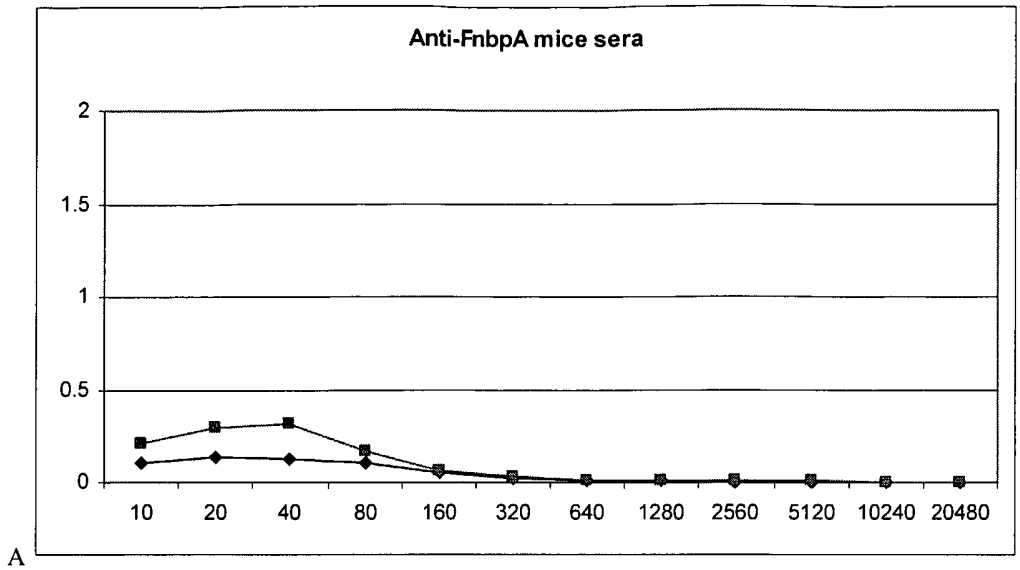

Anti-SdrC mice sera
490 nm O.D.
2
1.5
1
0.5
0
10 20 40 80 160 320 640 1280 2560 5120 10240 20480
Dilutions

B

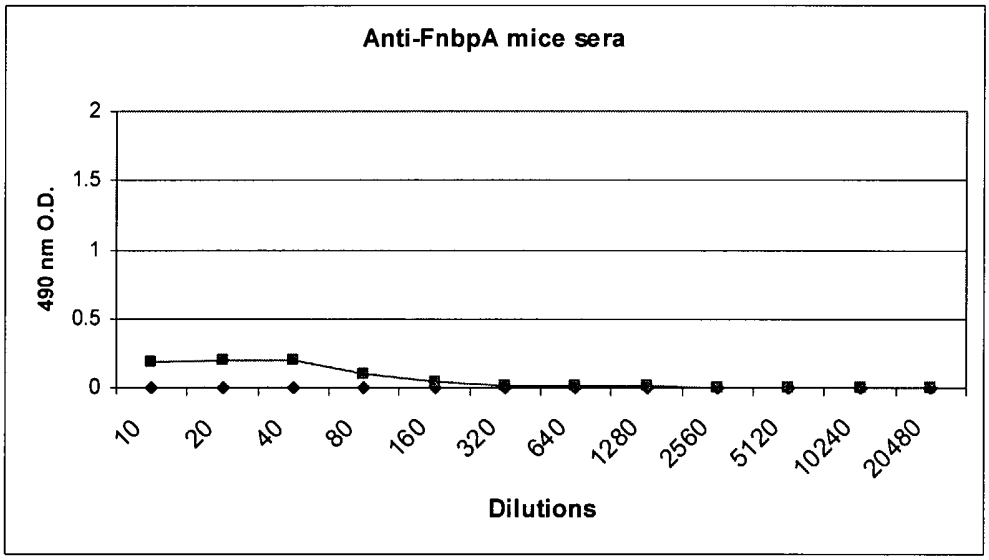

Anti-SdrC mice sera
490 nm O.D.
2
1.5
1
0.5
0
10 20 40 80 160 320 640 1280 2560 5120 10240 20480
Dilutions

C

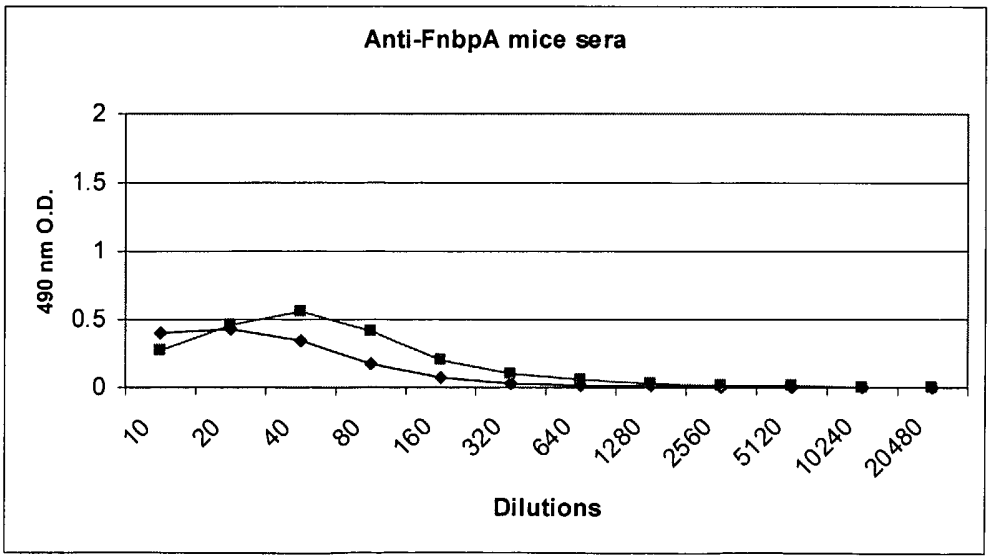
Figure 6


Anti-FnbpA mice sera
2
1.5
1
0.5
0
10
20
40
80
160
320
640
1280
2560
5120
10240
20480

A

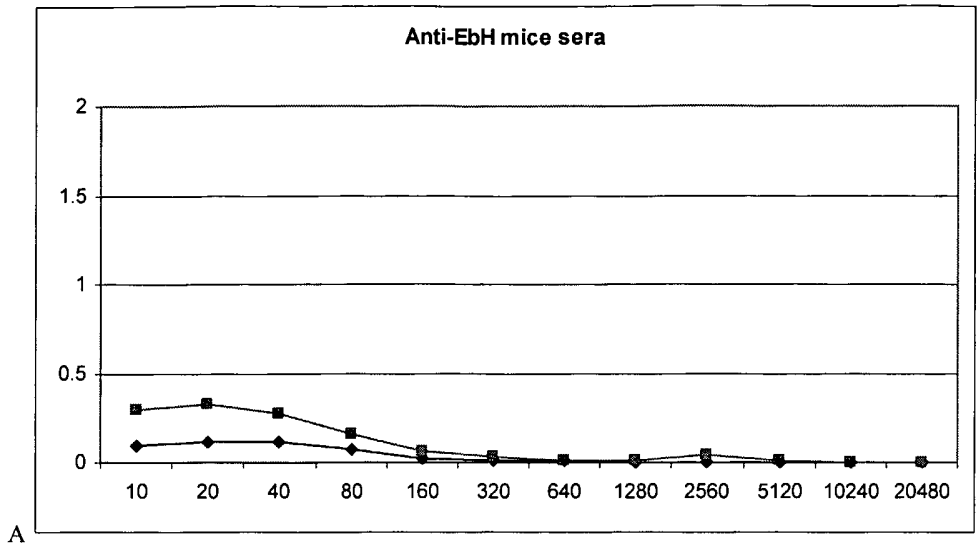

Anti-FnbpA mice sera
490 nm O.D.
2
1.5
1
0.5
0
10
20
40
80
160
320
640
1280
2560
5120
10240
20480
Dilutions

B

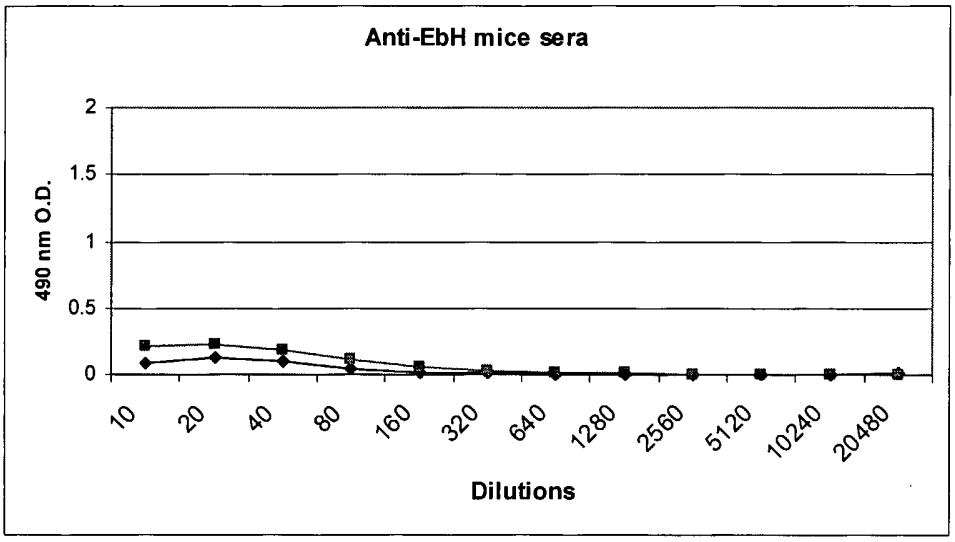

Anti-FnbpA mice sera
490 nm O.D.
2
1.5
1
0.5
0
10
20
40
80
160
320
640
1280
2560
5120
10240
20480
Dilutions

C

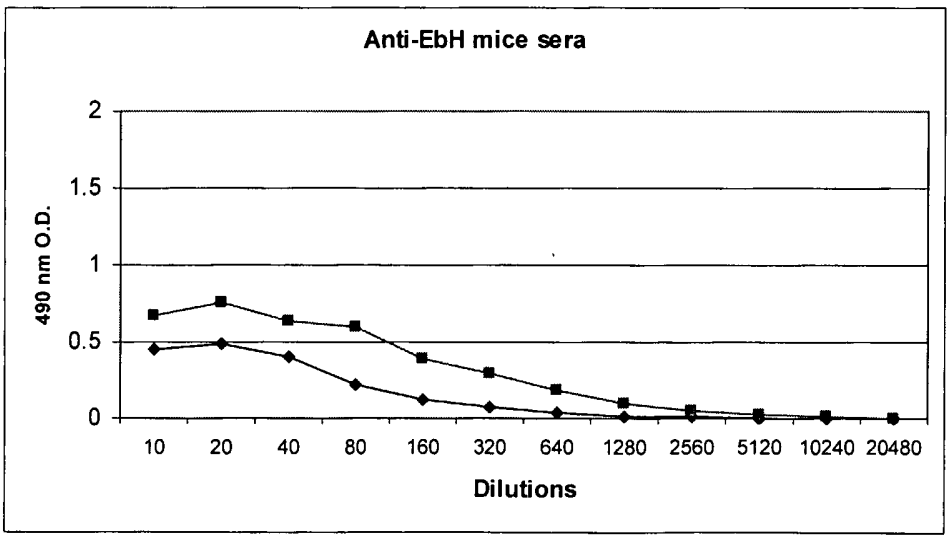
Figure 6


Anti-EbH mice sera
2
1.5
1
0.5
0
10 20 40 80 160 320 640 1280 2560 5120 10240 20480

A

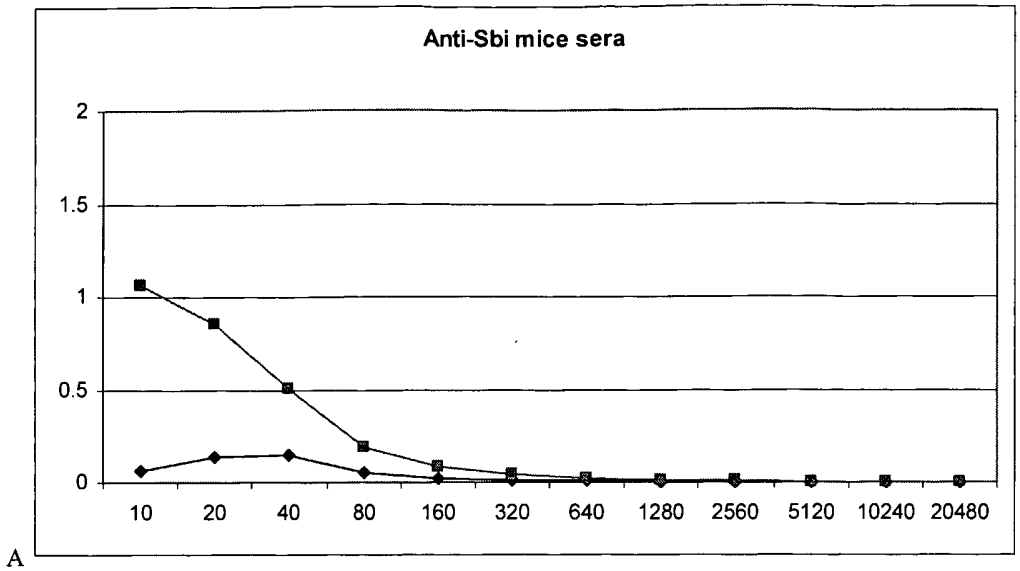

Anti-EbH mice sera
490 nm O.D.
2
1.5
1
0.5
0
10 20 40 80 160 320 640 1280 2560 5120 10240 20480
Dilutions

B

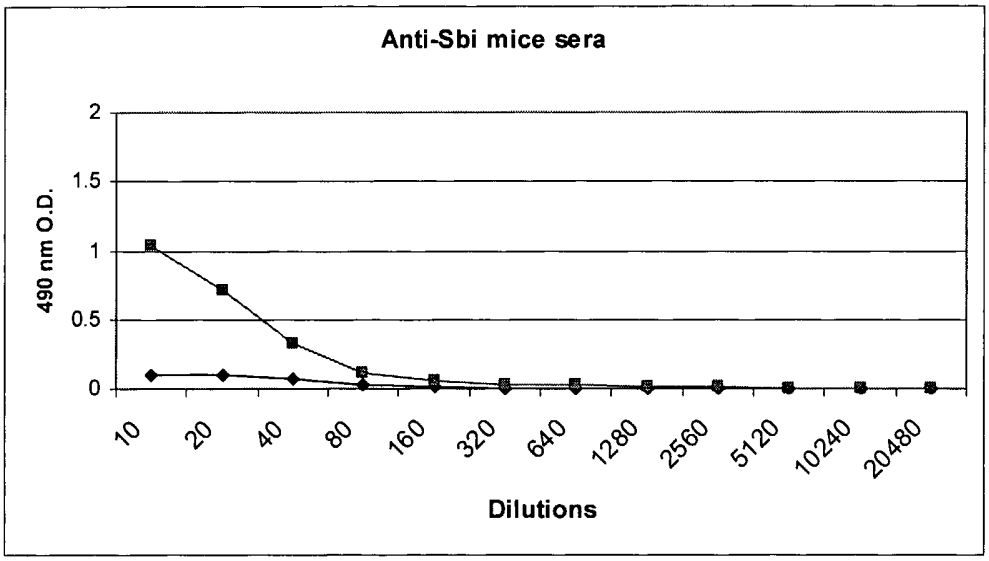

Anti-EbH mice sera
490 nm O.D.
2
1.5
1
0.5
0
10 20 40 80 160 320 640 1280 2560 5120 10240 20480
Dilutions

C

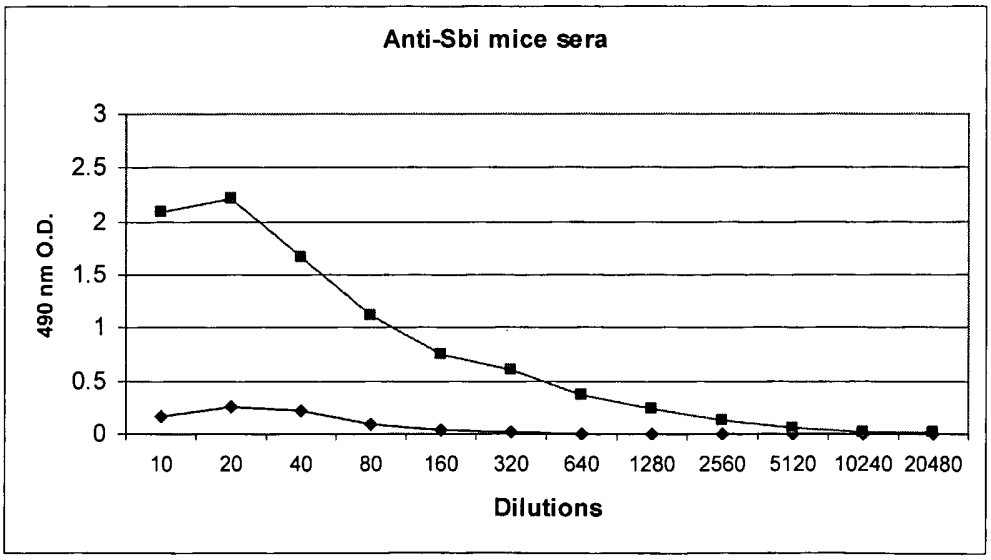
Figure 6


Anti-Sbi mice sera
2
1.5
1
0.5
0
10 20 40 80 160 320 640 1280 2560 5120 10240 20480

A

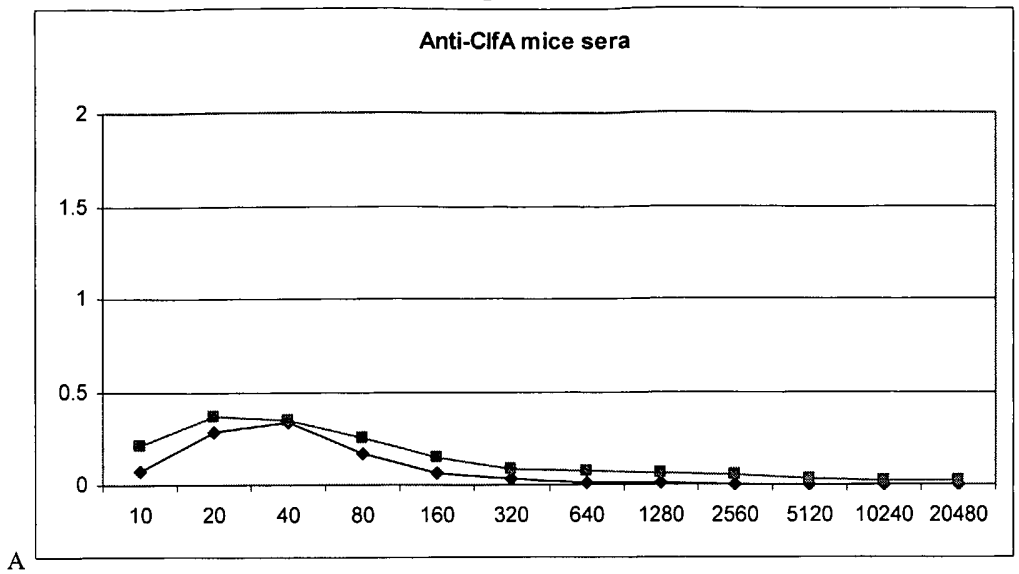

Anti-Sbi mice sera
490 nm O.D.
2
1.5
1
0.5
0
10 20 40 80 160 320 640 1280 2560 5120 10240 20480
Dilutions

B

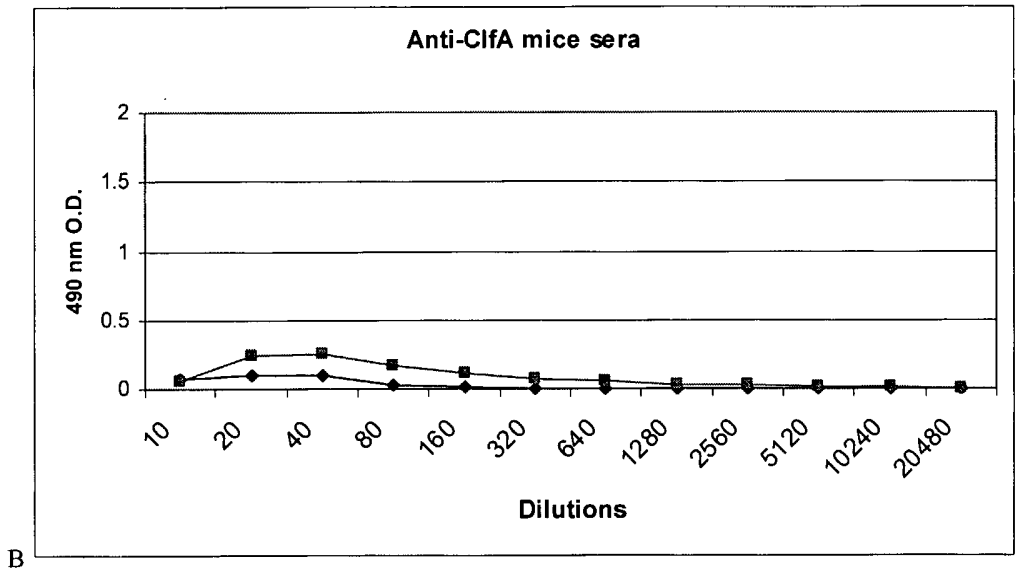

Anti-Sbi mice sera
490 nm O.D.
3
2.5
2
1.5
1
0.5
0
10 20 40 80 160 320 640 1280 2560 5120 10240 20480
Dilutions

C

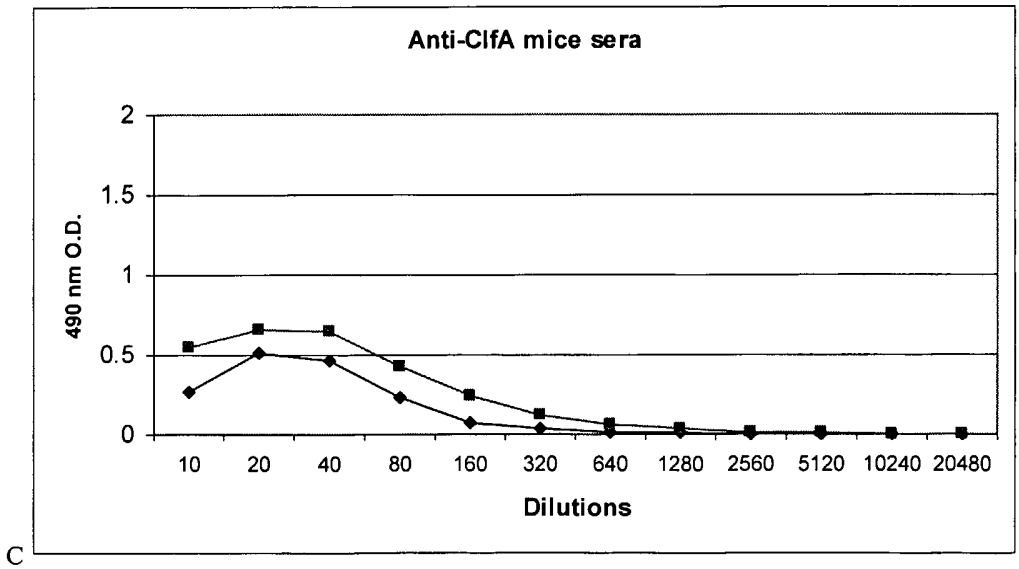
Figure 6


Anti-ClfA mice sera
2
1.5
1
0.5
0
10 20 40 80 160 320 640 1280 2560 5120 10240 20480

A

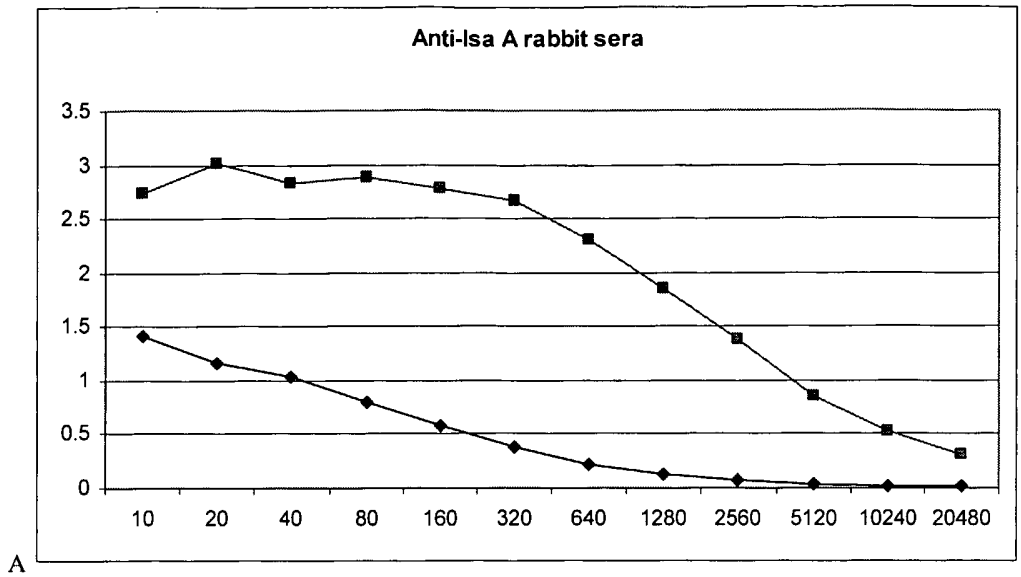

Anti-ClfA mice sera
490 nm O.D.
2
1.5
1
0.5
0
10 20 40 80 160 320 640 1280 2560 5120 10240 20480
Dilutions

B

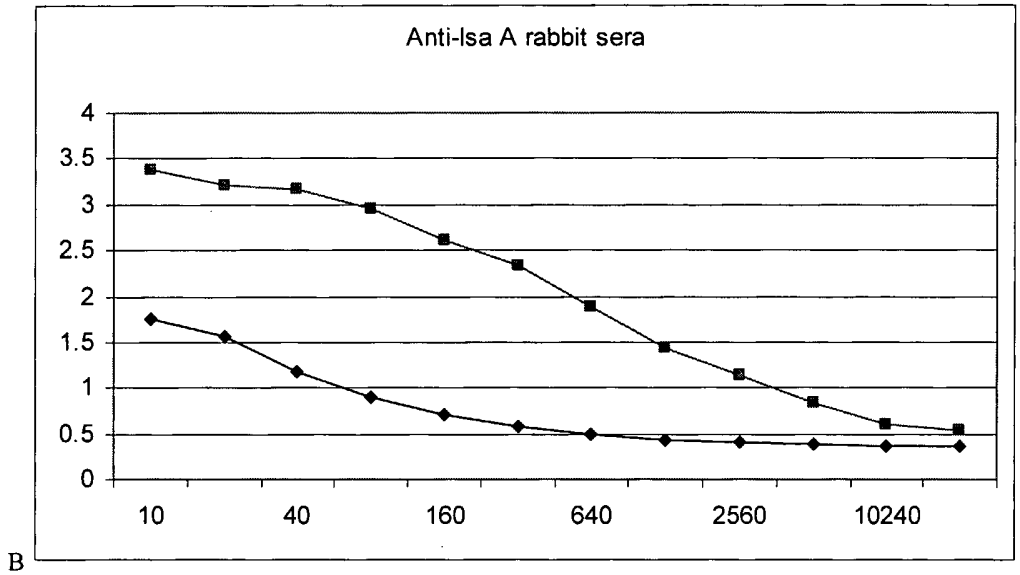

Anti-ClfA mice sera
490 nm O.D.
2
1.5
1
0.5
0
10 20 40 80 160 320 640 1280 2560 5120 10240 20480
Dilutions

C

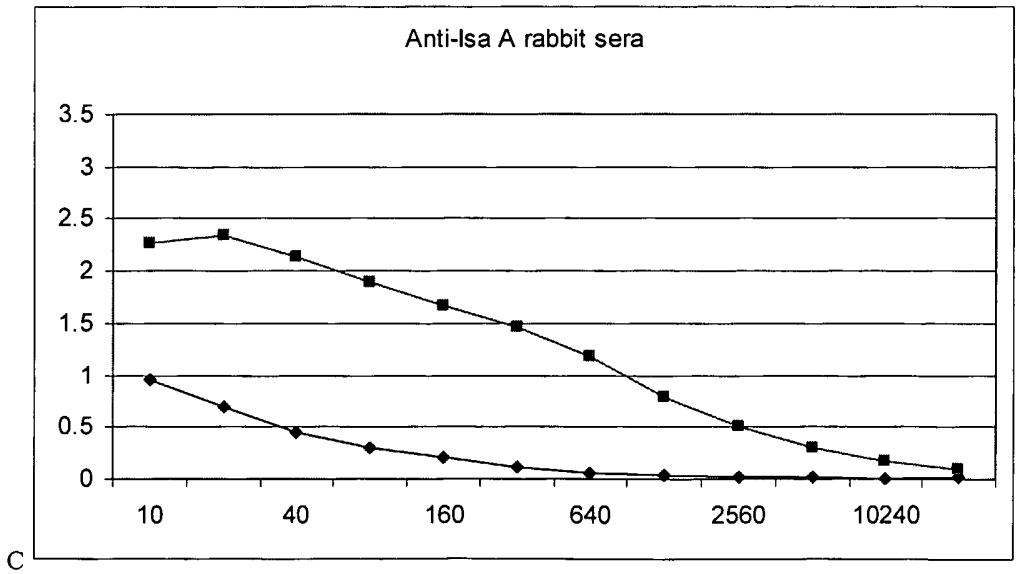
Figure 7


Anti-Isa A rabbit sera
3.5
3
2.5
2
1.5
1
0.5
0
10 20 40 80 160 320 640 1280 2560 5120 10240 20480

A

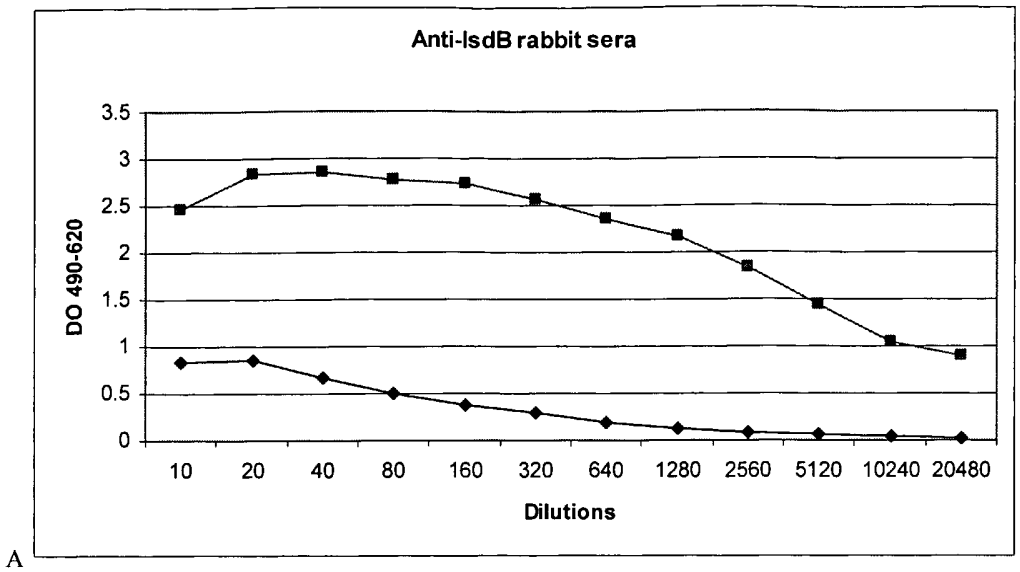

Anti-Isa A rabbit sera
4
3.5
3
2.5
2
1.5
1
0.5
0
10 40 160 640 2560 10240

B

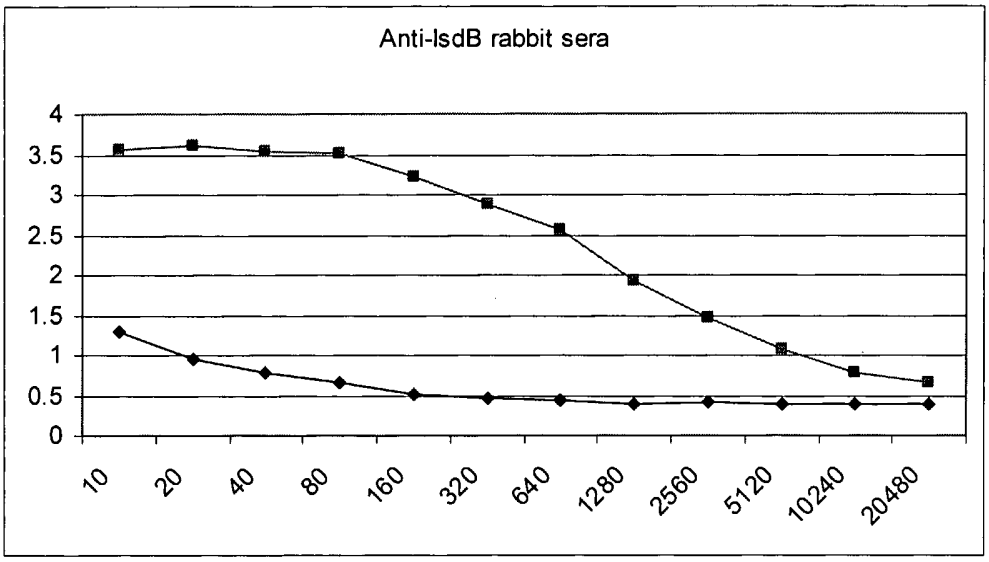

Anti-Isa A rabbit sera
3.5
3
2.5
2
1.5
1
0.5
0
10 40 160 640 2560 10240

C

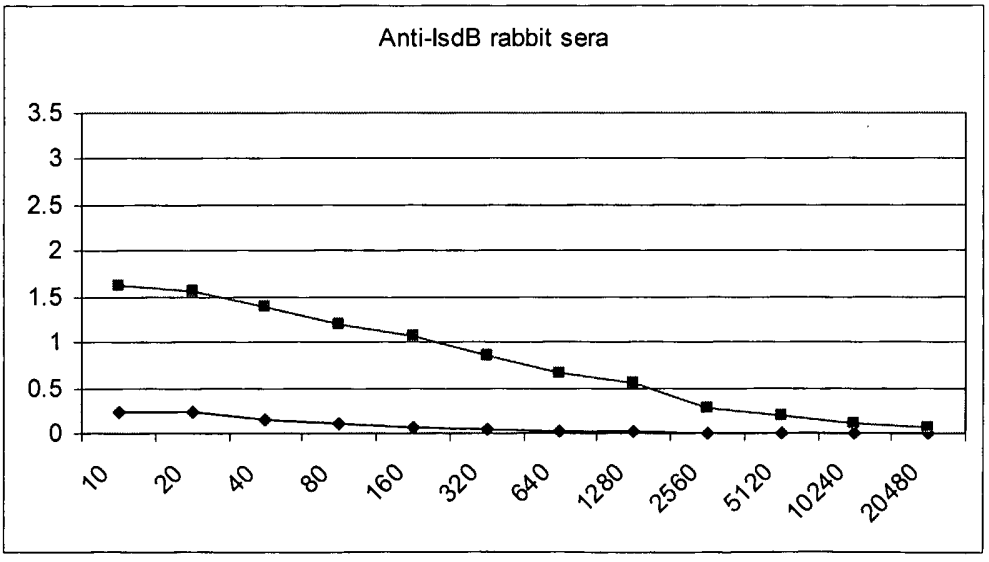
Figure 7


Anti-IsdB rabbit sera
DO 490-620
3.5
3
2.5
2
1.5
1
0.5
0
10 20 40 80 160 320 640 1280 2560 5120 10240 20480
Dilutions

A


Anti-IsdB rabbit sera
4
3.5
3
2.5
2
1.5
1
0.5
0
10 20 40 80 160 320 640 1280 2560 5120 10240 20480

B


Anti-IsdB rabbit sera
3.5
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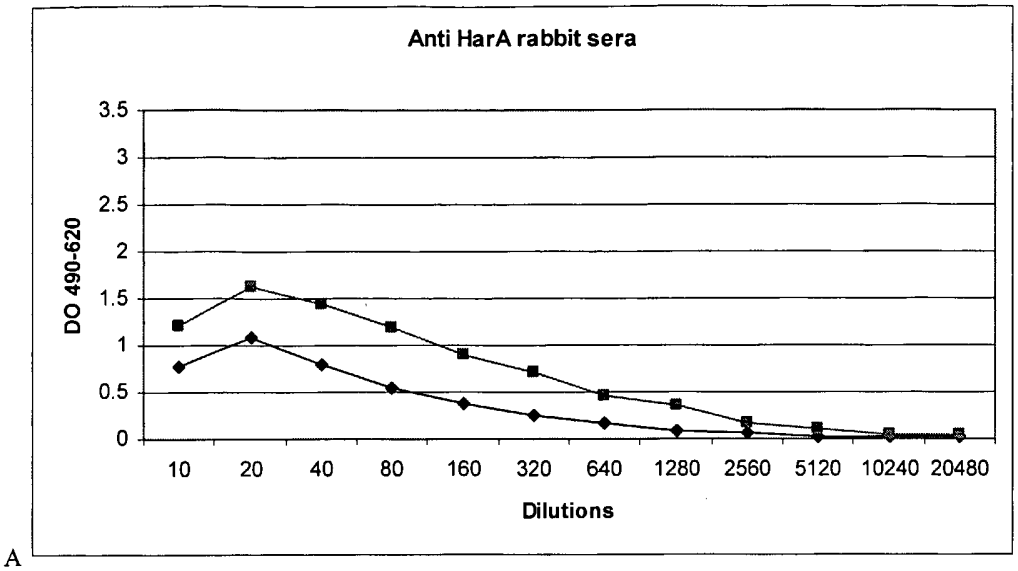
2.5
2
1.5
1
0.5
0
10 20 40 80 160 320 640 1280 2560 5120 10240 20480

C

Figure 7


Anti HarA rabbit sera
DO 490-620
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2.5
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1.5
1
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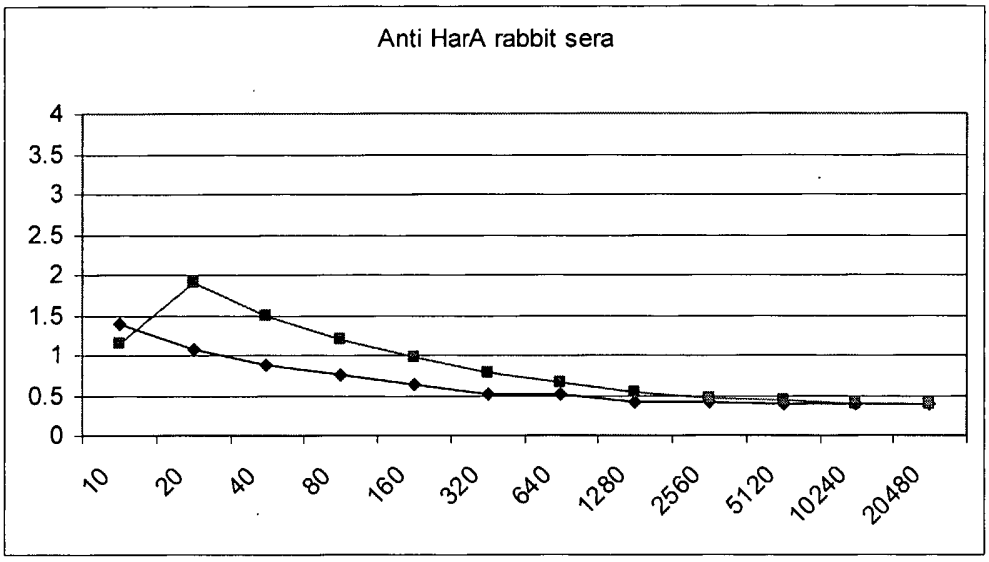
Dilutions

A


Anti HarA rabbit sera
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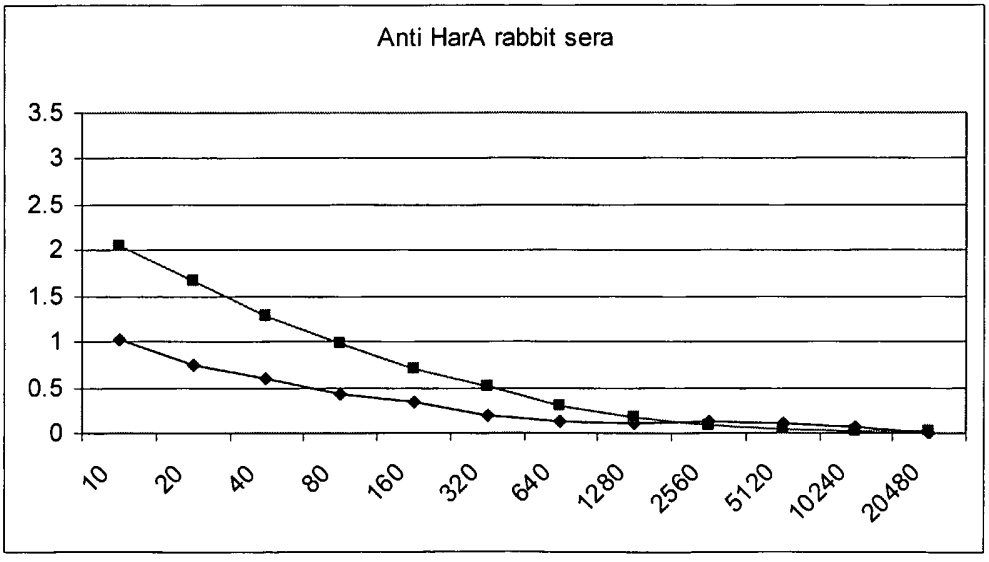
B


Anti HarA rabbit sera
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1
0.5
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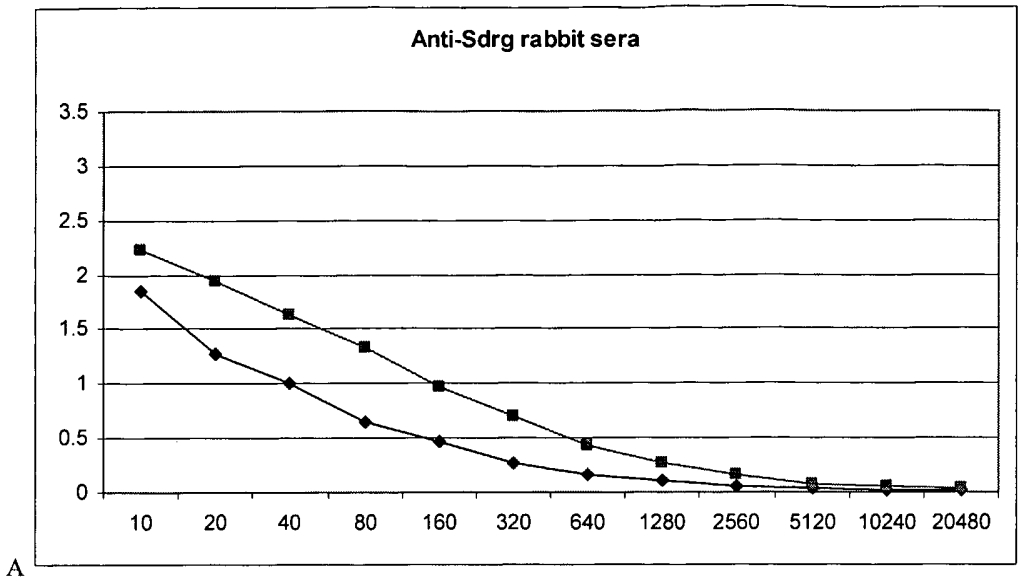
C

Figure 7


Anti-Sdrg rabbit sera
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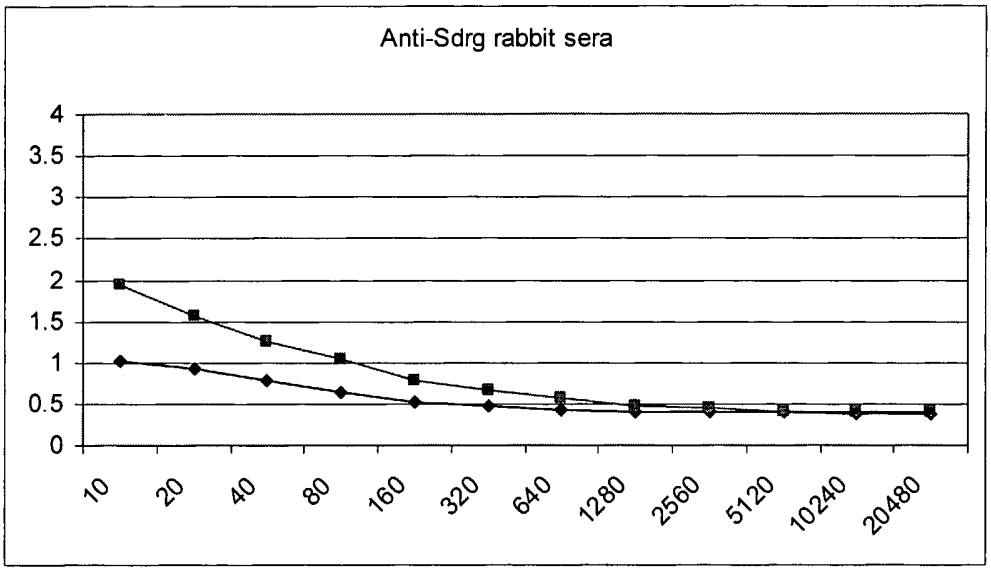
A


Anti-Sdrg rabbit sera
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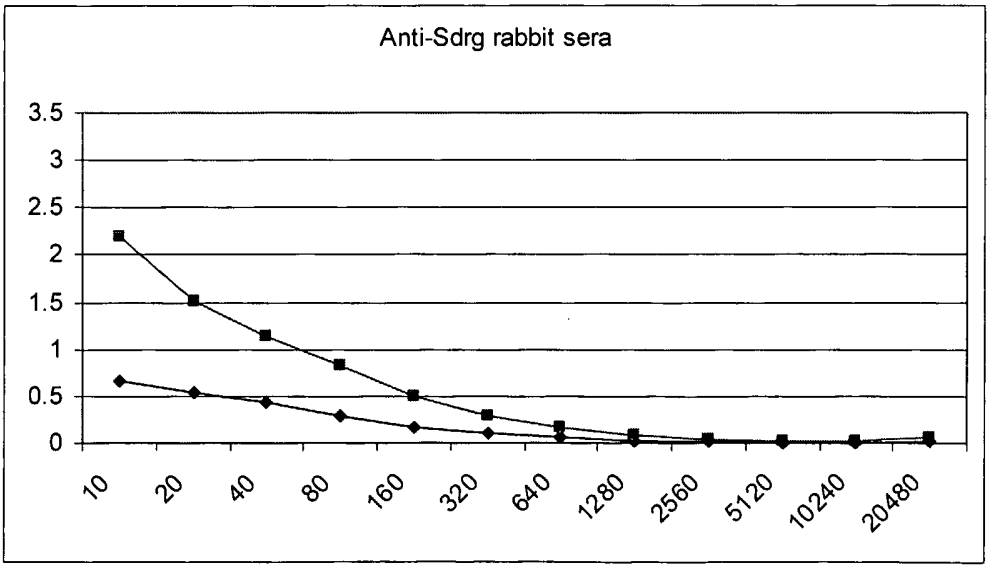
Anti-Sdrg rabbit sera
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0
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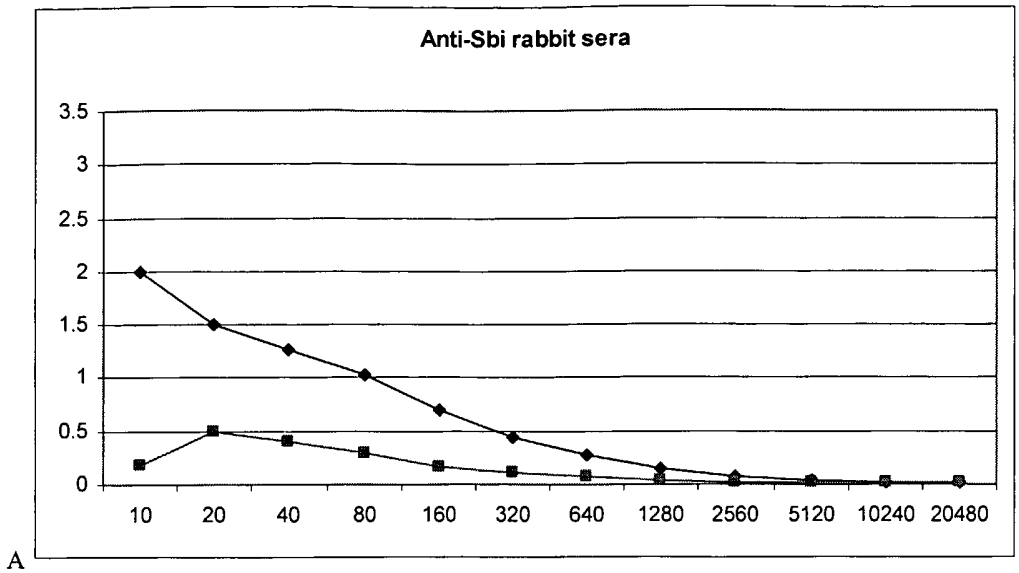
C

Figure 7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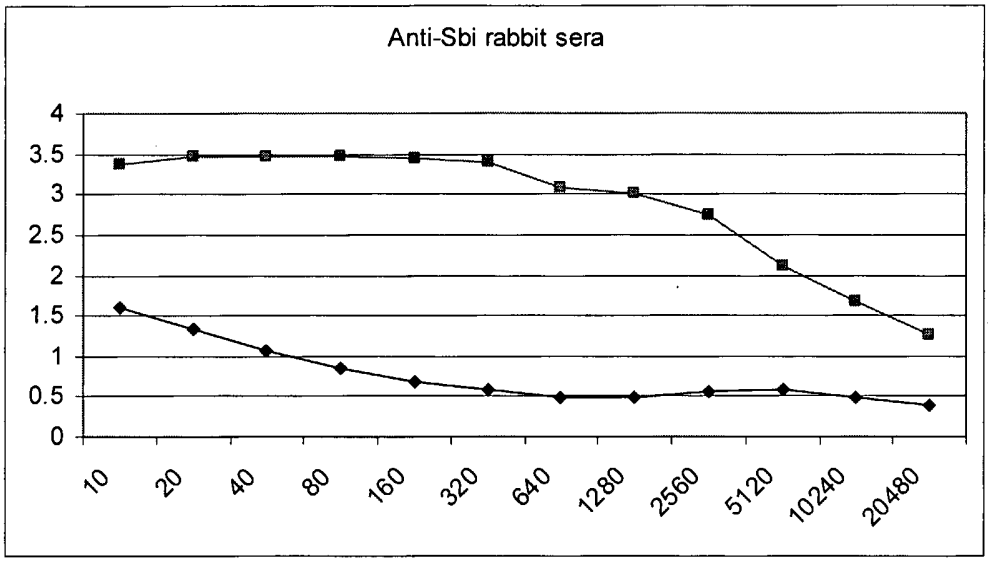
A


Anti-Sbi rabbit sera
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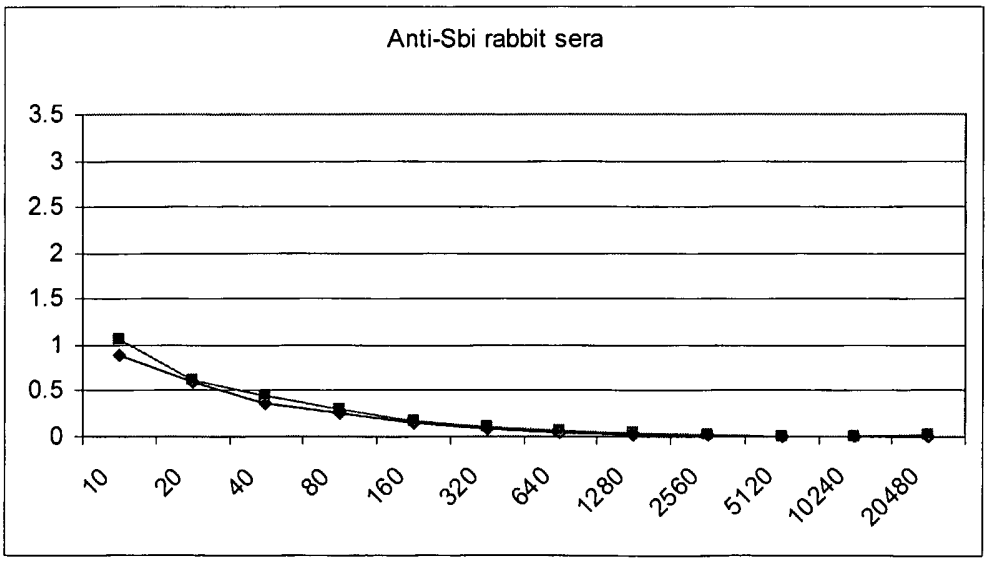
B


Anti-Sbi rabbit sera
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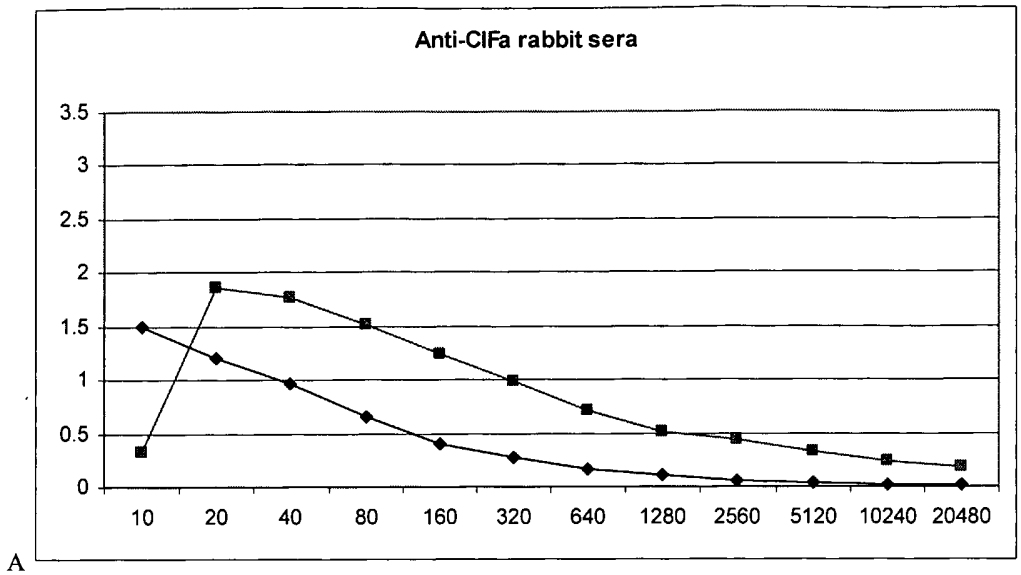
1.5
1
0.5
0
10 20 40 80 160 320 640 1280 2560 5120 10240 20480

C

Figure 7


Anti-ClFa rabbit sera
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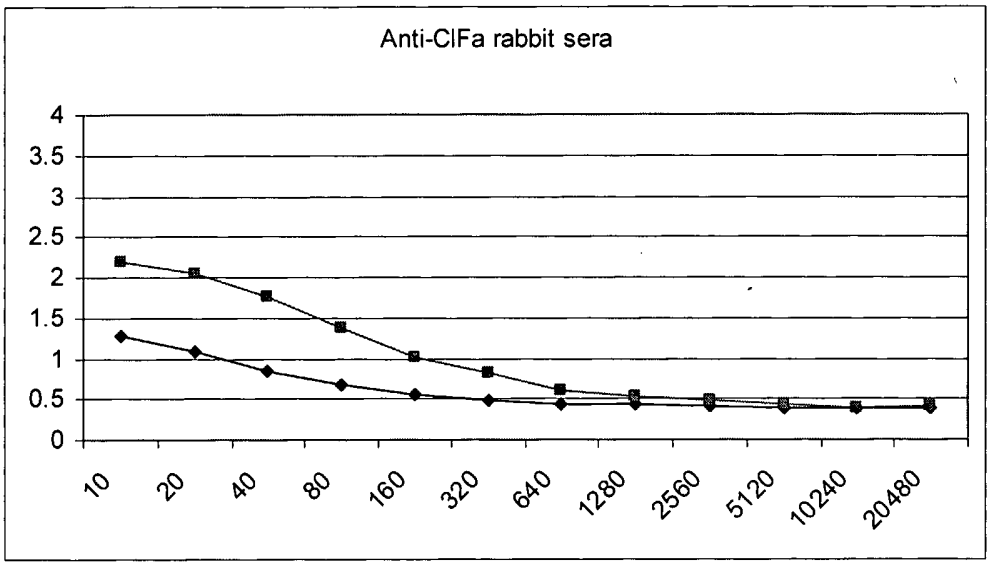
160
320
640
1280
2560
5120
10240
20480

A


Anti-ClFa rabbit sera
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160
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640
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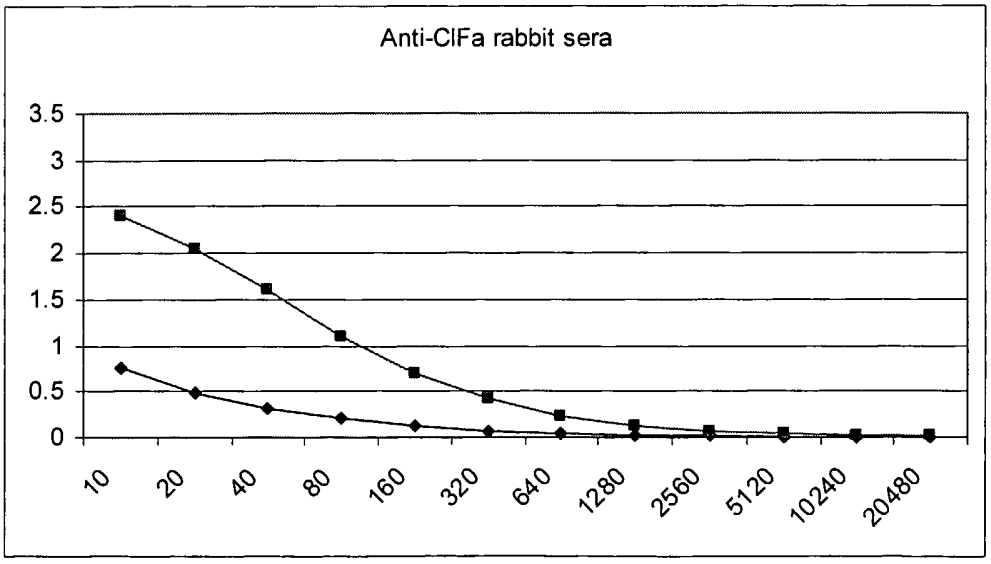
B


Anti-ClFa rabbit sera
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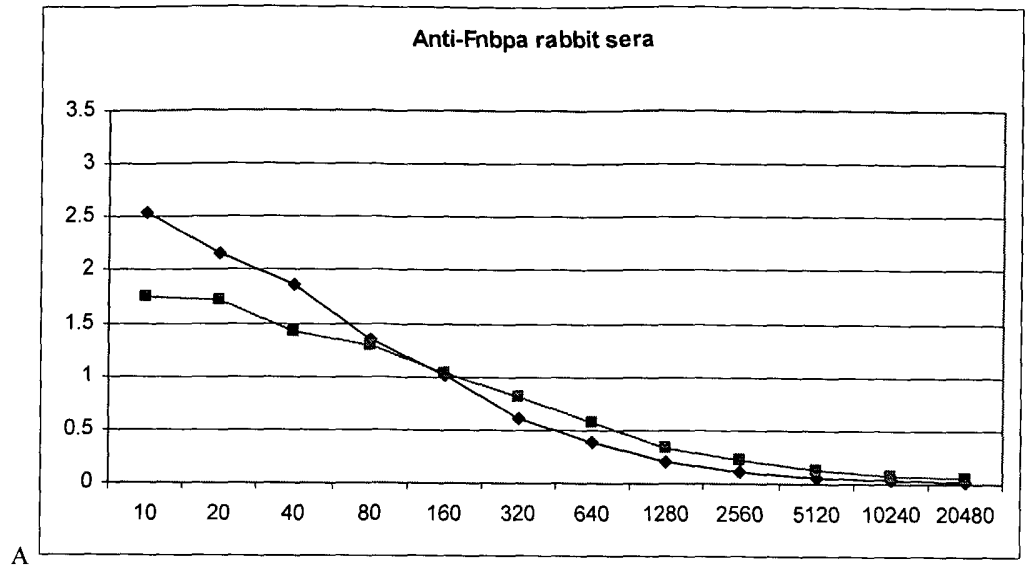
C

Figure 7


Anti-Fnbpa rabbit sera
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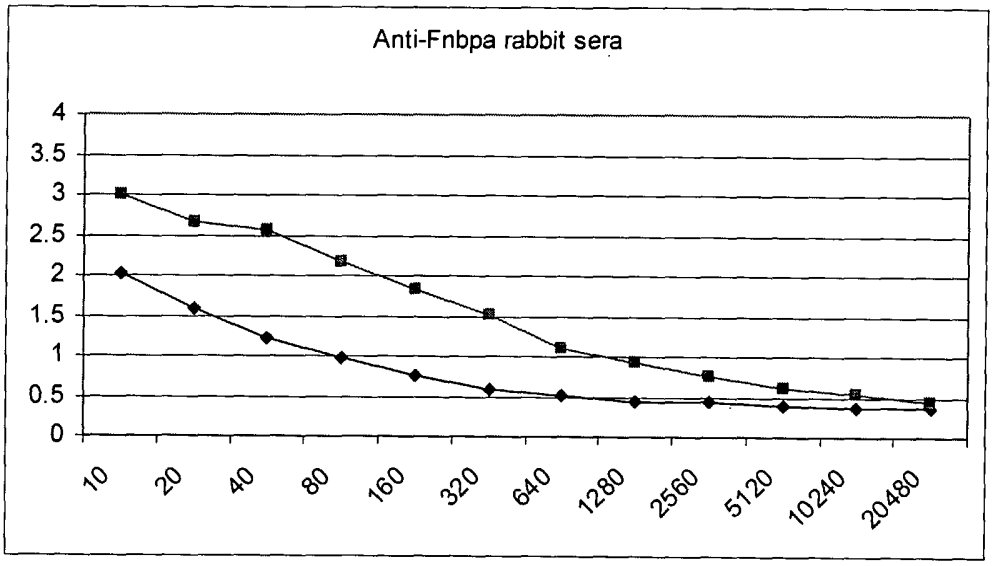
Anti-Fnbpa rabbit sera
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3.5
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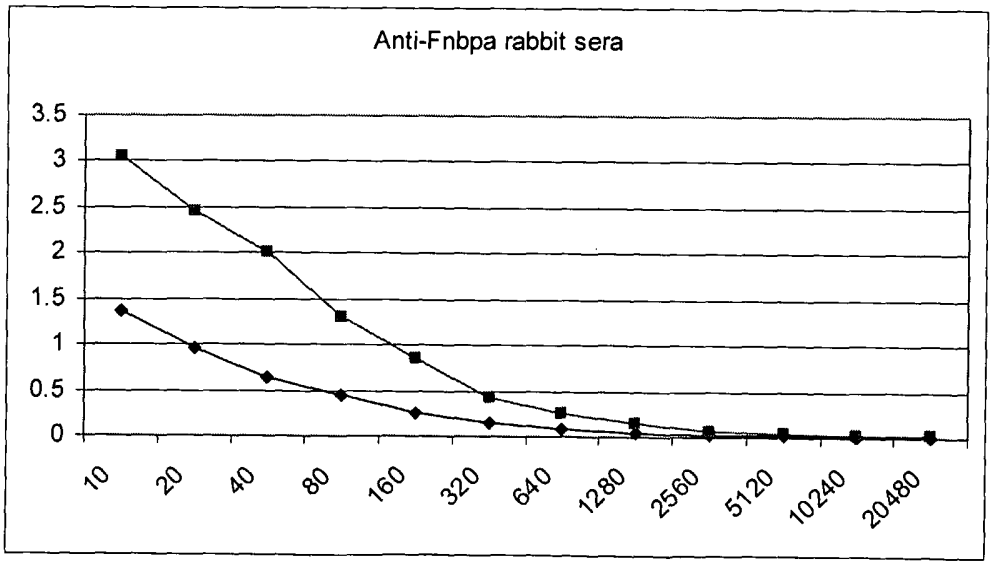
Anti-Fnbpa rabbit sera
3.5
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20480

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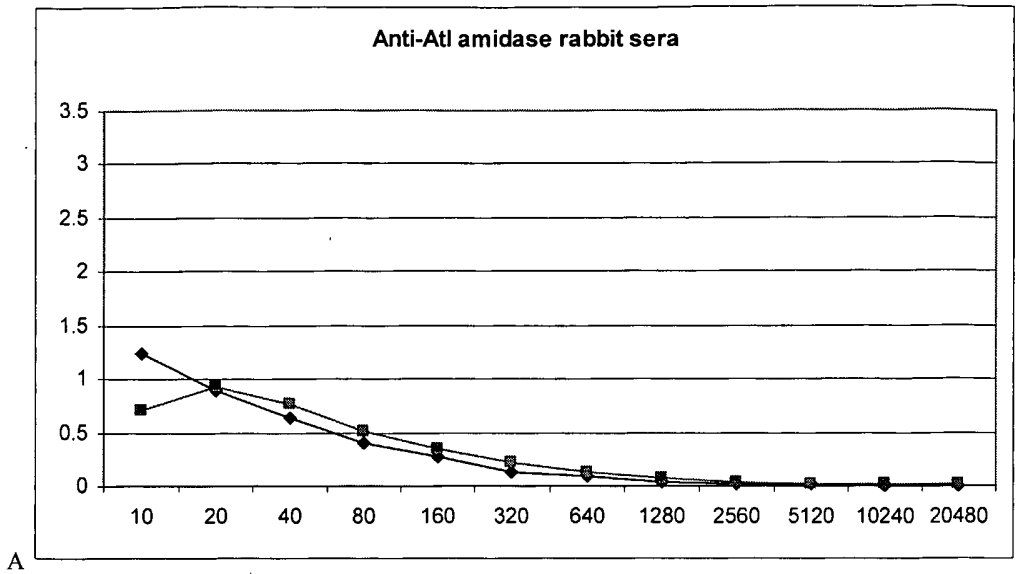
Figure 7


Anti-Atl amidase rabbit sera
3.5
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2.5
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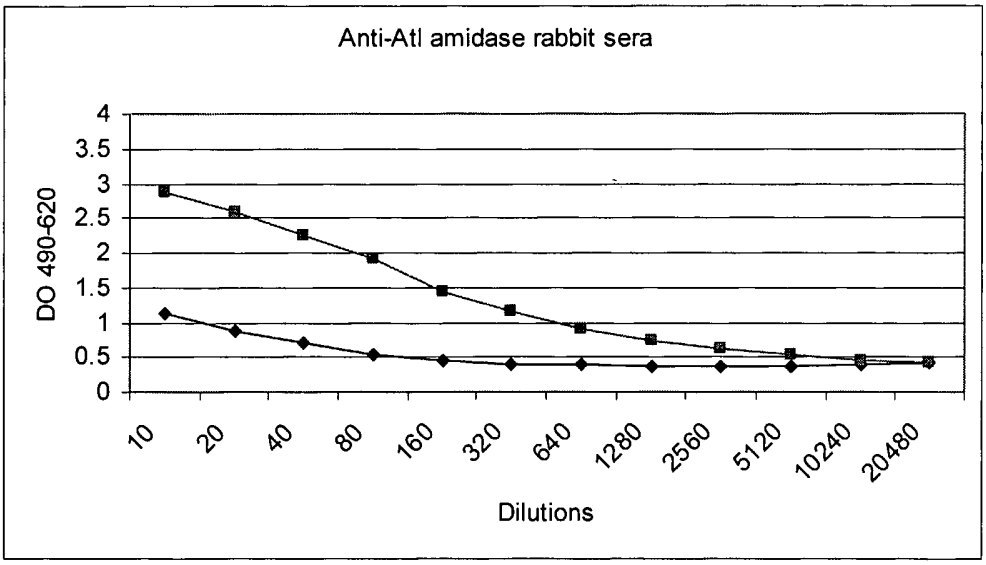
A


Anti-Atl amidase rabbit sera
DO 490-620
4
3.5
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2.5
2
1.5
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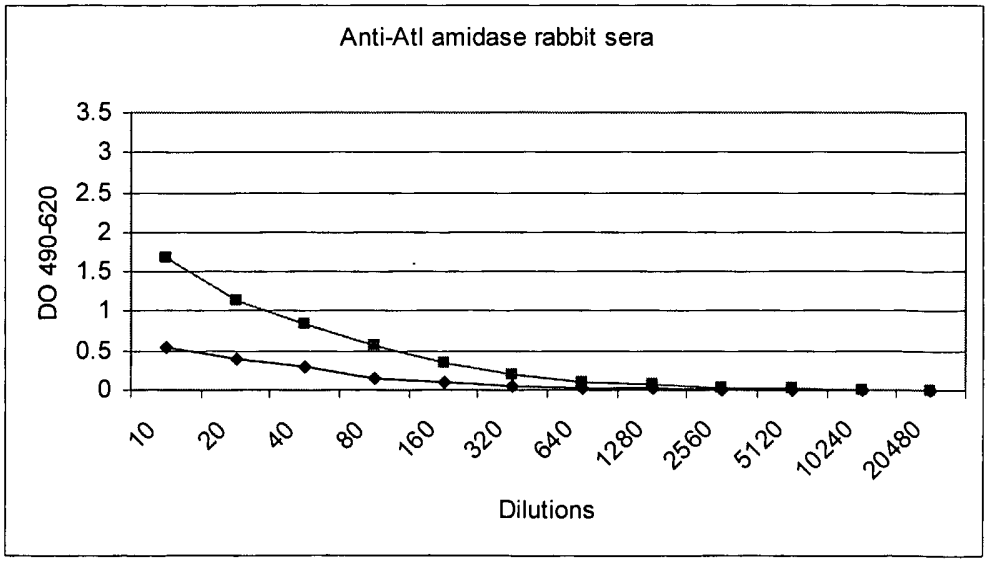
Dilutions

B


Anti-Atl amidase rabbit sera
DO 490-620
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Dilutions

C