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(54) **THERAPEUTICS AND DIAGNOSTICS FOR GROUP A STREPTOCOCCI**

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(57) **ABSTRACT**

Immunogenic compositions and vaccines are described comprising GAS Markers. Methods for detecting GAS diseases in a subject are also described comprising measuring GAS markers in a sample from the subject. The invention further provides kits for carrying out the methods of the invention and therapeutic applications for GAS diseases employing GAS markers, polynucleotides encoding the markers, and/or binding agents for the markers.

THERAPEUTICS AND DIAGNOSTICS FOR GROUP A STREPTOCOCCI

FIELD OF THE INVENTION

[0001] The invention relates to compositions and methods for the diagnosis, treatment, prevention and amelioration of diseases caused by Group A *Streptococcus*.

BACKGROUND OF THE INVENTION

[0002] Group A *Streptococcus* (GAS), also known as *Streptococcus pyogenes*, cause several types of disease in humans, including strep throat, scarlet fever, impetigo, cellulitis-erysipelas, rheumatic fever, acute glomerular nephritis, endocarditis, and necrotizing fasciitis and it is associated with significant morbidity and mortality worldwide (Carapetis, J. R., Steer, A. C. et al). The development of effective and safe vaccines against streptococcal infections has been ongoing (Bisno, A. L., Rubin, F. A. et al). A useful vaccine against GAS would reduce health care costs and numerous physician visits.

[0003] A number of group A *Streptococcus* vaccine candidates have been identified, such as M proteins (Bessen, D. et al; Fischetti, V. A. 1989 Infect. Immun. 64:1495-1501; Lancefield, R. C. 1962, J. Immun. 89:307-313), C5a peptidase (Cleary, P. P., Matsuka, Y. V. et al; Kapur, V. et al. 1994 Infect Immun. 65:2080-2087), cysteine protease (Dale, J. B., et al, Microb. Pathogenesis. 16:443-450) and lipoteichoic acid (Dale, J. B., et al., 1996 J. Infect. Dis. 169:319-323; Lancefield, R. C. 1962; Clin. Microbiol. 2:285-314). However, there are difficulties associated with a vaccine strategy involving the M protein, such as the large number of serologic M types, and the observation that some M proteins contain epitopes that cross-react with human tissues. Thus, a need still exists for a flexible, effective, and multivalent vaccine against GAS.

SUMMARY OF THE INVENTION

[0004] The invention provides markers and marker sets that distinguish Group A *Streptococcus* diseases (GAS diseases). A marker set may comprise or consist of a plurality of GAS polypeptides and/or polynucleotides selected from the polynucleotide and polypeptide markers set out in Tables 3, 4 and 5 (hereinafter "GAS markers"). GAS markers and marker sets can be used for diagnosis, monitoring (i.e. monitoring progression or therapeutic treatment), prognosis, treatment, or classification of a GAS disease. While the GAS markers are presented together in a group in Tables 3, 4 and 5, each of the sequences can be separately considered and claimed.

[0005] An aspect of the invention provides a composition of matter comprising a purified polypeptide consisting essentially of one or more of the polypeptides in Tables 3, 4 and 5, or a fragment thereof. The purified polypeptide may further comprise a carrier or be linked to an indicator reagent (e.g. detectable substance), an amino acid spacer, an amino acid linker, a signal sequence, a stop transfer sequence, a transmembrane domain, a protein purification ligand or a combination thereof.

[0006] The levels of markers or marker sets in a sample may be determined by methods as described herein and generally known in the art.

[0007] In an aspect, the invention provides a method for characterizing or classifying a patient sample comprising detecting a difference in the expression of a first plurality of GAS markers relative to a control, the first plurality of GAS markers consisting of one or more markers set out in Tables 3, 4 and 5.

[0008] In an embodiment of the invention, a method is provided for diagnosing a GAS disease in a patient comprising:

[0009] (a) obtaining a sample from a patient;

[0010] (b) detecting in the sample at least one GAS marker; and

[0011] (c) comparing the detected amount with an amount detected for a standard.

[0012] The term "detect" or "detecting" includes assaying or otherwise establishing the presence or absence of the target markers, subunits thereof, or combinations of reagent bound targets, and the like, or assaying for, ascertaining, establishing, or otherwise determining one or more factual characteristics of a GAS disease. The term encompasses diagnostic, prognostic, and monitoring applications for the markers.

[0013] The invention also provides a method of assessing whether a patient is afflicted with or has a pre-disposition for a GAS disease the method comprising comparing:

- **[0014]** (a) levels of GAS polypeptide or polynucleotide markers associated with a GAS disease in a sample from the patient; and
- **[0015]** (b) normal levels of GAS markers in samples of the same type obtained from control patients not afflicted with the disease, wherein altered levels of the markers relative to the corresponding normal levels of markers is an indication that the patient is afflicted with a GAS disease.

[0016] In an aspect of a method of the invention for assessing whether a patient is afflicted with or has a pre-disposition for a GAS disease, higher levels of the markers in a sample relative to the corresponding normal levels is an indication that the patient is afflicted with or has a pre-disposition for a GAS disease.

[0017] In another aspect of a method of the invention for assessing whether a patient is afflicted with or has a predisposition for a GAS disease, lower levels of GAS markers in a sample relative to the corresponding normal levels is an indication that the patient is afflicted with a GAS disease.

[0018] In a further aspect, a method for screening a subject for a GAS disease is provided comprising (a) obtaining a biological sample from a subject; (b) detecting the amount of GAS markers in said sample; and (c) comparing said amount of markers detected to a predetermined standard, where detection of a level of markers that differs significantly from the standard indicates a GAS disease.

[0019] In an embodiment, a significant difference between the levels of GAS marker levels in a patient and normal levels is an indication that the patient is afflicted with or has a predisposition to a GAS disease.

[0020] In a particular embodiment the amount of GAS marker(s) detected is greater than that of a standard and is indicative of a GAS disease. In another particular embodiment, the amount of GAS marker(s) detected is lower than that of a standard and is indicative of a GAS disease.

[0021] In particular, the invention provides a non-invasive method for detection, diagnosis or prediction of a GAS disease in a subject comprising: obtaining a sample of blood, plasma, serum, urine or saliva or a tissue sample from the subject; subjecting the sample to a procedure to detect GAS markers in the blood, plasma, serum, urine, saliva or tissue; detecting, diagnosing, and predicting GAS disease by comparing the levels of GAS markers to the levels of marker(s) or polynucleotide(s) obtained from a control subject with no GAS disease.

[0022] In aspect, the invention provides a method for monitoring the progression of a GAS disease in a patient the method comprising:

- **[0023]** (a) detecting GAS markers in a sample from the patient at a first time point;
- **[0024]** (b) repeating step (a) at a subsequent point in time; and
- **[0025]** (c) comparing the levels detected in (a) and (b), and therefrom monitoring the progression of the GAS disease.

[0026] The invention contemplates a method for determining the effect of an environmental factor on a GAS disease comprising comparing GAS markers in the presence and absence of the environmental factor.

[0027] The invention further relates to a method of assessing the efficacy of a therapy for inhibiting a GAS disease in a patient. A method of the invention comprises comparing: (a) levels of GAS markers in a first sample from the patient obtained from the patient prior to providing at least a portion of the therapy to the patient; and (b) levels of GAS markers in a second sample obtained from the patient following therapy.

[0028] In an embodiment, a significant difference between the levels of GAS markers in the second sample relative to the first sample is an indication that the therapy is efficacious for inhibiting GAS disease. In a particular embodiment, the method is used to assess the efficacy of a therapy for inhibiting GAS disease, where lower levels of GAS markers in the second sample relative to the first sample, is an indication that the therapy is efficacious for inhibiting the disease. The "therapy" may be any therapy for treating GAS disease, including but not limited to antibiotics. Therefore, the method can be used to evaluate a patient before, during, and after therapy.

[0029] Certain methods of the invention employ binding agents (e.g. antibodies) that specifically recognize GAS markers. In an embodiment, the invention provides methods for determining the presence or absence of GAS disease in a patient, comprising the steps of (a) contacting a biological sample obtained from a patient with one or more binding agent that specifically binds to one or more GAS markers; and (b) detecting in the sample an amount of marker that binds to the binding agent, relative to a predetermined standard or cut-off value, and therefrom determining the presence or absence of GAS disease in the patient.

[0030] In another embodiment, the invention relates to a method for diagnosing and monitoring a GAS disease in a subject by quantitating one or more GAS markers associated with the disease in a biological sample from the subject comprising (a) reacting the biological sample with one or more binding agent specific for the GAS markers (e.g. an antibody) that are directly or indirectly labelled with a detectable substance; and (b) detecting the detectable substance.

[0031] In another aspect the invention provides a method for using an antibody to detect expression of one or more GAS marker in a sample, the method comprising: (a) combining antibodies specific for one or more GAS marker with a sample under conditions which allow the formation of antibody marker complexes; and (b) detecting complex formation, wherein complex formation indicates expression of the marker in the sample. Expression may be compared with standards and is diagnostic of a GAS disease.

[0032] Embodiments of the methods of the invention involve (a) reacting a biological sample from a subject with antibodies specific for one or more GAS markers which are directly or indirectly labelled with an enzyme; (b) adding a substrate for the enzyme wherein the substrate is selected so that the substrate, or a reaction product of the enzyme and substrate forms fluorescent complexes; (c) quantitating one or more GAS markers in the sample by measuring fluorescence of the fluorescent complexes; and (d) comparing the quantitated levels to levels obtained for other samples from the subject patient, or control subjects.

[0033] In another embodiment the quantitated levels are compared to levels quantitated for control subjects without a GAS disease (e.g. uninfected individuals) wherein an increase in GAS marker levels compared with the control subjects is indicative of GAS disease.

[0034] A particular embodiment of the invention comprises the following steps

- **[0035]** (a) incubating a biological sample with first antibodies specific for one or more GAS markers which are directly or indirectly labeled with a detectable substance, and second antibodies specific for one or more GAS markers which are immobilized;
- **[0036]** (b) detecting the detectable substance thereby quantitating GAS markers in the biological sample; and
- **[0037]** (c) comparing the quantitated GAS markers with levels for a predetermined standard.

[0038] The standard may correspond to levels quantitated for samples from control subjects without a GAS disease (uninfected individuals) or from other samples of the subject. In an embodiment, increased levels of GAS markers as compared to the standard may be indicative of a GAS disease.

[0039] GAS marker levels can be determined by constructing an antibody microarray in which binding sites comprise immobilized antibodies (preferably monoclonal antibodies) specific to a substantial fraction of marker-derived GAS marker polypeptides of interest.

[0040] Other methods of the invention employ one or more polynucleotides capable of hybridizing to one or more polynucleotides encoding GAS markers. Thus, methods for detecting GAS markers can be used to monitor a GAS disease by detecting polynucleotide markers associated with the disease. Thus, the present invention relates to a method for diagnosing and monitoring a GAS disease in a sample from a subject comprising isolating nucleic acids, preferably mRNA, from the sample; and detecting GAS marker polynucleotides associated with the disease in the sample. The presence of different levels of GAS marker polynucleotides in the sample compared to a standard or control may be indicative of disease, disease stage, and/or a positive prognosis i.e. longer progression-free and overall survival.

[0041] The invention provides methods for determining the presence or absence of a GAS disease in a subject comprising detecting in the sample levels of nucleic acids that hybridize to one or more GAS marker polynucleotides, comparing the levels with a predetermined standard or cut-off value, and therefrom determining the presence or absence of GAS disease in the subject. In an embodiment, the invention provides methods for determining the presence or absence of a GAS disease in a subject comprising (a) contacting a sample obtained from the subject with oligonucleotides that hybridize to one or more GAS marker polynucleotides; and (b) detecting in the sample a level of nucleic acids that hybridize to the polynucleotides relative to a predetermined cut-off value, and therefrom determining the presence or absence of GAS disease in the subject.

[0042] Within certain embodiments, the amount of polynucleotides that are mRNA are detected via polymerase chain reaction using, for example, oligonucleotide primers that hybridize to one or more GAS marker polynucleotides, or complements of such polynucleotides. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing oligonucleotide probes that hybridize to one or more GAS marker polynucleotides, or complements thereof.

[0043] When using mRNA detection, the method may be carried out by combining isolated mRNA with reagents to convert to cDNA according to standard methods; treating the converted cDNA with amplification reaction reagents (such as cDNA PCR reaction reagents) in a container along with an appropriate mixture of nucleic acid primers; reacting the contents of the container to produce amplification products; and analyzing the amplification products to detect the presence of one or more GAS polynucleotide markers in the sample. For mRNA the analyzing step may be accomplished using Northern Blot analysis to detect the presence of GAS markers. The analysis step may be further accomplished by quantitatively detecting the presence of GAS markers in the amplification product, and comparing the quantity of markers detected against a panel of expected values for the known presence of the markers in samples from uninfected individuals derived using similar primers.

[0044] Therefore, the invention provides a method wherein mRNA is detected by (a) isolating mRNA from a sample and combining the mRNA with reagents to convert it to cDNA; (b) treating the converted cDNA with amplification reaction reagents and nucleic acid primers that hybridize to one or more GAS marker polynucleotides to produce amplification products; (d) analyzing the amplification products to detect an amount of mRNA encoding the GAS markers; and (e) comparing the amount of mRNA to an amount detected against a panel of expected values for normal samples (derived using similar nucleic acid primers).

[0045] In particular embodiments of the invention, the methods described herein utilize the GAS marker polynucleotides placed on a microarray so that the expression status of each of the markers is assessed simultaneously.

[0046] In a particular aspect, the invention provides a microarray comprising a defined set of genes (e.g., at least 5, 10, 15 or 20 of the genes in Tables 3, 4 and 5). The invention further relates to the use of the microarray as a prognostic tool to predict a GAS disease.

[0047] In an embodiment, the invention provides for oligonucleotide arrays comprising GAS marker sets described herein. The microarrays provided by the present invention may comprise probes to markers able to distinguish a GAS disease. In particular, the invention provides oligonucleotide arrays comprising probes to a subset or subsets of gene markers up to a full set of markers which distinguish GAS disease.

[0048] The invention provides a method of detecting antibodies that specifically bind GAS or a GAS marker polypeptide. The method can comprise reacting one or more GAS marker polypeptide, in particular a polypeptide in Tables 3, 4 and 5 with a test sample suspected of comprising antibodies specific for a GAS marker polypeptide under conditions that allow polypeptide/antibody complexes to form and detecting polypeptide/antibody complexes. The detection of polypeptide/antibody complexes is an indication that antibodies specific for a GAS marker polypeptide are present in the test sample, and the absence of the polypeptide/antibody complexes is an indication that antibodies specific for GAS marker polypeptides are not present in the test sample. The antibodies can be fragments of antibodies. In aspects of this method of the invention, the amount of antibodies in the test sample can be determined. In aspects of this method of the invention the polypeptide can be attached to a carrier or support. In aspects of this method of the invention the polypeptide can be attached to a detectable substance. In aspects of this method of the invention the polypeptide/antibody complexes can be detected using a labeled anti-species antibody. The method can comprise an assay selected from the group consisting of a microtiter plate assay, a reversible flow chromatographic binding assay, a lateral flow immunoassay, an enzyme linked immunosorbent assay, a radioimmunoassay, a hemaglutination assay, a western blot assay, a fluorescence polarization immunoassay and an indirect immunofluorescence assay.

[0049] The invention provides a method of detecting a GAS disease or infection in a subject. The method comprises obtaining a sample from the subject, contacting one or more GAS marker polypeptide or purified GAS marker polypeptide with the sample under conditions that allow polypeptide/antibody complexes to form; and detecting polypeptide/antibody complexes. The detection of polypeptide/antibody complexes is an indication that the mammal has a GAS disease and the absence of polypeptide/antibody complexes is an indication that the mammal does not have a GAS disease. In a method of the invention for detecting antibodies specific for GAS marker polypeptides, the GAS marker polypeptides or antigens comprise one or more epitopes (i.e., antigenic determinants).

[0050] In an aspect, the invention provides a method of detecting presence or absence of an antibody specific for a GAS marker polypeptide in a test sample comprising: contacting a test sample with a purified immunogenic GAS marker polypeptide, wherein the polypeptide specifically binds an antibody specific for a GAS marker polypeptide under conditions that allow formation of an immunocomplex between the antibody and the polypeptide; and detecting an immunocomplex, wherein detection of the immunocomplex indicates the presence of antibody specific for a GAS marker polypeptide in the test sample.

[0051] The invention also relates to kits for carrying out the methods of the invention, in particular diagnostic methods of the invention. In an embodiment, a kit is for assessing whether a patient is afflicted with a GAS disease and it comprises reagents for assessing one or more GAS markers or antibodies specific for GAS markers. The invention further provides kits comprising marker sets described herein. In an aspect the kit contains a microarray ready for hybridization to target GAS markers, plus software for the data analyses.

[0052] The invention also provides a diagnostic composition comprising one or more GAS marker. A composition is also provided comprising a probe that specifically hybridizes to a GAS marker or a fragment thereof, or an antibody specific for GAS markers or a fragment thereof. In another aspect, a composition is provided comprising one or more GAS marker polynucleotide specific primer pairs capable of amplifying the polynucleotides using polymerase chain reaction methodologies. The probes, primers or antibodies can be labeled with a detectable substance.

[0053] The invention provides an immunogenic composition for protecting mammals, in particular humans, against infection by Group A *Streptococcus*. An immunogenic composition of the invention comprises an immunogenic amount of a region of a GAS marker. In a composition of the invention, the region of a GAS marker defines an epitope which induces the formation of bactericidal antibodies against GAS. In an aspect, an immunogenic composition is provided for protecting mammals against infection by Group A *Streptococcus* comprising an effective amount of a region of at least one Group A *Streptococcus* marker listed in Tables 3, 4 and 5 that defines an epitope which induces the formation of bactericidal antibodies against GAS. In aspects of the invention the region of the GAS marker is immunoreactive and found in the most prevalent GAS serotypes associated with a selected disease.

[0054] The region of a GAS marker present in the immunogenic compositions of the invention may be in the form of a polypeptide or part of a polypeptide (e.g. an epitope). Thus, in an aspect of the invention the immunogenic composition comprises a polypeptide encoded by at least one GAS marker in Tables 3, 4 and 5, or a portion, isoform, homolog, variant, or precursor of the polypeptide, including modified forms of the polypeptide and derivative. An immunogenic protein may also be a chimeric or fusion polypeptide or conjugate.

[0055] In embodiments of the invention an immunogenic composition comprises synthetic peptides about 5 to 200, 10 to 150, 10 to 100, 20 to 100, 10 to 50 or 20 to 25 amino acids in length which are portions of one or more GAS marker. In embodiments, the synthetic peptides are serotype specific peptides. In embodiments, the synthetic peptides comprise an epitope of a GAS marker. Synthetic peptides may be used, for example, individually, in a mixture, or in a polypeptide or protein. For example, a polypeptide or protein can be created by fusing or linking the peptides to each other, synthesizing the polypeptide or protein based on the peptide sequences, and linking or fusing the peptides to a backbone.

[0056] Immunogenic compositions of the invention are preferably recognized by GAS marker specific antibodies and are capable of eliciting functional opsonic antibodies and/or anti-attachment antibodies without eliciting tissue cross-reactive antibodies.

[0057] Immunogenic compositions of the invention may be useful for raising antibodies which have application for prophylactic and diagnostic purposes. Therefore, the invention also provides isolated antibodies that specifically bind to a GAS marker, and in particular antibodies elicited in response to an immunogenic composition or vaccine of the invention. An antibody may be a monoclonal or polyclonal antibody or an antibody fragment (e.g., Fab or $F(ab')_2$ fragment). In an aspect, the invention provides antibodies specific for a GAS marker that can be used therapeutically to destroy or inhibit a GAS disease or to block a GAS marker associated with a GAS disease. In an aspect, GAS markers may be used in various immunotherapeutic methods to promote immune-mediated destruction or inhibition of GAS expressing GAS markers. In an aspect, the invention relates to compositions comprising antibodies specific for one or more GAS markers, peptides derived therefrom, or chemically produced (synthetic) peptides, and a pharmaceutically acceptable carrier, excipient, or diluent.

[0058] An immunogenic composition of the invention may be useful as a vaccine and the invention contemplates a vaccine comprising an immunogenic composition of the invention.

[0059] In an aspect, the invention contemplates vaccines for stimulating or enhancing in a subject to whom the vaccine is administered production of antibodies directed against GAS markers, peptides derived therefrom, or chemically produced (synthetic) peptides, or any combination of these molecules.

[0060] An immunogenic composition of this invention may be capable of eliciting active and passive protection against infection by Group A *Streptococcus*. For passive protection, immunogenic antibodies can be produced by immunizing a human with a vaccine comprising an immunogenic composition of the invention and then recovering the immunogenic antibodies from the human. Thus, the invention contemplates a composition for passive immunization comprising antibodies specific for GAS markers.

[0061] In aspects of the invention, an immunogenic composition or vaccine of the invention may be used to inhibit or reduce the growth of Group A Streptococcal bacteria, in particular, *S. pyogenes*, in blood and/or reduce phagocytic resistance. Accordingly, the invention contemplates the use of GAS markers, peptides derived therefrom, or chemically produced (synthetic) peptides, or any combination of these molecules, for use as vaccines or in the preparation of vaccines to prevent a GAS disease and/or to treat a GAS disease.

[0062] An immunogenic composition or vaccine may further comprise additional components, including but not limited to, carriers, diluents, excipients, vehicles (e.g., encapsulated, liposomes), and other immune-stimulatory molecules (e.g., adjuvants, other vaccines). In an aspect, a vaccine further comprises an adjuvant such as aluminum hydroxide, aluminum phosphate, monophosphoryl lipid A, QS21 or stearyl tyrosine.

[0063] A polypeptide in an immunogenic composition or vaccine may be conjugated to a native or recombinant bacterial protein such as tetanus toxoid, cholera toxin, diphtheria toxoid, or CRM_{197}.

[0064] In an aspect, the invention provides methods of immunizing a mammal against infection by Group A *Streptococcus* by administering an immunogenic amount of a composition of the invention. In an aspect, an immunogenic composition of the invention is used to provide protection against infection by Group A *Streptococcus* in those populations most at risk of contracting GAS infections and disease namely adults, pregnant women and, in particular, infants and children.

[0065] A method for treating or preventing a GAS disease in a patient is also provided comprising administering to a patient in need thereof antibodies specific for one or more GAS markers associated with a GAS disease. The method comprises administering to the subject a vaccine of the invention in a dose effective for stimulating or enhancing production of the antibodies.

[0066] The invention further provides a method for treating, preventing, or delaying recurrence of a GAS disease. The method comprises administering to the subject a composition or vaccine of the invention in a dose effective for treating, preventing, or delaying recurrence of a GAS disease.

[0067] In further aspects, the invention also relates to methods for using the immunogenic compositions, vaccines, or antibodies and methods for tailoring vaccines. In aspects, the invention also relates to methods for using the immunogenic compositions, vaccines, or antibodies for treating a GAS disease or in the preparation of a medicament for treating a GAS disease.

[0068] Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

Glossary

[0069] In accordance with the present invention there may be employed conventional biochemistry, enzymology, molecular biology, microbiology, and recombinant DNA techniques within the skill of the art. Such techniques are explained fully in the literature. See for example, Sambrook et al, Molecular Cloning: A Laboratory Manual, Third Edition (2001) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y); DNA Cloning: A Practical Approach, Volumes I and II (D. N. Glover ed. 1985); Oligonucleotide Synthesis (M. J. Gait ed. 1984); Nucleic Acid Hybridization B. D. Hames & S. J. Higgins eds. (1985); Transcription and Translation B. D. Hames & S. J. Higgins eds (1984); Animal Cell Culture R. I. Freshney, ed. (1986); Immobilized Cells and enzymes IRL Press, (1986); and B. Perbal, A Practical Guide to Molecular Cloning (1984).

[0070] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0071] Numerical ranges recited herein by endpoints include all numbers and fractions subsumed within that range (e.g. 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.90, 4, and 5). It is also to be understood that all numbers and fractions thereof are presumed to be modified by the term "about". The term "about" means plus or minus 0.1 to 50%, 5-50%, or 10-40%, preferably 10-20%, more preferably 10% or 15%, of the number to which reference is being made.

[0072] The term "sample" means a material known or suspected of expressing or containing one or more GAS markers. A test sample can be used directly as obtained from the source or following a pretreatment to modify the character of the sample. The sample can be a biological sample derived from any biological source, such as tissues, extracts, or cell cultures, including cells, cell lysates, and physiological fluids, such as, for example, blood, plasma, serum, saliva, sputum, ocular lens fluid, cerebrospinal fluid, sweat, urine, feces, amniotic fluid, milk, ascites fluid, synovial fluid, peritoneal fluid, lavage fluid, wound exudates, and the like. The sample can be obtained from animals, preferably mammals, most preferably humans. A sample can also be an environmental sample or a laboratory sample. A sample can be treated prior to use, such as preparing plasma from blood, diluting viscous fluids, and the like. Methods of treatment can involve filtration, distillation, extraction, concentration, inactivation of interfering components, the addition of reagents, and the like. Depending upon the type of test sample, it can be diluted with a suitable buffer reagent, concentrated, or contacted with a solid phase without any manipulation. For example, prior to testing serum or plasma samples can be diluted, or specimens such as urine can be concentrated. In an embodiment the sample is a human physiological fluid. In a particular embodiment, the sample is human serum, urine or plasma.

[0073] The terms "subject", "individual" or "patient" refer to a warm-blooded animal such as a mammal. In particular, the terms refer to a human. The term also includes domestic animals bred for food or as pets, including horses, cows, sheep, poultry, fish, pigs, cats, dogs, and zoo animals. A subject, individual or patient may be afflicted with or suspected of having or being pre-disposed to a GAS disease or at risk of developing a GAS disease. A subject suspected of suffering from a GAS disease or an infection by a GAS displays one or more symptoms of a GAS disease or a GAS infection, or may have come into contact with a person suffering from a GAS disease. A subject at risk of developing a GAS disease is a subject that is exposed to a condition or suffers from a condition that increases the risk of developing a GAS disease or being infected with a GAS.

[0074] Methods herein for administering an agent or composition to subjects/individuals/patients contemplate treatment as well as prophylactic use. Typical subjects for treatment or diagnosis include persons susceptible to, suffering from or that have suffered a GAS disease.

[0075] The terms "peptide", "polypeptide" and "protein" are used interchangeably and as used herein refer to more than one amino acid joined by a peptide bond.

[0076] "Optional" or "optionally" means that the subsequently described element, event or circumstance may or may not occur, and that the description includes instances where said element, event, or circumstance occurs and instances where it does not.

[0077] The term "effective amount" or "effective dose" refers to a non-toxic but sufficient amount of an agent (e.g. antibody) to provide the desired biological effect. The exact amount required will vary from subject to subject, depending on the species, age and general condition of the subject, the particular agent used, its mode of administration, and the like. An appropriate effective amount or effective dose may be determined by one of ordinary skill in the art using routine experimentation.

[0078] "Pharmaceutically acceptable" refers to a material that is not biologically or otherwise undesirable, i.e., the material may be administered to an individual without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of a composition in which it is contained.

[0079] "Synthetic" refers to items, e.g., peptides, which are not naturally occurring, in that they are isolated, synthesized or otherwise manipulated by man.

[0080] "Immunogenic" as used herein encompasses materials which are capable of producing an immune response.

[0081] "Composition" includes any composition of matter, including peptides, polypeptides, proteins, mixtures, vaccines, antibodies, or markers of the present invention.

[0082] A "GAS disease" means a disease associated with a Group A *Streptococcus*, including without limitation streptococcal sore throat (strep throat, pharyngitis), streptococcal skin infections (impetigo, cellulitis, erysipelas), cellulitis and arthritis, peritonitis, scarlet fever, rheumatic fever, postpartum fever, wound infections, pneumonia, invasive group A strep infection, acute glomerulonephritis, necrotizing fasciitis and streptococcal toxic shock syndrome. In aspects of the invention the GAS disease is associated with a clinical strain listed in Table 1. In particular aspects, the GAS disease is a disease listed in Table 2.

[0083] A "GAS marker" includes a polypeptide associated with GAS described herein (GAS marker polypeptide"), namely the polypeptides listed in Tables 3, 4 and 5. A "GAS Marker" also includes a polynucleotide associated with GAS described herein ("GAS marker polynucleotide"), namely polynucleotides listed in Tables 3, 4 and 5.

[0084] A Gas marker polypeptide includes the native-sequence polypeptide, isoforms, chimeric polypeptides, all homologs, fragments, precursors, complexes, and modified forms and derivatives thereof. A "native-sequence polypeptide" comprises a polypeptide having the same amino acid sequence of a polypeptide derived from nature. Such native-sequence polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term specifically encompasses naturally occurring truncated or secreted forms of a polypeptide, polypeptide variants including naturally occurring variant forms (e.g. alternatively spliced forms or splice variants), and naturally occurring allelic variants.

[0085] The term "polypeptide variant" includes a polypeptide having at least about 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, or 99% amino acid sequence identity, particularly at least about 70-80%, more particularly at least about 85%, still more particularly at least about 90%, most particularly at least about 95% amino acid sequence identity with a native-sequence polypeptide. Variants include, for instance, polypeptides wherein one or more amino acid residues are added to, or deleted from, the N- or C-terminus of the full-length or mature sequences of the polypeptide, including variants from other species, but excludes a native-sequence polypeptide. In aspects of the invention variants retain the immunogenic activity of the corresponding native-sequence polypeptide.

[0086] Percent identity of two amino acid sequences, or of two nucleic acid sequences is defined as the percentage of amino acid residues or nucleotides in a candidate sequence that are identical with the amino acid residues or nucleotides in a polypeptide or nucleic acid sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid or nucleic acid sequence identity can be achieved in various conventional ways, for instance, using publicly available computer software including the GCG program package (Devereux J. et al., Nucleic Acids Research 12(1): 387, 1984); BLASTP, BLASTN, and FASTA (Atschul, S. F. et al. J. Molec. Biol. 215: 403-410, 1990). The BLAST X program is publicly available from NCBI and other sources (BLAST Manual, Altschul, S. et al. NCBI NLM NIH Bethesda, Md. 20894; Altschul, S. et al. J. Mol. Biol. 215: 403-410, 1990). Skilled artisans can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. Methods to determine identity and similarity are codified in publicly available computer programs.

[0087] A variant may be created by introducing substitutions, additions, or deletions into a polynucleotide encoding a native polypeptide sequence such that one or more amino acid substitutions, additions, or deletions are introduced into the encoded protein. Mutations may be introduced by standard methods, such as site-directed mutagenesis and PCR-mediated mutagenesis. In an embodiment, conservative substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which an amino acid residue is replaced with an amino acid residue with a similar side chain. Amino acids with similar side chains are known in the art and include amino acids with basic side chains (e.g. Lys, Arg, His), acidic side chains (e.g. Asp, Glu), uncharged polar side chains (e.g. Gly, Asp, Glu, Ser, Thr, Tyr and Cys), nonpolar side chains (e.g. Ala, Val, Leu, Iso, Pro, Trp), beta-branched side chains (e.g. Thr, Val, Iso), and aromatic side chains (e.g. Tyr, Phe, Trp, His). Mutations can also be introduced randomly along part or all of the native sequence, for example, by saturation mutagenesis. Following mutagenesis the variant polypeptide can be recombinantly expressed and the activity of the polypeptide may be determined.

[0088] Polypeptide variants include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of a native polypeptide which include fewer amino acids than the full length polypeptides. A portion of a polypeptide can be a polypeptide which is for example, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100 or more amino acids in length. Portions in which regions of a polypeptide are deleted can be prepared by recombinant techniques and can be evaluated for one or more functional activities such as the ability to form antibodies specific for a polypeptide.

[0089] A naturally occurring allelic variant may contain conservative amino acid substitutions from the native polypeptide sequence or it may contain a substitution of an amino acid from a corresponding position in a polypeptide homolog, for example, a murine polypeptide.

[0090] A polypeptide variant may be identified by modifying a GAS marker polypeptide sequence and evaluating the antigenic properties of the modified polypeptide using for example, an immunohistochemical assay, an enzyme linked immunosorbant assay (ELISA), a radioimmunoassay (RIA) or a western blot assay.

[0091] A GAS marker polypeptide may comprise a biologically functional equivalent of at least about 5, 10, 15, 20, 25, 50, 100, 150 or 200 amino acids of a GAS marker polypeptide of Table 3, 4 or 5. A biologically equivalent polypeptide is a polypeptide that reacts substantially the same as a GAS marker polypeptide in an assay such as an immunohistochemcial assay, an ELISA, an RIA or western blot assay, i.e. it has 90-110% of the activity of the original polypeptide. In an aspect of a competition assay of the invention, the biologically equivalent polypeptide reduces binding of the polypeptide to a corresponding reactive antigen or antibody by about 80%, 85% 90%, 95%, 99% or 100%.

[0092] A GAS marker polypeptide includes truncated amino acid sequences preferably comprising or consisting essentially of at least one epitope. The truncated sequences can be used as reagents in methods of the invention or as subunit antigens in compositions for antiserum production or vaccines. Truncated sequences can be produced by various known treatments of native polypeptides or by making synthetic or recombinant polypeptides comprising a GAS marker polypeptide sequence. Polypeptides comprising truncated sequences can be made up entirely of GAS marker polypeptide sequences (one or more epitopes, either contiguous or noncontiguous), or GAS marker polypeptide sequences and heterologous sequences in a chimeric or fusion protein. Examples of heterologous sequences include sequences that provide for secretion from a recombinant host, enhance immunological reactivity of the GAS marker polypeptide epitopes or facilitate the coupling of the polypeptide to an immunoassay support or vaccine carrier. [See for example, U.S. Pat. Nos. 4,772,840 and 4,629,783 and EPO Publication Nos. 116201 and 259149.] The size of truncated GAS marker polypeptides can vary, but preferably the minimum size is a sequence sufficient to provide a GAS marker polypeptide epitope and the maximum size is not substantially greater than that required to provide the desired epitope. Generally, the truncated amino acid sequence ranges from about 5 to about 100 amino acids in length. In aspects of the invention, the sequence will be a maximum of about 50 amino acids in length, preferably a maximum of about 30 amino acids. It preferred aspects of the invention, sequences of at least about 10, 12, or 15 amino acids up to a maximum of about 20 to 25 amino acids are selected.

[0093] In aspects of the invention, in particular methods involving detecting antibodies specific for GAS marker polypeptides, the GAS marker polypeptides can comprise or consist essentially of one or more epitopes (i.e., antigenic determinants of the polypeptides). Epitopes include without limitation linear epitopes, sequential epitopes or conformational epitopes. An epitope could comprise amino acids in a spatial conformation which is unique to the epitope. Generally an epitope consists of at least 5 amino acids, and more usually consists of at least 8-10 amino acids. Epitopes within a GAS marker polypeptide can be identified by methods known in the art such as immunoassays. [See for example, the methods described in U.S. Pat. No. 4,554,101 and Jameson & Wolf, *CABIOS* 4:181-186 (1988).] By way of example, a GAS marker polypeptide can be isolated and screened, and a series of short peptides and overlapping peptides, which together span an entire polypeptide sequence, can be prepared by proteolytic cleavage. By starting with various polypeptide fragments, each fragment can be tested for the presence of epitopes recognized in an ELISA. For example, in an ELISA assay a GAS marker polypeptide, such as a 100-mer polypeptide fragment, can be attached to a solid support or carrier. Labeled antibodies are added to the solid support and allowed to bind to the unlabeled antigen fragments, under conditions where non-specific absorption is blocked, and any unbound antibody and other polypeptides are washed away. Antibody binding is detected by, for example, a reaction that converts a colorless substrate into a colored reaction product. Progressively smaller and overlapping fragments can then be tested to map an epitope of interest. A computer analysis of a GAS marker polypeptide sequence can also be carried out to identify potential epitopes and the oligopeptides can be prepared comprising the identified regions for screening.

[0094] A "chimeric protein" or "fusion protein" comprises all or part (preferably biologically active) of a GAS marker polypeptide operably linked to a heterologous polypeptide (i.e., a polypeptide other than a GAS marker polypeptide). Within the fusion protein, the term "operably linked" is intended to indicate that a GAS marker polypeptide and the heterologous polypeptide are fused in-frame to each other. The heterologous polypeptide can be fused to the N-terminus or C-terminus of a GAS marker polypeptide. A useful fusion protein is a GST fusion protein in which a GAS marker polypeptide is fused to the C-terminus of GST sequences. Chimeric and fusion proteins can be produced by standard recombinant DNA techniques.

[0095] A GAS marker polypeptide may be prepared by recombinant or synthetic methods, or isolated from a variety of sources, or by any combination of these and similar techniques. In aspects of the invention, a GAS marker polypeptide including truncations or fragments thereof can be produced recombinantly. A polynucleotide encoding a GAS marker polypeptide can be introduced into a recombinant expression vector, which can be expressed in a suitable expression host cell system using techniques well known in the art. A variety of bacterial, yeast, plant, mammalian, and insect expression systems are available in the art and any such expression system can be used. Optionally, a polynucleotide encoding a polypeptide can be translated in a cell-free translation system. A polypeptide can be chemically synthesized using standard techniques and equipment for preparing synthetic peptides. By way of example, the polypeptides/peptides may be prepared using a 9600 Millegen/Biosearch synthesizer or a 40 well multiple peptide synthesizer (MPS 396, Advanced Chem Tech, Louisville, Ky.), and purified by reverse HPLC and characterized by electrospray ionization spectrometry. A GAS marker polypeptide can also be obtained from GAS cells.

[0096] A GAS marker polynucleotide includes polynucleotides that encode a GAS marker polypeptide listed in Tables 3, 4 and 5 or a polynucleotide listed in Tables 3, 4 and 5. The polynucleotide markers include complementary nucleic acid sequences, and nucleic acids that are substantially identical to these sequences (e.g. having at least about 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, or 99% sequence identity). Polynucleotide markers also include sequences that differ from a native sequence due to degeneracy in the genetic code. Polynucleotide markers also include nucleic acids that hybridize under stringent conditions, preferably high stringency conditions to a GAS polynucleotide marker. Appropriate stringency conditions which promote DNA hybridization are known to those skilled in the art, or can be found in Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. For example, 6.0× sodium chloride/sodium citrate (SSC) at about 45° C., followed by a wash of 2.0×SSC at 50° C. may be employed. The stringency may be selected based on the conditions used in the wash step. By way of example, the salt concentration in the wash step can be selected from a high stringency of about 0.2×SSC at 50° C. In addition, the temperature in the wash step can be at high stringency conditions, at about 65° C.

[0097] Polynucleotide markers also include truncated nucleic acids or nucleic acid fragments and variant forms of the nucleic acids that arise by alternative splicing of an mRNA corresponding to a DNA. A truncated polynucleotide marker or fragment can comprise about 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150 or 200 nucleotides. In aspects of the invention, the GAS marker polynucleotides are cloned fragments of GAS genes identified in Table 3, 4 or 5.

[0098] Polynucleotide markers are intended to include DNA and RNA (e.g. mRNA) and can be either double stranded or single stranded. A polynucleotide may, but need not, include additional coding or non-coding sequences, or it may, but need not, be linked to other molecules and/or carrier or support materials. The polynucleotide markers for use in the methods of the invention may be of any length suitable for a particular method. In certain applications the term refers to antisense polynucleotides (e.g. mRNA or DNA strand in the reverse orientation to sense polynucleotide markers). GAS marker polynucleotides include unmodified forms of the polynculeotides as well as known modifications, including without limitation, labels which are known in the art, methylation, "caps", substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, etc.) and with charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), those containing pendant moieties, such as, for example proteins (including for e.g., nucleases, toxins, antibodies, signal peptides, poly-L-lysine, etc.), those with intercalators (e.g., acridine, psoralen, etc.), those containing chelators (e.g., metals, radioactive metals, boron, oxidative metals, etc.), those containing alkylators, and those with modified linkages (e.g., alpha anomeric nucleic acids, etc).

[0099] GAS marker polynucleotides can be cloned into an expression vector comprising regulatory elements (e.g. origins of replication, promoters, enhancers) that control expression of the polynucleotides in host cells. Examples of expression vectors include without limitation a plasmid, such as pBR322, pUC, or ColE1, an adenovirus vector, such as an adenovirus Type 2 vector or Type 5 vector, Sindbis virus, simian virus 40, alphavirus vectors, poxvirus vectors, cytomegalovirus, retroviral vectors, such as murine sarcoma virus, mouse mammary tumor virus, Moloney murine leukemia virus and Rous sarcoma virus. In addition, minichromosomes (e.g., MC and MC1), bacteriophages, phagemids, yeast artificial chromosomes, bacterial artificial chromosomes, virus particles, virus-like particles, cosmids and replicons can also be used.

[0100] GAS marker polynucleotides can be isolated from nucleic acid sequences present in samples, such as blood, serum, plasma, urine, feces, cerebrospinal fluid, amniotic fluid, wound exudate, or tissue from an infected subject. GAS marker polynucleotides can also be synthesized in the laboratory using automatic synthesizers or the polynucleotides can be amplified from either genomic DNA or cDNA encoding the polypeptides.

[0101] Statistically different levels", "significantly altered levels", or "significant difference" in levels of markers in a patient sample compared to a control or standard (e.g. normal levels or levels in other samples from a patient) may represent levels that are higher or lower than the standard error of the detection assay. In particular embodiments, the levels may be 1.5, 2, 3, 4, 5, or 6 times higher or lower than the control or standard.

[0102] "Microarray" and "array," refer to nucleic acid or nucleotide arrays or protein or peptide arrays that can be used to detect biomolecules associated with a GAS disease, for instance to measure gene expression. A variety of arrays are made in research and manufacturing facilities worldwide, some of which are available commercially. By way of example, spotted arrays and in situ synthesized arrays are two kinds of nucleic acid arrays that differ in the manner in which the nucleic acid materials are placed onto the array substrate. A widely used in situ synthesized oligonucleotide array is GeneChip™ made by Affymetrix, Inc. Oligonucleotide probes that are 20- or 25-bases long can be synthesized in silico on the array substrate. These arrays can achieve high densities (e.g., more than 40,000 genes per cm^2). Generally spotted arrays have lower densities, but the probes, typically partial cDNA molecules, are much longer than 20- or 25-mers. Examples of spotted cDNA arrays include LifeArray made by Incyte Genomics and DermArray made by IntegriDerm (or Invitrogen). Pre-synthesized and amplified cDNA sequences are attached to the substrate of spotted arrays. Protein and peptide arrays also are known (see for example, Zhu et al., *Science* 293:2101 (2001).

[0103] "Binding agent" refers to a substance such as a polypeptide or antibody that specifically binds to one or more GAS markers. A substance "specifically binds" to one or more GAS markers if it reacts at a detectable level with one or more GAS markers, and does not react detectably with peptides containing an unrelated or different sequence. Binding properties may be assessed using an ELISA, which may be readily performed by those skilled in the art (see for example, Newton et al, Develop. Dynamics 197: 1-13, 1993).

[0104] A binding agent may be a ribosome, with or without a peptide component, an aptamer, an RNA molecule, or a polypeptide. A binding agent may be a polypeptide that comprises one or more GAS marker sequence, a peptide variant thereof, or a non-peptide mimetic of such a sequence.

[0105] An aptamer includes a DNA or RNA molecule that binds to nucleic acids and proteins. An aptamer that binds to a protein (or binding domain) of a GAS marker can be produced using conventional techniques, without undue experimentation. (For example, see the following publications describing in vitro selection of aptamers: Klug et al., Mol. Biol. Reports 20:97-107 (1994); Wallis et al., Chem. Biol. 2:543-552 (1995); Ellington, Curr. Biol. 4:427-429 (1994); Lato et al., Chem. Biol. 2:291-303 (1995); Conrad et al., Mol. Div. 1:69-78 (1995); and Uphoff et al., Curr. Opin. Struct. Biol. 6:281-287 (1996)).

[0106] Antibodies for use in the present invention include but are not limited to monoclonal antibodiesm, polyclonal antibodies, immunologically active fragments (e.g. Fab, (Fab)$_2$ Fab', and Fav'-SH fragments), antibody heavy chains, humanized antibodies, antibody light chains, genetically engineered single chain F, molecules (Ladner et al, U.S. Pat. No. 4,946,778), chimeric antibodies, for example, antibodies which contain the binding specificity of murine antibodies, but in which the remaining portions are of human origin, or derivatives, such as enzyme conjugates or labelled derivatives. An antibody can be any antibody class, including IgG, IgM, IgA, IgD and IgE. In an embodiment of the invention, antibodies are reactive against a GAS marker if they bind with a K_a of greater than or equal to 10^{-7} M.

[0107] Antibodies including monoclonal and polyclonal antibodies, fragments and chimeras, may be prepared using methods known to those skilled in the art. Isolated native or recombinant GAS markers may be utilized to prepare antibodies. An antibody can be made in vivo in suitable laboratory animals or in vitro using recombinant procedures or chemical techniques. (See, for example, Kohler et al. (1975) Nature 256:495-497; Kozbor et al. (1985) J. Immunol. Methods 81:31-42; Cote et al. (1983) Proc Natl Acad Sci 80:2026-2030; and Cole et al. (1984) Mol Cell Biol 62:109-120 for the preparation of monoclonal antibodies; Huse et al. (1989) Science 246:1275-1281 for the preparation of monoclonal Fab fragments; Pound (1998) Immunochemical Protocols, Humana Press, Totowa, N.J. for the preparation of phagemid or B-lymphocyte immunoglobulin libraries to identify antibodies; U.S. Pat. No. 4,676,980 for methods for chemically constructing antibodies; U.S. Pat. No. 5,482,856, Jones et al, Nature 321:522, 1986; Reichmann et al., Nature 332:323, 1988, and Presta, Curr. Op Struct. Biol. 2:593 1992, for methods for producing chimeric antibodies). Antibodies specific for a GAS marker may also be obtained from scientific or commercial sources.

[0108] Antibodies against GAS marker polypeptides comprising epitopes can also be readily produced. By way of example, hybridomas producing antibodies specific for GAS marker polypeptides derived from normal B cells obtained from a mammal immunized with GAS marker polypeptides can be identified using RIA or ELISA and isolated by cloning or limited dilution. The clones can be further screened to identify clones producing antibodies specific for GAS marker polypeptides. Monoclonal antibodies can be screened for specificity using procedures known in the art such as an ELISA. Isotopes of monoclonal antibodies can be selected from an initial fusion or prepared from a parental hybridoma secreting a different isotype using a sib selection technique to isolate class-switch variants. [See, for example, Steplewski et al, PNAS USA 82:8653, 1985 and Spria et al, J. Immunolog. Meth. 74:307, 1984.]

Markers

[0109] The invention provides a set of markers correlated with GAS disease. A set of these markers identified as useful for detection, diagnosis, prevention and therapy of GAS disease comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 or more of the polynucleotides and polypeptides listed in Tables 3, 4 and 5. The invention provides a marker set that distinguish GAS disease and uses therefore comprising or consisting of one or more polypeptides or polynucleotides listed in Tables 3, 4 and 5.

[0110] In an aspect, the invention provides a method for classifying a GAS disease comprising detecting a difference in the expression of a first plurality of GAS markers relative to a control, the first plurality of GAS markers consisting of one or more polypeptides or polynucleotides listed in Tables 3, 4 and 5. In an aspect, the control comprises markers derived from a pool of samples from individual patients with no GAS disease.

[0111] Any of the markers provided herein may be used alone or with other markers of GAS disease, or with markers for other phenotypes or conditions.

Nucleic Acid Methods/Assays

[0112] As noted herein a GAS disease may be detected based on the amount/level of GAS marker polynucleotides in a sample. Techniques for detecting polynucleotides such as polymerase chain reaction (PCR) and hybridization assays are well known in the art.

[0113] Probes may be used in hybridization techniques to detect GAS marker polynucleotides. The technique generally involves contacting and incubating nucleic acids (e.g. recombinant DNA molecules, cloned genes) obtained from a sample from a patient or other cellular source with a probe under conditions favorable for the specific annealing of the probes to complementary sequences in the nucleic acids. After incubation, the non-annealed nucleic acids are removed, and the presence of nucleic acids that have hybridized to the probe if any are detected.

[0114] Nucleotide probes for use in the detection of nucleic acid sequences in samples may be constructed using conventional methods known in the art. Suitable probes may be based on nucleic acid sequences encoding at least 5 sequential amino acids from regions of a GAS marker, preferably they comprise 10-200, more particularly 10-30, 10-40, 20-50, 40-80, 50-150, 80-120 nucleotides in length.

[0115] The probes may comprise DNA or DNA mimics (e.g., derivatives and analogues) corresponding to a portion of an organism's genome, or complementary RNA or RNA mimics. Mimics are polymers comprising subunits capable of specific, Watson-Crick-like hybridization with DNA, or of specific hybridization with RNA. The nucleic acids can be modified at the base moiety, at the sugar moiety, or at the phosphate backbone.

[0116] DNA can be obtained using standard methods such as polymerase chain reaction (PCR) amplification of genomic DNA or cloned sequences. (See, for example, in Innis et al., eds., 1990, PCR Protocols: A Guide to Methods and Applications, Academic Press Inc., San Diego, Calif.). Computer programs known in the art can be used to design primers with the required specificity and optimal amplification properties, such as Oligo version 5.0 (National Biosciences). Controlled robotic systems may be useful for isolating and amplifying nucleic acids.

[0117] A nucleotide probe may be labeled with a detectable substance such as a radioactive label that provides for an adequate signal and has sufficient half-life such as ^{32}P, ^{3}H, ^{14}C or the like. Other detectable substances that may be used include antigens that are recognized by a specific labeled antibody, fluorescent compounds, enzymes, antibodies specific for a labeled antigen, and luminescent compounds. An appropriate label may be selected having regard to the rate of hybridization and binding of the probe to the nucleotide to be detected and the amount of nucleotide available for hybridization. Labeled probes may be hybridized to nucleic acids on solid supports such as nitrocellulose filters or nylon membranes as generally described in Sambrook et al, 1989, Molecular Cloning, A Laboratory Manual (2nd ed.). The nucleic acid probes may be used to detect GAS marker polynucleotides. The nucleotide probes may also be useful in the diagnosis of a GAS disease involving one or more GAS markers, in monitoring the progression of such disorder, or monitoring a therapeutic treatment.

[0118] The detection of GAS marker polynucleotides may involve the amplification of specific gene sequences using an amplification method such as polymerase chain reaction (PCR), followed by the analysis of the amplified molecules using techniques known to those skilled in the art. Suitable primers can be routinely designed by one of skill in the art.

[0119] By way of example, at least two oligonucleotide primers may be employed in a PCR based assay to amplify a portion of a polynucleotide encoding one or more GAS marker derived from a sample, wherein at least one of the oligonucleotide primers is specific for (i.e. hybridizes to) a polynucleotide encoding the GAS marker. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis.

[0120] In order to maximize hybridization under assay conditions, primers and probes employed in the methods of the invention generally have at least about 60%, preferably at least about 75%, and more preferably at least about 90% identity to a portion of a polynucleotide encoding a GAS marker; that is, they are at least 10 nucleotides, and preferably at least 20 nucleotides in length. In an embodiment the primers and probes are at least about 10-40 nucleotides in length.

[0121] Hybridization and amplification techniques described herein may be used to assay qualitative and quantitative aspects of GAS marker polynucleotide expression. For example, RNA may be isolated from a cell type or tissue known to express a GAS marker polynucleotide and tested utilizing the hybridization (e.g. standard Northern analyses) or PCR techniques referred to herein.

[0122] The primers and probes may be used in the above-described methods in situ i.e. directly on tissue sections (fixed and/or frozen) of patient tissue obtained from biopsies or resections.

[0123] In an aspect of the invention, a method is provided employing reverse transcriptase-polymerase chain reaction (RT-PCR), in which PCR is applied in combination with reverse transcription. Generally, RNA is extracted from a sample tissue using standard techniques (for example, guanidine isothiocyanate extraction as described by Chomcynski and Sacchi, Anal. Biochem. 162:156-159, 1987) and is reverse transcribed to produce cDNA. The cDNA is used as a template for a polymerase chain reaction. The cDNA is hybridized to a set of primers, at least one of which is specifically designed against a GAS marker sequence. Once the primer and template have annealed a DNA polymerase is employed to extend from the primer, to synthesize a copy of the template. The DNA strands are denatured, and the procedure is repeated many times until sufficient DNA is generated to allow visualization by ethidium bromide staining and agarose gel electrophoresis.

[0124] Amplification may be performed on samples obtained from a subject with a suspected GAS disease and an individual who is not afflicted with a GAS disease. The reaction may be performed on several dilutions of cDNA spanning at least two orders of magnitude. A statistically significant difference in expression in several dilutions of the subject sample as compared to the same dilutions of the non-disease sample may be considered positive for the presence of a GAS disease.

[0125] In an embodiment, the invention provides methods for determining the presence or absence of a GAS disease in a subject comprising (a) contacting a sample obtained from the subject with oligonucleotides that hybridize to GAS marker polynucleotides; and (b) detecting in the sample a level of nucleic acids that hybridize to the polynucleotides relative to a predetermined cut-off value, and therefrom determining the presence or absence of a GAS disease in the subject. In an aspect, the GAS marker polynucleotides are one or more of the polynucleotides listed in Tables 3, 4 and 5.

[0126] The invention provides a method wherein an GAS marker mRNA is detected by (a) isolating mRNA from a sample and combining the mRNA with reagents to convert it to cDNA; (b) treating the converted cDNA with amplification reaction reagents and nucleic acid primers that hybridize to one or more GAS marker polynucleotides, to produce amplification products; (d) analyzing the amplification products to detect amounts of mRNA encoding GAS markers; and (e) comparing the amount of mRNA to an amount detected against a panel of expected values for normal subjects derived using similar nucleic acid primers.

[0127] GAS marker-positive samples or alternatively higher levels in patients compared to a control (e.g. non-infected individual) may be indicative of disease, late stage disease, and/or that the patient is not responsive to therapy.

[0128] In another embodiment, the invention provides methods for diagnosing or determining the presence or absence of a GAS disease in a subject comprising (a) contacting a sample obtained from the subject with oligonucleotides that hybridize to one or more GAS marker polynucleotides; and (b) detecting in the sample levels of nucleic acids that hybridize to the oligonucleotides relative to a predetermined cut-off value, and therefrom determining the presence or absence of a GAS disease in the subject.

[0129] In particular, the invention provides a method wherein a GAS marker mRNA is detected by (a) isolating mRNA from a sample and combining the mRNA with reagents to convert it to cDNA; (b) treating the converted cDNA with amplification reaction reagents and nucleic acid primers that hybridize to the GAS marker to produce amplification products; (d) analyzing the amplification products to detect an amount of the GAS marker mRNA; and (e) comparing the amount of mRNA to an amount detected against a panel of expected values for healthy individuals derived using similar nucleic acid primers.

[0130] Marker-positive samples or alternatively higher levels, in particular significantly higher levels of a GAS marker in patients compared to a control (e.g. normal) are indicative of a GAS disease.

[0131] Oligonucleotides or longer fragments derived from GAS marker polynucleotides may be used as targets in a microarray. The microarray can be used to simultaneously monitor the expression levels of large numbers of genes and to identify genetic variants and mutations. The information from the microarray may be used to determine gene function, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents.

[0132] The preparation, use, and analysis of microarrays are well known to a person skilled in the art. (See, for example, Brennan, T. M. et al. (1995) U.S. Pat. No. 5,474,796; Schena, et al. (1996) Proc. Natl. Acad. Sci. 93:10614-10619; Baldeschweiler et al. (1995), PCT Application WO95/251116; Shalon, D. et al. (I 995) PCT application WO95/35505; Heller, R. A. et al. (1997) Proc. Natl. Acad. Sci. 94:2150-2155; and Heller, M. J. et al. (1997) U.S. Pat. No. 5,605,662.)

[0133] Thus, the invention also includes an array comprising one or more GAS marker polynucleotides and optionally other markers. The array can be used to assay expression of GAS marker polynucleotides in the array. The invention allows the quantitation of expression of one or more GAS marker polynucleotides.

[0134] Microarrays typically contain at separate sites nanomolar quantities of individual genes, cDNAs, or ESTs on a substrate (e.g., nitrocellulose or silicon plate), or photolithographically prepared glass substrate. The arrays are hybridized to cDNA probes using conventional techniques with gene-specific primer mixes. The target polynucleotides to be analyzed are isolated, amplified and labeled, typically with fluorescent labels, radiolabels or phosphorous label probes. After hybridization is completed, the array is inserted into the scanner, where patterns of hybridization are detected. Data are collected as light emitted from the labels incorporated into the target, which becomes bound to the probe array. Probes that completely match the target generally produce stronger signals than those that have mismatches. The sequence and position of each probe on the array are known, and thus by complementarity, the identity of the target nucleic acid applied to the probe array can be determined.

[0135] Microarrays are prepared by selecting polynucleotide probes and immobilizing them to a solid support or surface. The probes may comprise DNA sequences, RNA sequences, copolymer sequences of DNA and RNA, DNA and/or RNA analogues, or combinations thereof. The probe sequences may be full or partial fragments of genomic DNA, or they may be synthetic oligonucleotide sequences synthesized either enzymatically in vivo, enzymatically in vitro (e.g., by PCR), or non-enzymatically in vitro.

[0136] The probe or probes used in the methods of the invention can be immobilized to a solid support or surface which may be either porous or non-porous. For example, the probes can be attached to a nitrocellulose or nylon membrane or filter covalently at either the 3' or the 5' end of the polynucleotide probe. The solid support may be a glass or plastic surface. In an aspect of the invention, hybridization levels are measured to microarrays of probes consisting of a solid support on the surface of which are immobilized a population of polynucleotides, such as a population of DNA or DNA mimics, or, alternatively, a population of RNA or RNA mimics. A solid support may be a nonporous or, optionally, a porous material such as a gel.

[0137] In accordance with embodiments of the invention, a microarray is provided comprising a support or surface with an ordered array of hybridization sites or "probes" each representing one of the markers described herein. The microarrays can be addressable arrays, and in particular positionally addressable arrays. Each probe of the array is typically located at a known, predetermined position on the solid support such that the identity of each probe can be determined from its position in the array. In preferred embodiments, each probe is covalently attached to the solid support at a single site.

[0138] Microarrays used in the present invention are preferably (a) reproducible, allowing multiple copies of a given array to be produced and easily compared with each other; (b) made from materials that are stable under hybridization conditions; (c) small, (e.g., between 1 cm^2 and 25 cm^2, between 12 cm^2 and 13 cm^2, or 3 cm^2; and (d) comprise a unique set of binding sites that will specifically hybridize to the product of a single gene in a cell (e.g., to a specific mRNA, or to a specific cDNA derived therefrom). However, it will be appreciated that larger arrays may be used particularly in screening arrays, and other related or similar sequences will cross hybridize to a given binding site.

[0139] In accordance with an aspect of the invention, the microarray is an array in which each position represents one of the GAS marker polynucleotides described herein. Each position of the array can comprise a DNA or DNA analogue based on genomic DNA to which a particular RNA or cDNA transcribed from a genetic marker can specifically hybridize. A DNA or DNA analogue can be a synthetic oligomer or a gene fragment. In an embodiment, probes representing each of the GAS markers is present on the array.

[0140] Probes for the microarray can be synthesized using N-phosphonate or phosphoramidite chemistries (Froehler et al., 1986, Nucleic Acid Res. 14:5399-5407; McBride et al., 1983, Tetrahedron Lett. 24:246-248). Synthetic sequences are typically between about 10 and about 500 bases, 20-100 bases, or 40-70 bases in length. Synthetic nucleic acid probes can include non-natural bases, such as, without limitation, inosine. Nucleic acid analogues such as peptide nucleic acid may be used as binding sites for hybridization. (see, e.g., Egholm et al., 1993, Nature 363:566-568; U.S. Pat. No. 5,539,083).

[0141] Probes can be selected using an algorithm that takes into account binding energies, base composition, sequence complexity, cross-hybridization binding energies, and secondary structure (see Friend et al., International Patent Publication WO 01/05935, published Jan. 25, 2001).

[0142] Positive control probes, (e.g., probes known to be complementary and hybridize to sequences in the target polynucleotides), and negative control probes, (e.g., probes known to not be complementary and hybridize to sequences in the target polynucleotides) are typically included on the array. Positive controls can be synthesized along the perimeter of the array or synthesized in diagonal stripes across the array. A reverse complement for each probe can be next to the position of the probe to serve as a negative control.

[0143] The probes can be attached to a solid support or surface, which may be made from glass, plastic (e.g., polypropylene, nylon), polyacrylamide, nitrocellulose, gel, or other porous or nonporous material. The probes can be printed on surfaces such as glass plates (see Schena et al., 1995, Science 270:467-470). This method may be particularly useful for preparing microarrays of cDNA (See also, DeRisi et al., 1996, Nature Genetics 14:457-460; Shalon et al., 1996, Genome Res. 6:639-645; and Schena et al., 1995, Proc. Natl. Acad. Sci. U.S.A. 93:10539-11286).

[0144] High-density oligonucleotide arrays containing thousands of oligonucleotides complementary to defined sequences, at defined locations on a surface can be produced using photolithographic techniques for synthesis in situ (see, Fodor et al., 1991, Science 251:767-773; Pease et al., 1994, Proc. Natl. Acad. Sci. U.S.A. 91:5022-5026; Lockhart et al., 1996, Nature Biotechnology 14:1675; U.S. Pat. Nos. 5,578,832; 5,556,752; and 5,510,270) or other methods for rapid synthesis and deposition of defined oligonucleotides (Blanchard et al., Biosensors & Bioelectronics 11:687-690). Using these methods oligonucleotides (e.g., 60-mers) of known sequence are synthesized directly on a surface such as a derivatized glass slide. The array produced may be redundant, with several oligonucleotide molecules per RNA.

[0145] Microarrays can be made by other methods including masking (Maskos and Southern, 1992, Nuc. Acids. Res. 20:1679-1684). In an embodiment, microarrays of the present invention are produced by synthesizing polynucleotide probes on a support wherein the nucleotide probes are attached to the support covalently at either the 3' or the 5' end of the polynucleotide.

[0146] The invention provides microarrays comprising a disclosed marker set. In one embodiment, the invention provides a microarray for distinguishing GAS disease samples comprising a positionally-addressable array of polynucleotide probes bound to a support, the polynucleotide probes comprising a plurality of polynucleotide probes of different nucleotide sequences, each of the different nucleotide sequences comprising a sequence complementary and hybridizable to a plurality of genes, the different nucleotide sequences selected from the group consisting of the polynucleotides listed in Tables 3, 4 and 5.

[0147] The invention provides gene marker sets that distinguish GAS disease and uses thereof. In an aspect, the invention provides a method for classifying a GAS disease comprising detecting a difference in the expression of a first plurality of genes relative to a control, the first plurality of genes consisting of 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 or 25 or more of the genes listed in Tables 3, 4 and 5. In another specific aspect, the control comprises nucleic acids derived from a pool of samples from individual control patients.

Protein Methods

[0148] Binding agents may be used for a variety of diagnostic and assay applications. There are a variety of assay formats known to the skilled artisan for using a binding agent to detect a target molecule in a sample. (For example, see Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988). In general, the presence or absence of a GAS disease in a subject may be determined by (a) contacting a sample from the subject with a binding agent; (b) detecting in the sample a level of a GAS marker polypeptide that binds to the binding agent; and (c) comparing the level of protein with a predetermined standard or cut-off value.

[0149] In particular embodiments of the invention, the binding agent is an antibody. Antibodies specifically reactive with one or more GAS marker polypeptide, or derivatives, such as enzyme conjugates or labeled derivatives, may be used to detect one or more GAS marker polypeptide in various samples (e.g. biological materials). They may be used as diagnostic or prognostic reagents and they may be used to detect abnormalities in the levels of one or more GAS marker polypeptide, and/or temporal, tissue, cellular, or subcellular location of one or more GAS marker polypeptide. Antibodies may also be used to screen potentially therapeutic compounds in vitro to determine their effects on GAS diseases involving one or more GAS marker proteins and other conditions. In vitro immunoassays may also be used to assess or monitor the efficacy of particular therapies.

[0150] In an aspect, the invention provides a method for monitoring or diagnosing a GAS disease in a subject by quantitating one or more GAS marker polypeptides in a biological sample from the subject comprising reacting the sample with antibodies specific for one or more GAS marker polypeptides, which are directly or indirectly labeled with detectable substances and detecting the detectable substances. In a particular embodiment of the invention, GAS marker polypeptides are quantitated or measured.

[0151] In an aspect of the invention, a method for diagnosing or detecting a GAS disease is provided comprising:

[0152] (a) obtaining a sample suspected of containing one or more GAS marker polypeptides associated with a GAS disease;

[0153] (b) contacting said sample with antibodies that specifically bind to the GAS marker polypeptides under conditions effective to bind the antibodies and form complexes;

[0154] (c) measuring the amount of GAS marker polypeptides present in the sample by quantitating the amount of the complexes; and

[0155] (d) comparing the amount of GAS marker polypeptides present in the samples with the amount of GAS marker polypeptides in a control, wherein a change or significant difference in the amount of GAS marker polypeptides in the sample compared with the amount in the control is indicative of a GAS disease.

[0156] In an embodiment, the invention contemplates a method for monitoring the progression of a GAS disease in an individual, comprising:

[0157] (a) contacting antibodies which bind to one or more GAS marker polypeptides with a sample from the individual so as to form complexes comprising the antibodies and one or more GAS marker polypeptides in the sample;

[0158] (b) determining or detecting the presence or amount of complex formation in the sample;

[0159] (c) repeating steps (a) and (b) at a point later in time; and

[0160] (d) comparing the result of step (b) with the result of step (c), wherein a difference in the amount of complex formation is indicative of disease, disease stage, and/or progression of the disease in said individual.

[0161] The amount of complexes may also be compared to a value representative of the amount of the complexes from an individual not afflicted with a GAS disease at different stages. A significant difference in complex formation may be indicative of advanced disease or an unfavourable prognosis.

[0162] In embodiments of the methods of the invention, selected GAS markers detected in samples and higher levels, in particular significantly higher levels, compared to a control (e.g. normal) is indicative of a GAS disease.

[0163] Antibodies may be used to detect and quantify one or more GAS marker polypeptides in a sample in order to diagnose and treat a GAS disease. Immunohistochemical methods for the detection of antigens in tissue samples are well known in the art. For example, immunohistochemical methods are described in Taylor, Arch. Pathol. Lab. Med. 102:112 (1978). Briefly, in the context of the present invention, a tissue sample obtained from a subject suspected of having a GAS disease is contacted with antibodies, preferably monoclonal antibodies recognizing one or more GAS marker polypeptides. The site at which the antibodies are bound is determined by selective staining of the sample by standard immunohistochemical procedures. The same procedure may be repeated on the same sample using other antibodies that recognize one or more GAS marker polypeptides. Alternatively, a sample may be contacted with antibodies against one or more GAS marker polypeptides simultaneously, provided that the antibodies are labeled differently or are able to bind to a different label.

[0164] Antibodies may be used in any known immunoassays that rely on the binding interaction between antigenic determinants of one or more GAS marker polypeptide and the antibodies. Immunoassay procedures for in vitro detection of antigens in fluid samples are also well known in the art. [See for example, Paterson et al., Int. J. Can. 37:659 (1986) and Burchell et al., Int. J. Can. 34:763 (1984) for a general description of immunoassay procedures]. Qualitative and/or quantitative determinations of one or more GAS marker in a sample may be accomplished by competitive or non-competitive immunoassay procedures in either a direct or indirect format. Detection of one or more GAS marker polypeptide using antibodies can be done utilizing immunoassays which are run in either the forward, reverse or simultaneous modes. Examples of immunoassays are radioimmunoassays (RIA), enzyme immunoassays (e.g. ELISA), immunofluorescence, immunoprecipitation, latex agglutination, hemagglutination, histochemical tests, and sandwich (immunometric) assays. These terms are well understood by those skilled in the art. A person skilled in the art will know, or can readily discern, other immunoassay formats without undue experimentation.

[0165] According to an embodiment of the invention, an immunoassay for detecting one or more GAS marker polypeptides in a biological sample comprises contacting binding agents that specifically bind to GAS marker polypeptides in the sample under conditions that allow the formation of first complexes comprising a binding agent and GAS marker polypeptides and determining the presence or amount of the complexes as a measure of the amount of GAS marker polypeptides contained in the sample. In a particular embodiment, the binding agents are labeled differently or are capable of binding to different labels.

[0166] An antibody microarray in which binding sites comprise immobilized, preferably monoclonal, antibodies specific to a substantial fraction of GAS marker polypeptides of interest can be utilized in the present invention. Antibody arrays can be prepared using methods known in the art [(see for example, Zhu et al., *Science* 293:2101 (2001) and reference 20].

[0167] Antibodies specific for one or more GAS marker polypeptides may be labelled with a detectable substance and localised in biological samples based upon the presence of the detectable substance. Examples of detectable substances include, but are not limited to, the following: radioisotopes (e.g., ^{3}H, ^{14}C, ^{35}S, ^{125}I, ^{131}I), fluorescent labels (e.g., FITC, rhodamine, lanthanide phosphors), luminescent labels such as luminol; enzymatic labels (e.g., horseradish peroxidase, beta-galactosidase, luciferase, alkaline phosphatase, and acetylcholinesterase), biotinyl groups (which can be detected by marked avidin e.g., streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods), predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, labels are attached via spacer arms of various lengths to reduce potential steric hindrance. Antibodies may also be coupled to electron dense substances, such as ferritin or colloidal gold, which are readily visualised by electron microscopy.

[0168] One of the ways an antibody can be detectably labeled is to link it directly to an enzyme. The enzyme when later exposed to its substrate will produce a product that can be detected. Examples of detectable substances that are enzymes are horseradish peroxidase, beta-galactosidase, luciferase, alkaline phosphatase, acetylcholinesterase, malate dehydrogenase, ribonuclease, urease, catalase, glucose-6-phosphate, staphylococcal nuclease, delta-5-steriod isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate, triose phosphate isomerase, asparaginase, glucose oxidase, and acetylcholine esterase.

[0169] For increased sensitivity in an immunoassay system a fluorescence-emitting metal atom such as Eu (europium) and other lanthanides can be used. These can be attached to the desired molecule by means of metal-chelating groups such as DTPA or EDTA.

[0170] A bioluminescent compound may also be used as a detectable substance. Bioluminescence is a type of chemiluminescence found in biological systems where a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent molecule is determined by detecting the presence of luminescence. Examples of bioluminescent detectable substances are luciferin, luciferase and aequorin.

[0171] Indirect methods may also be employed in which the primary antigen-antibody reaction is amplified by the introduction of a second antibody, having specificity for the antibody reactive against one or more GAS marker polypeptides. By way of example, if the antibody having specificity against one or more GAS marker polypeptides is a rabbit IgG antibody, the second antibody may be goat anti-rabbit gamma-globulin labelled with a detectable substance as described herein.

[0172] Methods for conjugating or labelling the antibodies discussed above may be readily accomplished by one of ordinary skill in the art. (See for example Inman, Methods In Enzymology, Vol. 34, Affinity Techniques, Enzyme Purification: Part B, Jakoby and Wichek (eds.), Academic Press, New York, p. 30, 1974; and Wilchek and Bayer, "The Avidin-Biotin Complex in Bioanalytical Applications," Anal. Biochem. 171:1-32, 1988 re methods for conjugating or labelling the antibodies with enzyme or ligand binding partner).

[0173] Cytochemical techniques known in the art for localizing antigens using light and electron microscopy may be used to detect one or more GAS marker polypeptides. Generally, antibodies may be labeled with detectable substances and one or more GAS marker polypeptides may be localised in tissues and cells based upon the presence of the detectable substances.

[0174] In the context of the methods of the invention, the sample, binding agents (e.g. antibodies specific for one or more GAS marker polypeptides), or one or more GAS marker polypeptides may be immobilized on a carrier, substrate or support. Examples of suitable carriers, substrates or supports are agarose, cellulose, nitrocellulose, dextran, Sephadex, Sepharose, liposomes, carboxymethyl cellulose, polyacrylamides, polystyrene, gabbros, filter paper, magnetite, ion-exchange resin, plastic film, plastic tube, glass, polyamine-methyl vinyl-ether-maleic acid copolymer, amino acid copolymer, ethylene-maleic acid copolymer, nylon, silk, etc. A carrier, support or substrate can comprise microtiter wells, magnetic beads, non-magnetic beads, columns, matrices, membranes, fibrous mats composed of synthetic or natural fibers (e.g., glass or cellulose-based materials or thermoplastic polymers, such as, polyethylene, polypropylene, or polyester), sintered structures composed of particulate materials (e.g., glass or various thermoplastic polymers), or cast membrane films composed of nitrocellulose, nylon, polysulfone or the like (generally synthetic in nature. The support material may have any possible configuration including spherical (e.g. bead), cylindrical (e.g. inside surface of a test tube or well, or the external surface of a rod), or flat (e.g. sheet, test strip). Thus, the carrier, substrate or support may be in the shape of, for example, a tube, test plate, well, beads, disc, sphere, film, sheet, etc. A support or substrate material may be coated onto or bonded or laminated to appropriate inert carriers, such as paper, glass, plastic films, or fabrics. The immobilized sample, binding agents (e.g. antibodies specific for one or more GAS marker polypeptides), or one or more GAS marker polypeptides may be prepared by reacting the material with a suitable insoluble carrier using known chemical or physical methods, for example, cyanogen bromide coupling. An antibody may be indirectly immobilized using a second antibody specific for the antibody. For example, mouse antibody specific for a GAS marker may be immobilized using sheep anti-mouse IgG Fc fragment specific antibody coated on the carrier or support.

[0175] Where a radioactive label is used as a detectable substance, one or more GAS marker polypeptides may be localized by radioautography. The results of radioautography may be quantitated by determining the density of particles in the radioautographs by various optical methods, or by counting the grains.

[0176] Time-resolved fluorometry may be used to detect a signal. For example, the method described in Christopoulos TK and Diamandis EP Anal Chem 1992:64:342-346 may be used with a conventional time-resolved fluorometer.

[0177] In accordance with an embodiment of the invention, a method is provided wherein one or more GAS marker polypeptides antibodies are directly or indirectly labelled with enzymes, substrates for the enzymes are added wherein the substrates are selected so that the substrates, or a reaction product of an enzyme and substrate, form fluorescent complexes with a lanthanide metal (e.g. europium, terbium, samarium, and dysprosium, preferably europium and terbium). A lanthanide metal is added and one or more GAS markers are quantitated in the sample by measuring fluorescence of the fluorescent complexes. Enzymes are selected based on the ability of a substrate of the enzyme, or a reaction product of the enzyme and substrate, to complex with lanthanide metals such as europium and terbium. Suitable enzymes and substrates that provide fluorescent complexes are described in U.S. Pat. No. 5,312,922 to Diamandis. Examples of suitable enzymes include alkaline phosphatase and β-galactosidase. Preferably, the enzyme is alkaline phosphatase.

[0178] Examples of enzymes and substrates for enzymes that provide such fluorescent complexes are described in U.S. Pat. No. 5,312,922 to Diamandis. By way of example, when the antibody is directly or indirectly labelled with alkaline phosphatase the substrate employed in the method may be 4-methylumbelliferyl phosphate, 5-fluorosalicyl phosphate, or diflunisal phosphate. The fluorescence intensity of the complexes is typically measured using a time-resolved fluorometer e.g. a CyberFluor 615 Immunoanalyzer (Nordion International; Kanata, Ontario).

[0179] One or more GAS marker polypeptides antibodies may also be indirectly labelled with an enzyme. For example, the antibodies may be conjugated to one partner of a ligand binding pair, and the enzyme may be coupled to the other partner of the ligand binding pair. Representative examples include avidin-biotin, and riboflavin-riboflavin binding protein. In an embodiment, the antibodies are biotinylated, and the enzyme is coupled to streptavidin. In another embodiment, an antibody specific for a GAS marker polypeptide antibody is labeled with an enzyme.

[0180] In accordance with an embodiment, the present invention provides means for determining one or more GAS marker polypeptides in a sample by measuring one or more GAS marker polypeptides by immunoassay. It will be evident to a skilled artisan that a variety of immunoassay methods can be used to measure one or more GAS marker polypeptides. In general, an immunoassay method may be competitive or non-competitive. Competitive methods typically employ an immobilized or immobilizable antibody to one or more GAS marker polypeptides and a labeled form of one or more GAS marker polypeptides. Sample GAS marker polypeptides and labeled GAS marker polypeptides compete for binding to antibodies to GAS marker polypeptides. After separation of the resulting labeled GAS marker polypeptides that have become bound to antibodies (bound fraction) from that which has remained unbound (unbound fraction), the amount of the label in either bound or unbound fraction is measured and may be correlated with the amount of GAS marker polypeptides in the test sample in any conventional manner, e.g., by comparison to a standard curve.

[0181] In an aspect, a non-competitive method is used for the determination of one or more GAS marker polypeptides, with the most common method being the "sandwich" method. In this assay, two antibodies to GAS marker polypeptides are employed. One of the antibodies to GAS marker polypeptides is directly or indirectly labeled (sometimes referred to as the "detection antibody") and the other is immobilized or immobilizable (sometimes referred to as the "capture antibody"). The capture and detection antibodies can be contacted simultaneously or sequentially with the test sample. Sequential methods can be accomplished by incubating the capture antibody with the sample, and adding the detection antibody at a predetermined time thereafter (sometimes referred to as the "forward" method); or the detection antibody can be incubated with the sample first and then the capture antibody added (sometimes referred to as the "reverse" method). After the necessary incubation(s) have occurred, to complete the assay, the capture antibody is separated from the liquid test mixture, and the label is measured in at least a portion of the separated capture antibody phase or the remainder of the liquid test mixture. Generally it is measured in the capture antibody phase since it comprises GAS markers bound by ("sandwiched" between) the capture and detection antibodies. In an embodiment, the label may be measured without separating the capture antibodies and liquid test mixture.

[0182] In a typical two-site immunometric assay for GAS marker polypeptides, one or both of the capture and detection antibodies are polyclonal antibodies or one or both of the capture and detection antibodies are monoclonal antibodies (i.e. polyclonal/polyclonal, monoclonal/monoclonal, or monoclonal/polyclonal). The label used in the detection antibody can be selected from any of those known conventionally in the art. The label may be an enzyme or a chemiluminescent moiety, but it can also be a radioactive isotope, a fluorophor, a detectable ligand (e.g., detectable by a secondary binding by a labeled binding partner for the ligand), and the like. In a particular aspect, the antibody is labelled with an enzyme which is detected by adding a substrate that is selected so that a reaction product of the enzyme and substrate forms fluorescent complexes. The capture antibody may be selected so that it provides a means for being separated from the remainder of the test mixture. Accordingly, the capture antibody can be introduced to the assay in an already immobilized or insoluble form, or can be in an immobilizable form, that is, a form which enables immobilization to be accomplished subsequent to introduction of the capture antibody to the assay. An immobilized capture antibody may comprise an antibody covalently or noncovalently attached to a solid phase such as a magnetic particle, a latex particle, a microtiter plate well, a bead, a cuvette, or other reaction vessel. An example of an immobilizable capture antibody is antibody which has been chemically modified with a ligand moiety, e.g., a hapten, biotin, or the like, and which can be subsequently immobilized by contact with an immobilized form of a binding partner for the ligand, e.g., an antibody, avidin, or the like. In an embodiment, the capture antibody may be immobilized using a species specific antibody for the capture antibody that is bound to the solid phase.

[0183] Antibodies specific for a GAS marker polypeptide may be used to isolate GAS organisms or GAS marker antigens by immunoaffinity columns. The antibodies may be conjugated to a substrate, support or carrier for example by adsorption or covalent linkage with or without a spacer group. The immobilized antibodies can be used to bind GAS organisms or GAS marker antigens from a sample. The GAS organisms or antigens can be recovered from the substrate, support or carrier using methods known to a skilled artisan (e.g., change in pH).

[0184] GAS markers can be used to detect antibodies or antibody fragments specific for GAS markers or a GAS disease in a test sample. In aspects of the invention, the sample is a biological sample including, for example, sera, blood, cells, plasma, or tissue from a mammal such as a horse, cat, dog or human. A test sample can be untreated, precipitated, fractionated, separated, diluted, concentrated, or purified before combining with a GAS marker polypeptide. Generally, the methods comprise contacting a GAS marker polypeptide with a test sample under conditions that allow a polypeptide/antibody complex or an immunocomplex, to form. A GAS marker polypeptide specifically binds to an antibody specific for a GAS marker polypeptide located in the sample.

[0185] Methods (i.e., assays) and conditions that can be used to detect antibody/polypeptide complex binding or immunocomplexes are known to persons skilled in the art and are discussed herein. For example, a method of the invention for detecting antibodies can comprise an assay selected from the group consisting of a microtiter plate assay, a reversible flow chromatographic binding assay, a lateral flow immunoassay, an enzyme linked immunosorbent assay, a radioimmunoassay, a hemaglutination assay, a western blot assay, a fluorescence polarization immunoassay and an indirect immunofluorescence assay.

[0186] Assays can use supports, substrates or carriers or can be performed by immunoprecipitation or any other methods that do not utilize solid phases. Where a solid phase is used, a GAS marker polypeptide is directly or indirectly attached to a solid support, substrate or a carrier described herein, for example, a microtiter well, magnetic bead, non-magnetic bead, column, matrix, membrane, fibrous mat composed of synthetic or natural fibers, sintered structure composed of particulate materials, or cast membrane film composed of nitrocellulose, nylon, polysulfone or the like. In an aspect of the invention, one or more GAS marker polypeptides are coated on a solid phase or substrate. A test sample suspected of containing an anti-GAS marker polypeptide antibody or fragment thereof is incubated with an indicator reagent comprising a detectable substance or label conjugated to an antibody or antibody fragment specific for a GAS marker polypeptide for a time and under conditions sufficient to form antigen/antibody complexes of either antibodies of the test sample to the GAS marker polypeptides of the solid phase or the indicator reagent conjugated to an antibody specific for GAS marker polypeptides to the GAS marker polypeptides of the solid phase. The reduction in binding of the indicator reagent to the solid phase can be quantitatively measured. A measurable reduction in the signal compared to the signal generated from a confirmed negative test sample indicates the presence of antibody to the GAS marker polypeptides in the test sample. This type of assay can quantitate the amount of antibodies specific for GAS marker polypeptides in a test sample.

[0187] In another aspect, one or more GAS marker polypeptides are coated onto a support or substrate and a GAS marker polypeptide is conjugated to a detectable substance or label and added to a test sample. This mixture is applied to the support or substrate. If GAS marker polypeptide antibodies are present in the test sample they will bind the polypeptide conjugated to the detectable substance and to the GAS marker polypeptide immobilized on the support. The polypeptide/antibody/detectable complex can then be detected. This type of assay can quantitate the amount of antibodies specific for GAS marker polypeptides in a test sample.

[0188] In another aspect, one or more GAS marker polypeptides are coated onto a support or substrate and the test sample is applied to the support or substrate and incubated. The solid support is washed to remove unbound components from the sample. If antibodies specific for GAS marker polypeptides are present in the test sample, they will bind to the polypeptide coated on the solid phase. This polypeptide/antibody complex can be detected using a second species-specific antibody that is conjugated to a detectable substance. The polypeptide/antibody/anti-species antibody detectable substance complex can then be detected. This type of assay can quantitate the amount of antibodies specific for GAS marker polypeptides in a test sample.

[0189] The formation of a polypeptide/antibody complex or a polypeptide/antibody/detectable substance complex can be detected by radiometric, colormetric, fluorometric, size-separation, or precipitation methods. A polypeptide/antibody complex can also be detected by the addition of a secondary antibody that is coupled to a detectable substance. Indicator reagents comprising detectable substances (labels) associated with an immunocomplex can be detected using the methods described above and include chromogenic agents, catalysts such as enzyme conjugates fluorescent compounds such as fluorescein and rhodamine, chemiluminescent compounds such as dioxetanes, acridiniums, phenanthridiniums, ruthenium, and luminol, radioactive elements, direct visual labels, as well as cofactors, inhibitors, magnetic particles, and the like.

[0190] The formation of a polypeptide/antibody complex is indicative of the presence of antibodies specific for GAS marker polypeptides in a test sample and therefore the methods of the invention can be used to diagnose GAS diseases or infections in a subject. The methods of the invention can also indicate the amount or quantity of antibodies specific for GAS marker polypeptides in a test sample. The amount of antibody present can be proportional to the signal generated, in particular the signal generated with indicator reagents where the detectable substance is an enzyme.

[0191] The above-described immunoassay methods and formats are intended to be exemplary and are not limiting.

Computer Systems

[0192] Analytic methods contemplated herein can be implemented by use of computer systems and methods described below and known in the art. Thus, the invention provides computer readable media comprising one or more GAS markers, and optionally other markers. "Computer readable media" refers to any medium that can be read and accessed directly by a computer, including but not limited to magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media. Thus, the invention contemplates computer readable medium having recorded thereon markers identified for patients and controls.

[0193] "Recorded" refers to a process for storing information on computer readable medium. The skilled artisan can readily adopt any of the presently known methods for recording information on computer readable medium to generate manufactures comprising information on one or more GAS markers, and optionally other markers.

[0194] A variety of data processor programs and formats can be used to store information on one or more GAS markers and other markers on computer readable medium. For example, the information can be represented in a word processing text file, formatted in commercially-available software such as WordPerfect and MicroSoft Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like. Any number of data processor structuring formats (e.g., text file or database) may be adapted in order to obtain computer readable medium having recorded thereon the marker information.

[0195] By providing the marker information in computer readable form, one can routinely access the information for a variety of purposes. For example, one skilled in the art can use the information in computer readable form to compare marker information obtained during or following therapy with the information stored within the data storage means.

[0196] The invention provides a medium for holding instructions for performing a method for determining whether a patient has a GAS disease, comprising determining the presence or absence of one or more GAS markers, and optionally other markers, and based on the presence or absence of the one or more GAS markers and optionally other markers, determining a GAS disease, and optionally recommending a procedure or treatment.

[0197] In an aspect of the invention a method is provided for detecting a GAS disease using a computer having a processor, memory, display, and input/output devices, the method comprising the steps of:

[0198] (a) creating records of one or more GAS markers, and optionally other markers of GAS disease in a sample suspected of containing GAS markers;

[0199] (b) providing a database comprising records of data comprising one or more GAS markers, and optionally other markers; and

[0200] (c) using a code mechanism for applying queries based upon a desired selection criteria to the data file in the database to produce reports of records of step (a) which provide a match of the desired selection criteria of the database of step (b), the presence of a match being a positive indication that the markers of step (a) have been isolated from a sample of an individual with a GAS disease.

[0201] In an aspect of the invention, the computer systems, components, and methods described herein are used to monitor disease or determine the stage of disease.

Kits

[0202] The invention also contemplates kits for carrying out the methods of the invention. Kits may typically comprise two or more components required for performing a diagnostic assay. Components include but are not limited to compounds, reagents, containers, and/or equipment.

[0203] The methods described herein may be performed by utilizing pre-packaged diagnostic kits comprising one or more specific GAS marker polynucleotide or antibody described herein, which may be conveniently used, e.g., in clinical settings to screen and diagnose patients and to screen and identify those individuals exhibiting a predisposition to developing a GAS disease.

[0204] In an embodiment, a container with a kit comprises a binding agent as described herein. By way of example, the kit may contain antibodies or antibody fragments which bind specifically to epitopes of one or more GAS marker polypeptides and optionally other markers, antibodies against the antibodies labelled with an enzyme; and a substrate for the enzyme. The kit may also contain microtiter plate wells, standards, assay diluent, wash buffer, adhesive plate covers, and/or instructions for carrying out a method of the invention using the kit.

[0205] In an aspect of the invention, the kit includes antibodies or fragments of antibodies which bind specifically to an epitope of one or more GAS marker polypeptide and means for detecting binding of the antibodies to their epitopes, either as concentrates (including lyophilized compositions), which may be further diluted prior to use or at the concentration of use, where the vials may include one or more dosages. Where the kits are intended for in vivo use, single dosages may be provided in sterilized containers, having the desired amount and concentration of agents. Containers that provide a formulation for direct use, usually do not require other reagents, as for example, where the kit contains a radiolabelled antibody preparation for in vivo imaging.

[0206] A kit may be designed to detect the level of GAS marker polynucleotides in a sample. In an embodiment, the polynucleotides encode one or more GAS marker polynucleotides listed in Tables 3, 4 and 5. Such kits generally comprise at least one oligonucleotide probe or primer, as described herein, that hybridizes to a polynucleotide encoding one or more GAS marker polypeptide. Such an oligonucleotide may be used, for example, within a PCR or hybridization procedure. Additional components that may be present within the kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate detection of a polynucleotide encoding one or more GAS marker polypeptide.

[0207] The invention provides a kit containing a microarray described herein ready for hybridization to target GAS polynucleotide markers, plus software for the analysis of the results. The software to be included with the kit comprises data analysis methods, in particular mathematical routines for marker discovery, including the calculation of correlation coefficients between clinical categories and marker expression. The software may also include mathematical routines for calculating the correlation between sample marker expression and control marker expression, using array-generated fluorescence data, to determine the clinical classification of the sample.

[0208] The reagents suitable for applying the screening methods of the invention to evaluate compounds may be packaged into convenient kits described herein providing the necessary materials packaged into suitable containers.

[0209] The invention contemplates a kit for assessing the presence of GAS, wherein the kit comprises antibodies specific for one or more GAS markers, or primers or probes for polynucleotides encoding same, and optionally probes, primers or antibodies specific for other markers associated with a GAS disease.

[0210] The invention comprises assay kits (e.g., articles of manufacture) for detecting anti-GAS marker polypeptide antibodies or antibody fragments in a sample. A kit comprises one or more GAS marker polypeptides and means for determining binding of the polypeptides to antibodies or antibody fragments in the sample. A kit can comprise a device containing one or more GAS marker polypeptides and instructions for use of the one or more polypeptides e.g., the identification of a GAS disease or GAS infection in a mammal. The kit can also comprise packaging material comprising a label that indicates that the one or more polypeptides of the kit can be used for the identification of a GAS disease or infection. Other components such as buffers, controls, and the like, known to those of ordinary skill in art, can be included in such test kits. The polypeptides, antibodies, assays, and kits of the invention are useful, for example, in the diagnosis of individual cases of GAS disease or infection in a patient, as well as epidemiological studies of GAS outbreaks.

[0211] The invention relates to a kit for assessing the suitability of each of a plurality of test compounds for inhibiting a GAS disease in a patient. The kit comprises reagents for assessing one or more GAS markers, and optionally a plurality of test agents or compounds.

Therapeutic Applications

[0212] One or more GAS markers may be targets for immunotherapy. Immunotherapeutic methods include the use of antibody therapy, in vivo vaccines, and ex vivo immunotherapy approaches.

[0213] In one aspect, the invention provides one or more antibodies specific for one or more GAS marker polypeptide that may be used systemically to treat a GAS disease associated with the marker. In particular, the GAS disease is strep throat, scarlet fever, impetigo, cellulitis-erysipelas, rheumatic fever, acute glomerular nephritis, endocarditis, or necrotizing fasciitis and one or more GAS marker antibodies may be used systemically to treat such disease.

[0214] Thus, the invention provides a method of treating a patient susceptible to, or having a disease that expresses one or more GAS marker polypeptide comprising administering to the patient an effective amount of an antibody that binds specifically to one or more GAS marker polypeptide.

[0215] One or more GAS marker antibodies may also be used in a method for selectively inhibiting the growth or, or killing GAS expressing one or more GAS marker comprising reacting one or more GAS marker antibody immunoconjugate or immunotoxin with the cell in an amount sufficient to inhibit the growth of, or kill GAS.

[0216] By way of example, unconjugated antibodies to GAS marker polypeptides may be introduced into a patient such that the antibodies bind to GAS expressing GAS marker polypeptides and mediate growth inhibition of such GAS (including the destruction thereof). In addition to unconjugated antibodies to GAS marker polypeptides, one or more GAS marker polypeptide antibodies conjugated to therapeutic agents (e.g. immunoconjugates) may also be used therapeutically to deliver the agent directly to one or more GAS expressing GAS marker polypeptides and thereby destroy the GAS. Examples of such agents include abrin, ricin A, *Pseudomonas* exotoxin, or diphtheria toxin.

[0217] In the practice of a method of the invention, GAS marker polypeptide antibodies capable of inhibiting the growth of GAS expressing GAS marker polypeptides are administered in a therapeutically effective amount to patients with a GAS disease. The invention may provide a specific and effective treatment for a GAS disease. The antibody therapy methods of the invention may be combined with other therapies including antibiotics.

[0218] GAS marker polypeptide antibodies useful in treating a GAS disease include those that are capable of initiating a potent immune response against the disease and those that are capable of direct cytotoxicity. In this regard, GAS marker polypeptide antibodies may elicit cell lysis by either complement-mediated or antibody-dependent cell cytotoxicity (ADCC) mechanisms, both of which require an intact Fc portion of the immunoglobulin molecule for interaction with effector cell Fc receptor sites or complement proteins.

[0219] GAS marker polypeptide antibodies that exert a direct biological effect on GAS may also be useful in the practice of the invention. Such antibodies may not require the complete immunoglobulin to exert the effect. Potential mechanisms by which such directly cytotoxic antibodies may act include inhibition of cell growth. The mechanism by which a particular antibody exerts an effect may be evaluated using any number of in vitro assays designed to determine ADCC, antibody-dependent macrophage-mediated cytotoxicity (ADMMC), complement-mediated cell lysis, and others known in the art.

[0220] The methods of the invention contemplate the administration of single GAS marker antibodies as well as combinations, or "cocktails", of different individual antibodies such as those recognizing different epitopes of other markers. Such cocktails may have certain advantages inasmuch as they contain antibodies that bind to different epitopes of GAS markers. Such antibodies in combination may exhibit synergistic therapeutic effects. In addition, the administration of one or more GAS marker polypeptide specific antibodies may be combined with other therapeutic agents, including but not limited to antibiotics. The GAS marker specific antibodies may be administered in their "naked" or unconjugated form, or may have therapeutic agents conjugated to them.

[0221] The GAS marker polypeptide specific antibodies used in the methods of the invention may be formulated into pharmaceutical compositions comprising a carrier suitable for the desired delivery method. Suitable carriers include any material which when combined with the antibodies retains the function of the antibody and is non-reactive with the subject's immune systems. Examples include any of a number of standard pharmaceutical carriers such as sterile phosphate buffered saline solutions, bacteriostatic water, and the like (see, generally, Remington: The Science and Practice of Pharmacy, 21st Edition. University of the Sciences in Philadelphia (Editor), Mack Publishing Company).

[0222] One or more GAS marker polypeptide specific antibody formulations may be administered via any route capable of delivering the antibodies to the disease site. Routes of administration include, but are not limited to, intravenous, intraperitoneal, intramuscular, intradermal, and the like. Preferably, the route of administration is by intravenous injection. Antibody preparations may be lyophilized and stored as a sterile powder, preferably under vacuum, and then reconstituted in bacteriostatic water containing, for example, benzyl alcohol preservative, or in sterile water prior to injection.

[0223] Treatment will generally involve the repeated administration of the antibody preparation via an acceptable route of administration such as intravenous injection (IV), at an effective dose. Dosages will depend upon various factors generally appreciated by those of skill in the art, including the type of disease and the severity, stage of the disease, the binding affinity and half life of the antibodies used, the degree of GAS marker expression in the patient, the extent of GAS markers, the desired steady-state antibody concentration level, frequency of treatment, and the influence of any therapeutic agents used in combination with the treatment method of the invention. Daily doses may range from about 0.1 to 100 mg/kg. Doses in the range of 10-500 mg antibodies per week may be effective and well tolerated, although even higher weekly doses may be appropriate and/or well tolerated. A determining factor in defining the appropriate dose is the amount of a particular antibody necessary to be therapeutically effective in a particular context. Repeated administrations may be required to achieve disease inhibition or regression. Direct administration of one or more GAS marker antibodies is also possible and may have advantages in certain situations.

[0224] Patients may be evaluated for serum GAS markers in order to assist in the determination of the most effective dosing regimen and related factors. Assay methods described herein, or similar assays, may be used for quantitating circulating GAS marker levels in patients prior to treatment. Such assays may also be used for monitoring throughout therapy, and may be useful to gauge therapeutic success in combination with evaluating other parameters such as serum levels of GAS markers.

[0225] The invention further provides vaccines formulated to contain one or more GAS marker or fragment thereof. In an embodiment, the invention provides a method of vaccinating an individual against one or more GAS marker polypeptide comprising the step of inoculating the individual with the marker or fragment thereof that lacks activity, wherein the inoculation elicits an immune response in the individual thereby vaccinating the individual against the marker.

[0226] Viral gene delivery systems may be used to deliver one or more GAS marker polynucleotides. Various viral gene delivery systems which can be used in the practice of this aspect of the invention include, but are not limited to, vaccinia, fowlpox, canarypox, adenovirus, influenza, poliovirus, adeno-associated virus, lentivirus, and sindbus virus (Restifo, 1996, Curr. Opin. Immunol. 8: 658-663). In aspects of the invention, vectors derived from retroviruses, adenovirus, herpes or vaccinia viruses, or from various bacterial plasmids, may be used to deliver polynucleotides encoding GAS marker polypeptides to a targeted site. Methods well known to those skilled in the art may be used to construct recombinant vectors that will express antisense polynucleotides for GAS marker polypeptides. (See, for example, the techniques described in Sambrook et al (supra) and Ausubel et al [5]). Methods for introducing vectors into cells or tissues include those methods discussed herein and which are suitable for in vivo, in vitro and ex vivo therapy. For ex vivo therapy, vectors may be introduced into stem cells obtained from a patient and clonally propagated for autologous transplant into the same patient (See U.S. Pat. Nos. 5,399,493 and 5,437,994). Delivery by transfection and by liposome are well known in the art. Non-viral delivery systems may also be employed by using naked DNA encoding one or more GAS marker polypeptide or fragment thereof introduced into the patient (e.g., intramuscularly) to induce a response.

[0227] Anti-idiotypic GAS marker polypeptide specific antibodies can also be used in therapy as a vaccine for inducing an immune response to GAS that express one or more GAS markers. The generation of anti-idiotypic antibodies is well known in the art and can readily be adapted to generate anti-idiotypic GAS marker polypeptide specific antibodies that mimic an epitope on one or more GAS marker polypeptides (see, for example, Wagner et al., 1997, Hybridoma 16: 33-40; Foon et al., 1995, J Clin Invest 96: 334-342). Such an antibody can be used in anti-idiotypic therapy as presently practiced with other anti-idiotypic antibodies directed against antigens associated with disease.

[0228] Genetic immunization methods may be utilized to generate prophylactic or therapeutic humoral and cellular immune responses directed against GAS expressing one or more GAS marker polypeptides. One or more DNA molecules encoding GAS markers, constructs comprising DNA encoding one or more GAS markers/immunogens and appropriate regulatory sequences may be injected directly into muscle or skin of an individual, such that the cells of the muscle or skin take-up the construct and express the encoded GAS markers/immunogens. The GAS markers/immunogens may be expressed as cell surface proteins or be secreted. Expression of one or more GAS markers results in the generation of prophylactic or therapeutic humoral and cellular immunity against a GAS disease. Various prophylactic and therapeutic genetic immunization techniques known in the art may be used.

[0229] In another aspect, the invention provides methods for selectively inhibiting GAS expressing GAS marker polypeptide by reacting any one or a combination of the immunoconjugates of the invention with the GAS in an amount sufficient to inhibit the GAS. Amounts include those that are sufficient to kill the GAS or sufficient to inhibit cell growth

[0230] One or more GAS markers and fragments thereof may be used in the treatment of a GAS disease in a subject. The GAS markers may be formulated into compositions for administration to subjects suffering from a GAS disease. Therefore, the present invention also relates to a composition comprising one or more GAS markers, or a fragment thereof, and a pharmaceutically acceptable carrier, excipient or diluent. A method for treating or preventing a GAS disease in a subject is also provided comprising administering to a patient in need thereof, one or more GAS markers, or a composition of the invention.

[0231] The invention further provides a method of inhibiting a GAS disease in a patient comprising:

[0232] (a) obtaining a sample containing GAS markers from the patient;

[0233] (b) separately maintaining aliquots of the sample in the presence of a plurality of test agents;

[0234] (c) comparing levels of one or more GAS markers in each aliquot;

[0235] (d) administering to the patient at least one of the test agents which alters the levels of the GAS markers in the aliquot containing that test agent, relative to the other test agents.

[0236] An active therapeutic substance described herein may be administered in a convenient manner such as by injection (subcutaneous, intravenous, etc.), oral administration, inhalation, transdermal application, or rectal administration. Depending on the route of administration, the active substance may be coated in a material to protect the substance from the action of enzymes, acids and other natural conditions that may inactivate the substance. Solutions of an active compound as a free base or pharmaceutically acceptable salt can be prepared in an appropriate solvent with a suitable surfactant. Dispersions may be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof, or in oils.

[0237] The compositions described herein can be prepared by per se known methods for the preparation of pharmaceutically acceptable compositions which can be administered to subjects, such that an effective quantity of the active substance is combined in a mixture with a pharmaceutically acceptable vehicle. Suitable vehicles are described, for example, in Remington's Pharmaceutical Sciences (Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., USA 1985; Remington: The Science and Practice of Pharmacy, 21st Edition. University of the Sciences in Philadelphia (Editor), Mack Publishing Company). On this basis, the compositions include, albeit not exclusively, solutions of the active substances in association with one or more pharmaceutically acceptable vehicles or diluents, and contained in buffered solutions with a suitable pH and iso-osmotic with the physiological fluids.

[0238] The compositions are indicated as therapeutic agents either alone or in conjunction with other therapeutic agents or other forms of treatment. The compositions of the invention may be administered concurrently, separately, or sequentially with other therapeutic agents or therapies.

[0239] The therapeutic activity of compositions and agents/compounds identified using a method of the invention and may be evaluated in vivo using a suitable animal model.

[0240] The following non-limiting examples are illustrative of the present invention:

EXAMPLE 1

[0241] The pathogenesis of invasive GAS infections was investigated using in vivo induced antigen technology (IVIAT) (See Handfield, M et al, 2000. Trends Microbiol. 8:336-339; Handfield, M et al., 2003. Methods Mol. Med. 71:225-242), a technique that relies on antibodies produced during a natural infection. The IVIAT scheme consists of three steps: (i) serum selection and adsorption, (ii) construction of a GAS genomic expression library, and screening of the GAS genomic library with the selected, pooled, absorbed sera.

Experimental Procedures

[0242] The materials and methods used in the studies in this example are set out below.

[0243] Bacterial strains, media and growth conditions: To obtain in vitro induced antigens, GAS strains (Table 1) were cultured overnight at 37° C. in Todd-Hewitt (TH) broth (Difco Laboratories, Detriot, Mich.), under either aerobic or microaerobic (5.0% CO_2) conditions and whole cells, cell extracts and spent media were prepared as described below. GAS strains for inoculation of mice were prepared as previously described (1). The *E. coli* strains utilized for the construction of the GAS genomic library were grown in Luria-Bertani (LB) broth (Difco Laboratories) at 37° C. under aerobic conditions.

[0244] In vitro antigen preparation: Equal volumes of each strain (Table 1) of GAS cultures grown to late-log phase were pooled, centrifuged, the spent media removed, and whole cells re-suspended in 1× phosphate-buffered saline (PBS). Cell extracts were prepared from whole cells that were concentrated 10-fold and processed with an FP120 Fastprep Machine (BIO 101, Mississauga, Canada) at a setting of 6.0 for 30 sec, placed on ice for 30 min to allow the beads to settle, and cell extracts removed by aspiration. Denatured cell extracts were obtained by placing cell extracts in a boiling water bath for 10 min. The pooled, cell-free supernatant was freeze-dried using a Benchtop 3.3/Vacu-Freeze Dryer (Vir-Tris Company, Gardiner, N.Y.) and re-suspended in 1×PBS. All antigen preparations were stored at −70° C., for up to 1 month, until ready for use.

[0245] Human Sera: Convalescent human sera, collected between 2 to 3 weeks following diagnosis, were selected from 14 of 21 patients with invasive GAS infections, such as NF and STSS (Table 2). Note, that these serum samples were not from the same patients as those from whom the 8 invasive GAS isolates were collected (Table 1). Hence, the strain and serum samples were not paired. Control human sera were obtained from human subjects with no previous history of invasive GAS infection.

[0246] Mice sera: Immunocompetent 4 week-old, female, crl:SKH1 (hrhr) hairless mice (Charles River Laboratories, Wilmington, Mass.) were utilized for the invasive subcutaneous infection model of GAS (1). This mouse model was used for generating anti-GAS mouse antibodies for screening the GAS genomic library. Two mice were infected with each of the 8 invasive GAS strains (Table 1) to give a total of 16 infected mice. The immunization protocol included an initial inoculation of 10^6 colony forming units (CFU), followed by a primary boost (10^6 CFU for those mice that developed lesions and 10^8 CFU for those mice that did not develop a lesion) after 2 weeks, and a secondary boost (10^3 CFU) after an additional 2 weeks. Sera from 10 non-infected mice were used as controls against sera from GAS-immunized mice. Serum was obtained by cardiac puncture and stored at −70° C. All experimental procedures were in accordance with the principles of the Animal Care Committee of Mount Sinai Hospital, Toronto, Canada.

[0247] Indirect ELISA: An indirect ELISA was used for screening the human and mice sera using in vitro-derived GAS antigens (refer to in vitro antigen preparation). Immulon IIHB plates (Dynex Technologies, Chantilly, Va.) were coated overnight at 4° C. with each antigen (whole cells, cell extracts and spent media) which was diluted in freshly prepared carbonate bi-carbonate (C/BC) buffer consisting of 20 mM sodium carbonate (Fisher Scientific, Nepean, Canada) and 50 mM sodium bi-carbonate (BDH Chemicals, Toronto, Canada). The assay procedure described previously was followed (2). The antibody titre was defined as the highest serial dilution of serum at which the OD_{490} was 2 standard deviations above the mean OD_{490} of the negative controls (without primary antibody or without antigen). Antibody titres were converted to logarithmic values ($\log_2(x)$, where x equals the reciprocal of the serum dilution) for calculation of geometric means.

[0248] Sera adsorption: Equal volumes of selected invasive patient sera and GAS-immunized mice sera were pooled in a species-specific manner and successively adsorbed with in vitro-derived GAS antigens. In addition, sera from 14 healthy individuals were also pooled and successively adsorbed with in vitro-derived GAS antigens. The successive adsorption steps consisted of 5 times with whole cells, 1 time with cell extracts, 1 time with denatured cell extracts, and 1 time with spent media. Adsorptions were carried out by incubating the pooled sera overnight at 4° C. with antigen-saturated nitrocellulose membranes (Millipore, Bedford, Mass.). After each successive adsorption, the pooled sera were removed and the membrane was washed with 500 μl 1×PBS, which was then added to the pooled sera. To check the efficacy of each adsorption step, a 10 μl aliquot of the serum was removed after each adsorption and an indirect ELISA performed.

[0249] Construction of an inducible expression GAS genomic DNA library: Chromosomal DNA from 8 GAS strains (Table 1) was extracted using a cetyltrimethylammonium bromide (CTAB) protocol (5). The library was constructed by partial Sau3AI digestion of the genomic DNA that was ligated into pET30-abc vectors (Novagen Inc., Madison, Wis.), and electroporated into *E. coli* DH10B non-expression cells (Invitrogen, Ontario, Canada) as described previously (3).

[0250] Genomic library screening: An aliquot of the plasmid DNA library in *E. coli* DH10B non-expression hosts was extracted using the QIAprep Spin Miniprep kit (Qiagen Inc, Ontario, Canada) and transformed into chemically competent *E. coli* BL21 (DE3) expression host (Novagen). The library was screened by Colony Western blot analysis with pooled adsorbed or unadsorbed human and mouse sera in a species specific-manner as described previously (3) utilizing a Western Blotting Detection Kit (Bio-Rad Laboratories, Hercules, Calif.).

[0251] DNA sequencing: DNA sequencing was done with an ABI Prism 377 automatic DNA sequencer by the double-strand dideoxy-chain termination method at the Hospital for Sick Children Sequencing Facility, Toronto, Canada. Sequences were analyzed using the BLAST algorithm of the National Center for Biotechnology Information (NCBI).

Results

[0252] Antigenic determinants upregulated during invasive GAS infections were identified using in vivo antigen technology (IVIAT) [6]. The results are shown in Tables 3, 4 and 5. The markers listed in Tables 3, 4 and 5 are associated with GAS diseases and may be upregulated during invasive GAS infections.

[0253] The present invention is not to be limited in scope by the specific embodiments described herein, since such embodiments are intended as but single illustrations of one aspect of the invention and any functionally equivalent embodiments are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

[0254] All publications, patents and patent applications referred to herein are incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety. All publications, patents and patent applications mentioned herein are incorporated herein by reference for the purpose of describing and disclosing the antibodies, methodologies etc. which are reported therein which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

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TABLE 1

Eight invasive clinical strains of Group A *Streptococcus* used for the construction of the GAS genomic library and for deriving the in vitro antigens used to adsorb sera from patients with invasive disease, GAS-immunized mice, and healthy individuals.

M/T Type Of Gas Strain	Source Of Gas Isolate	Case Definition
M1/T1	Blood	Invasive
M1/T1	Throat	Invasive
M3/T3	Blood	STSS
M4/T4	Blood	Invasive
M6/Tnontyp.	Blood	STSS
M11/T11	Blood	Invasive
M12/T12	Blood	Invasive
M28/T11/28	Blood	Invasive

STSS = Streptococcal Toxic Shock Syndrome

ABLE 2

A list of sera from patients with invasive GAS disease used for screening the GAS genomic library.

Sera #	Diagnosis	Source of GAS isolate	M type of GAS isolate
1	NF & STSS	Abscess	M1
2	Cellulitis	Abscess	M non-typeable
3	Cellulitis	Blood & abscess	M1
4	Cellulitis & arthritis	Blood	M12
5	NF & STSS	Blood & abscess	M75
6	NF	Tissue	N/A
7	Cellulitis	Blood & abscess	M28
8	Arthritis	Throat/aspirate	M3
9	NF & STSS	Abscess	M1
10	Necrotizing myositis & STSS	Blood	N/A
11	Peritonitis	Blood	N/A
12	Pneumonia	Blood	M1
13	NF	Abscess	M4
14	Cellulitis	Abscess	M1

NF = Necrotizing Fasciitis
STSS = Streptococcal Toxic Shock Syndrome

TABLE 3

List of GAS Markers

Sera indicating positive	Insert size (bp)	Blast search - GAS Best hit - organism & gene Possible role
Human & Mouse	500	prfB (spy 0643/spy M18 0705) peptide chain release factor in *B. subtilis* putative peptide chain release factor 2 ftsE (spy 0644/spyM18 0706-230aa ftsE gene in *B. subtilis* putative cell division ATP-binding protein (spy 1149) hypothetical ABC transporter in *Thermatoga maritime* putative ABC transporter
Human & Mouse	2000	Hypothetical phage protein (spyM18 1298, spyM18 1299, spyM3 0966, spyM3 0967, & spyM3 1257)
Human	119	16S-23S intergenic spacer
Human & Mouse	415	dnaQ (spy 1864/spyM18 1928); 208aa/195aa Putative DNA pol. III (epsilon subunit) (spy 1865/spyM18 1929); 193aa/176aa unknown protein in *L. lactis* unknown function epf (spy 0737); extracellular matrix binding protein in *Abiotrophia* defective putative extracellular matrix binding protein rpoE (spy 1895/spyM18 1960); 191aa putative DNA-directed RNA pol. (delta subunit)
Human & Mouse	1500	htsA/siaA (spy 1795/spyM3 1560/spyM18 1867) ferrichrome binding protein
Human	2000	papS (spy 0866) putative polyA polymerase (M1, M3, & M18)
Mouse	281	nox (spy 1150/spyM18 1110/JRS4GAS strain); 456aa; 246aa in JRS NADH oxidase (water forming) in *S. mutans* NADH oxidase
Human & Mouse	184	amyA (spy 1302); 711aa cgtase from *Thermoanearo thermosulfurigens* Eml in complex with a maltohexaose inhibitor putative cyclomaltodextrin glucanotransferase
Human & Mouse	152	(spy 1733/spyM18 1741); 424aa/427aa attenuator for lytABC and lytR expression in *B. halodurans* putative transcription regulator
Human	196	(spy 0430/spyM18 0477); fibronectin binding protein SFS in *S. equi* hypothetical protein
-	195	dnaE (spy 1284/spyM18 1232); 1036aa DNA pol. III alpha subunit in *B. subtilis* DNA pol. III alpha subunit in *B. subtilis*
Human & Mouse	76	Insert corresponds to spacer between genes below clpP (spy 0395/spyM18 0446) ATP-dependent CLP protease proteolytic subunit (endopeptidase CLP) in *S. salivarius* Putative ATP-dependent protease proteolytic subunit (spy 0397/spyM18 0447) conserved hypothetical protein ylb in *B. subtilis* conserved hypothetical protein
Human & Mouse	355	nifS (spy 1122) iron-sulfur cofactor synthesis protein yrvO in B. subtilis; similar to NifS homolog in *B. subtilis* putative iron-sulfur cofactor synthesis protein (spy 1121/spyM18 1152); 115aa no blast hits unknown function
Mouse	833	(spy 2031/spyM18 2089); 224aa ABC transporter in *B. halodurans* Putative ABC transporter Spy 2032/spyM18 2090); 422aa Conserved hypothetical protein yrvP in *B. subtilis* Putative ATP-binding cassette transporter-like protein

TABLE 3-continued

List of GAS Markers

Sera indicating positive	Insert size (bp)	Blast search - GAS Best hit - organism & gene Possible role
Human & Mouse	3000	Spy 0630 & spy 0631 Putative PTS dependent N-acetyl-galactosamine IIC component & Putative PTS dependent N-acetyl-galactosamine IIB component SpyM3 1326 Conserved hypothetical protein - phage associated (phage 315.5) purD (Spy 0032) phosphoribosylamine glycine ligase Spy 1784 Putative ABC transporter (ATP-binding protein)
Human & Mouse	157	Spy 0319 atmB in *S. mutans* putative lipoprotein
Human Mouse	113	Spy 1233 coaA, putative pantothenate kinase
Human & Mouse	1733	spyM3 1096 putative N-acetylmuramoyle-L-alanine amidase (lysine phage-associated) (*S. pyogenes* phage 315.3)
Human & Mouse	302	Spy 1355 & spy 1356 Conserved hypothetical protein & putative acetyl transferase
Human & Mouse	2000	Spy 1961, spy 2060, & spy 2063 Putative DNA pol. III alpha subunit (polC), conserved hypothetical protein, & putative translation initiation inhibitor (tdcF)
Human & Mouse	584	Spy 0777 rexA
Human & Mouse	71	Spy 1649 pbp1A
Human & Mouse	1500	Spy 1198 Putative repressor protein
Human & Mouse	267	Spy 1733 & spy 1674 Putative transcription regulator (lytR) & putative ABC transporter
Human & Mouse	152	Spy 1105 Putative spermidine/putrecine ABC transporter (potD)

TABLE 4

GAS Markers

Marker #	Gene and Spy#	Sequence ID No.
1	purD (Spy 0032)	1, 2
2	atmB (Spy 0319)	3, 4
3	clpP (Spy 0395)	5, 6
4	Spy 0397	7, 8
5	Spy 0430	9, 10
6	Spy 0630	11, 12
7	Spy 0631	13, 14
8	prfB (Spy 0643)	15, 16
9	ftsE (Spy 0644)	17, 18
10	epf (Spy 0737)	19, 20
11	rexA (Spy 0777)	21, 22
12	papS (Spy 0866)	23, 24
13	Spy 1096	25, 26
14	potD (Spy 1105)	27, 28
15	Spy 1121	29, 30
16	nifS (Spy 1122)	31, 32
17	Spy 1149	33, 34
18	nox (Spy 1150)	35, 36
19	Spy 1198	37, 38
20	coaA (Spy 1233)	39, 40
21	dnaE (Spy 1284)	41, 42
22	amyA (Spy 1302)	43, 44
23	Spy 1355	45, 46

TABLE 4-continued

GAS Markers

Marker #	Gene and Spy#	Sequence ID No.
24	Spy 1356	47, 48
25	pbp1A (Spy 1649)	49, 50
26	Spy 1674	51, 52
27	lyt (Spy 1733)	53, 54
28	Spy 1784	55, 56
29	siaA/htsA (Spy 1795)	57, 58
30	dnaQ (Spy 1864)	59, 60
31	Spy 1865	61, 62
32	rpoE (Spy 1895)	63, 64
33	Spy 1921	65, 66
34	Spy 2031	67, 68
35	Spy 2032	69, 70
36	tdcF (Spy 2060)	71, 72
37	Spy 2063	73, 74
38	SpyM3 1257	75, 76
39	SpyM3 1326	77, 78
40	SpyM18 1298	79, 80
41	SpyM18 1299	81, 82
42	Spy 1961	83, 84, 85

TABLE 5

Serotype	Strain	Locus tag	GeneID
Gene name = phosphoribosylamine--glycine ligase (purD); Locus tag = Spy_0032; GeneID = 900390; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 1 and 2			
M1	MGAS5005	MGAS5005_Spy_0029	3572913
M1	*S. pyogenes* SSI-1	SPs0027	1066282
M28	MGAS6180	M28_0029	3573098
M2	MGAS10270	MGAS10270_Spy0030	4063297
M6	MGAS10394	M6_Spy0078	2949058
M12	MGAS9429	MGAS9429_Spy0029	4060501
M3	MGAS315	SpyM3_0026	1008340
M4	MGAS10750	MGAS10750_Spy0030	4067237
M5	Manfredo	SpyM50029	4962783
M49	M49 591	SpyoM01000109	n/a
M18	MGAS8232	SpyM18_0032	995239
M12	MGAS2096	MGAS2096_0030	4065258
Gene name = hypothetical protein; Locus tag = Spy_0319; GeneID = 900605 Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 3 and 4			
M1	MGAS5005	MGAS5005_Spy_0271	3572639
M1	*S. pyogenes* SSI-1	SPs1626	1066435
M28	MGAS6180	M28_0263	3574645
M2	MGAS10270	MGAS10270_Spy0268	4063807
M6	MGAS10394	M6_Spy0299	2942436
M12	MGAS9429	MGAS9429_Spy0270	4060766
M3	MGAS315	SpyM3_0233	1008547
M4	MGAS10750	MGAS10750_Spy0266	4066979
M5	Manfredo	SpyM51584	4963797
M18	MGAS8232	SpyM18_0314	994798
M12	MGAS2096	MGAS2096_0289	4064734
Gene name = clpP ATP-dependent Clp protease proteolytic subunit (clpP); Locus tag = Spy_0395; GeneID = 900660; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 5 and 6			
M1	MGAS5005	MGAS5005_Spy_0328	3572579
M1	*S. pyogenes* SSI-1	SPs1572	1066487
M28	MGAS6180	M28_0317	3574680
M2	MGAS10270	MGAS10270_Spy0324	4063843
M6	MGAS10394	M6_Spy0354	2942035
M12	MGAS9429	MGAS9429_Spy0328	4060785
M3	MGAS315	SpyM3_0287	1008601
M4	MGAS10750	MGAS10750_Spy0324	4066732
M5	Manfredo	SpyM51530	4963735
M49	M49 591	SpyoM01000726	n/a
M18	MGAS8232	SpyM18_0446	993567
M12	MGAS2096	MGAS2096_0347	4065059
Spy_0397 Gene name = Hypothetical protein; Locus tag = Spy_0397; GeneID = 900661; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 7 and 8			
M1	MGAS5005	MGAS5005_Spy_0329	3572580
M1	*S. pyogenes* SSI-1	SPs1571	1065198
M28	MGAS6180	M28_0318	3574681
M2	MGAS10270	MGAS10270_Spy0325	4063844
M6	MGAS10394	M6_Spy0355	2942147
M12	MGAS9429	MGAS9429_Spy0329	4060786
M3	MGAS315	SpyM3_0288	1008602
M4	MGAS10750	MGAS10750_Spy0325	4066733
M5	Manfredo	SpyM51529	4964573
M18	MGAS8232	SpyM18_0447	995255
M49	M49 591	SpyoM01000725	n/a
Gene name = Hypothetical protein; Locus tag = Spy_0430; GeneID = 900679 Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 9 and 10			
M1	MGAS5005	MGAS5005_Spy_0352	3572563
Gene name = PTS dependent N-acetyl-galactosamine IIC component (agaW) Locus tag = Spy_0630; GeneID = 900829; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 11 and 12			
M1	MGAS5005	MGAS5005_Spy_0520	3572380
M1	*S. pyogenes* SSI-1	SPs1411	1066591
M28	MGAS6180	M28_0499	3573372
M2	MGAS10270	MGAS10270_Spy0515	4063897
M6	MGAS10394	M6_Spy0541	2941679
M12	MGAS9429	MGAS9429_Spy0511	4062048
M3	MGAS315	SpyM3_0444	1008758
M4	MGAS10750	MGAS10750_Spy0539	4068022
M5	Manfredo	SpyM51343	4963991
M18	MGAS8232	SpyM18_0695	994449
M49	M49 591	SpyoM01000828	n/a
M12	MGAS2096	MGAS2096_Spy0532	4065411
Gene name = PTS dependent N-acetyl-galactosamine IIB component (agaV) Locus tag = Spy_0631; GeneID = 900830; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos 13 and 14			
M1	MGAS5005	MGAS5005_Spy_0521	3572381
M1	*S. pyogenes* SSI-1	SPs1410	1065268
M28	MGAS6180	M28_0500	3573373
M2	MGAS10270	MGAS10270_Spy0516	4063408
M6	MGAS10394	M6_Spy0542	2941680
M12	MGAS9429	MGAS9429_Spy0512	4060599
M3	MGAS315	SpyM3_0445	1008759
M4	MGAS10750	MGAS10750_Spy0540	4068023
M5	Manfredo	SpyM51342	4964655
M18	MGAS8232	SpyM18_0696	993480
M49	M49 591	SpyoM01000829	n/a
M12	MGAS2096	MGAS2096_Spy0533	4065412
Gene name = peptide chain release factor 2 (prfB); Locus tag = Spy_0643 GeneID = 900839; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 15 and 16			
M1	MGAS5005	MGAS5005_Spy_0530	3572390
M1	*S. pyogenes* SSI-1	SPs1402	1066597
M28	MGAS6180	M28_0509	3573382
M2	MGAS10270	MGAS10270_Spy0525	4063417
M6	MGAS10394	M6_Spy0551	2940713
M12	MGAS9429	MGAS9429_Spy0521	4060608
M3	MGAS315	SpyM3_0454	1008768
M4	MGAS10750	MGAS10750_Spy0549	4068032
M5	Manfredo	SpyM51333	4964163
M18	MGAS8232	prfB (gene name)	994061
M49	M49 591	SpyoM01000670	n/a
M12	MGAS2096	MGAS2096_Spy0542	4066242
Gene name = cell-division ATP-binding protein (ftsE); Locus tag = Spy_0644 GeneID = 900840; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. No. 17 and 18			
M1	MGAS5005	MGAS5005_Spy_0531	3572391
M1	*S. pyogenes* SSI-1	SPs1401	1065292
M28	MGAS6180	M28_0510	3573383
M2	MGAS10270	MGAS10270_Spy0526	4063418
M6	MGAS10394	M6_Spy0552	2940714
M12	MGAS9429	MGAS9429_Spy0522	4060609
M3	MGAS315	SpyM3_0455	1008769
M4	MGAS10750	MGAS10750_Spy0550	4068033
M5	Manfredo	SpyM51332	4964167

TABLE 5-continued

Serotype	Strain	Locus tag	GeneID
M18	MGAS8232	SpyM18_0706	995132
M12	MGAS2096	MGAS2096_Spy0543	4066243
Gene name = extracellular matrix binding protein (epf); Locus tag = Spy_0737 GeneID = 900919; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 19 and 20			
M1	MGAS5005	MGAS5005_Spy_0561	3572346
M28	MGAS6180	M28_0539	3574749
M12	MGAS9429	MGAS9429_Spy0613	4062181
M4	MGAS10750	MGAS10750_Spy0643	4067933
M49	M49 591	SpyoM01000212	n/a
M12	MGAS2096	MGAS2096_Spy0622	4066162
Gene name = ATP-dependent exonuclease, subunit A (rexA); Locus tag = Spy_0777; GeneID = 900953; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 21 and 22			
M1	MGAS5005	MGAS5005_Spy_0595	3572302
M1	*S. pyogenes* SSI-1	SPs1340	1065346
M28	MGAS6180	M28_0574	3574784
M2	MGAS10270	MGAS10270_Spy0650	4063145
M6	MGAS10394	M6_Spy0612	2942261
M12	MGAS9429	MGAS9429_Spy0649	4062412
M3	MGAS315	SpyM3_0514	1008828
M4	MGAS10750	MGAS10750_Spy0680	4067893
M5	Manfredo	SpyM51212	4963549
M18	MGAS8232	SpyM18_0836	994806
M12	MGAS2096	MGAS2096_Spy0658	4064540
Gene name = poly(A) polymerase (papS); Locus tag = Spy_0866; GeneID = 901027; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 23 and 24			
M1	MGAS5005	MGAS5005_Spy_0673	3572224
M1	*S. pyogenes* SSI-1	SPs1266	1065346
M28	MGAS6180	M28_0653	3574823
M2	MGAS10270	MGAS10270_Spy0731	4062468
M6	MGAS10394	M6_Spy0691	2942456
M12	MGAS9429	MGAS9429_Spy0728	4061993
M3	MGAS315	SpyM3_0587	1008901
M4	MGAS10750	MGAS10750_Spy0764	4067821
M5	Manfredo	SpyM51134	4963504
M18	MGAS8232	SpyM18_0927	994047
M49	M49 591	SpyoM01000092	n/a
M12	MGAS2096	MGAS2096_Spy0744	4066108
Gene name = putative folyl-polyglumate synthetase (folC.1); Locus tag = Spy_1096; GeneID = 901217; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); Sequence I.D. Nos. 25 and 26			
M1	MGAS5005	MGAS5005_Spy_0820	3572107
M1	*S. pyogenes* SSI-1	SPs0958	1066227
M28	MGAS6180	M28_0797	3573546
M2	MGAS10270	MGAS10270_Spy0936	4063937
M6	MGAS10394	M6_Spy0818	2942407
M12	MGAS9429	MGAS9429_Spy0939	4062278
M3	MGAS315	SpyM3_0758	1009072
M4	MGAS10750	MGAS10750_Spy0971	4067069
M5	Manfredo	SpyM50968	4964153
M18	MGAS8232	SpyM18_1058	993530
M49	M49 591	SpyoM01000299	n/a
M12	MGAS2096	MGAS2096_Spy0894	4065935
Gene name = putative spermidine/putrescine ABC transporter (periplasmic transport protein (potD); Locus tag = Spy_1105; GeneID = 901226; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1) SEQ I.D. Nos. 27 and 28			
M1	MGAS5005	MGAS5005_Spy_0829	3572077
M1	*S. pyogenes* SSI-1	SPs0967	1066226
M28	MGAS6180	M28_0806	3574881
M2	MGAS10270	MGAS10270_Spy0945	4063946
M6	MGAS10394	M6_Spy0827	2941036
M12	MGAS9429	MGAS9429_Spy0948	4062287
M3	MGAS315	SpyM3_0767	1009081
M4	MGAS10750	MGAS10750_Spy0908	4067098
M5	Manfredo	SpyM50959	4963387
M18	MGAS8232	SpyM18_1067	994023
M49	M49 591	SpyoM01000290	n/a
M12	MGAS2096	MGAS2096_Spy0903	4065887
Gene name = hypothetical protein; Locus tag = Spy_1121; GeneID = 901239 Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 29 and 30			
M1	MGAS5005	MGAS5005_Spy_0843	3572052
M1	*S. pyogenes* SSI-1	SPs0981	1066277
M28	MGAS6180	M28_0819	3574894
M2	MGAS10270	MGAS10270_Spy0959	4064057
M6	MGAS10394	M6_Spy0841	2941140
M12	MGAS9429	MGAS9429_Spy0962	4060549
M3	MGAS315	SpyM3_0780	1009094
M4	MGAS10750	MGAS10750_Spy0994	4067112
M5	Manfredo	SpyM50945	4963376
M18	MGAS8232	SpyM18_1082	994828
M49	M49 591	SpyoM01000612	n/a
M12	MGAS2096	MGAS2096_Spy0918	4065902
Gene name = putative iron-sulfur cofactor synthesis protein; Locus tag = Spy_1122 GeneID = 901240; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 31 and 32			
M1	MGAS5005	MGAS5005_Spy_0844	3572053
M1	*S. pyogenes* SSI-1	SPs0982	1066256
M28	MGAS6180	M28_0820	3574895
M2	MGAS10270	MGAS10270_Spy0960	4064058
M6	MGAS10394	M6_Spy0842	2942248
M12	MGAS9429	MGAS9429_Spy0963	4060550
M3	MGAS315	SpyM3_0781	1009095
M4	MGAS10750	MGAS10750_Spy0995	4067113
M5	Manfredo	SpyM50944	4964387
M18	MGAS8232	SpyM18_1083	994464
M49	M49 591	SpyoM01000611	n/a
M12	MGAS2096	MGAS2096_Spy0919	4065903
Gene name = putative ABC transporter; Locus tag = Spy_1149; GeneID = 901265 Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 33 and 34			
M1	MGAS5005	MGAS5005_Spy_0871	3572041
M1	*S. pyogenes* SSI-1	SPs1006	1066323
M28	MGAS6180	M28_0845	3573594
M2	MGAS10270	MGAS10270_Spy0985	4064445
M6	MGAS10394	M6_Spy0867	2941961
M12	MGAS9429	MGAS9429_Spy0989	4060826
M3	MGAS315	SpyM3_0807	1009121
M4	MGAS10750	MGAS10750_Spy1020	4067320
M5	Manfredo	SpyM50919	4964318
M18	MGAS8232	SpyM18_1109	993707
M49	M49 591	SpyoM01000341	n/a
M12	MGAS2096	MGAS2096_Spy0945	4065851
Gene name = NADH oxidase (nox); Locus tag = Spy_1150; GeneID = 901266 Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 35 and 36			
M1	MGAS5005	MGAS5005_Spy_0872	3572042
M1	*S. pyogenes* SSI-1	SPs1007	1066318
M28	MGAS6180	M28_0846	3573595
M2	MGAS10270	MGAS10270_Spy0986	4064446
M6	MGAS10394	M6_Spy0868	2941962
M12	MGAS9429	MGAS9429_Spy0990	4060827
M3	MGAS315	SpyM3_0808	1009122
M4	MGAS10750	MGAS10750_Spy1021	4067321
M5	Manfredo	SpyM50918	4964253

TABLE 5-continued

Serotype	Strain	Locus tag	GeneID
M18	MGAS8232	SpyM18_1110	994776
M49	M49 591	SpyoM01000340	n/a
M12	MGAS2096	MGAS2096_Spy0946	4065852
Gene name = putative repressor protein; Locus tag = Spy_1198; GeneID = 901304 Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 37 and 38			
M1	MGAS5005	MGAS5005_Spy_0914	3572006
M1	*S. pyogenes* SSI-1	SPs1040	1065479
M28	MGAS6180	M28_0886	3573577
M2	MGAS10270	MGAS10270_Spy1028	4063272
M6	MGAS10394	M6_Spy0903	2942214
M12	MGAS9429	MGAS9429_Spy1016	4061974
M3	MGAS315	SpyM3_0840	1009154
M4	MGAS10750	MGAS10750_Spy1063	4066566
M5	Manfredo	SpyM50884	4963336
M18	MGAS8232	SpyM18_1150	994630
M49	M49 591	SpyoM01001185	n/a
M12	MGAS2096	MGAS2096_Spy0973	4065840
Gene name = pantothenate kinase (coaA); Locus tag = Spy_1233; GeneID = 901335; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 39 and 40			
M1	MGAS5005	MGAS5005_Spy_0945	3571959
M1	*S. pyogenes* SSI-1	SPs1071	1065683
M28	MGAS6180	M28_0917	3573647
M2	MGAS10270	MGAS10270_Spy1059	4063674
M6	MGAS10394	M6_Spy0934	2941285
M12	MGAS9429	MGAS9429_Spy1048	4061315
M3	MGAS315	SpyM3_0871	1009186
M4	MGAS10750	MGAS10750_Spy1094	4068176
M5	Manfredo	SpyM50853	4964042
M18	MGAS8232	SpyM18_1183	994086
M49	M49 591	SpyoM01001329	n/a
M12	MGAS2096	MGAS2096_Spy1004	4065023
Gene name = DNA polymerase III subunit alpha (dnaE); Locus tag = Spy_1284 GeneID = 901377; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370 serotype M1); SEQ I.D. Nos. 41 and 42			
M1	MGAS5005	MGAS5005_Spy_0990	3571926
M1	*S. pyogenes* SSI-1	SPs1113	1065631
M28	MGAS6180	M28_0962	3573711
M2	MGAS10270	MGAS10270_Spy1104	4064427
M6	MGAS10394	M6_Spy0977	2942246
M12	MGAS9429	MGAS9429_Spy1094	4060986
M3	MGAS315	SpyM3_0914	1009229
M4	MGAS10750	MGAS10750_Spy1140	4067152
M5	Manfredo	SpyM50811	4963291
M18	MGAS8232	SpyM18_1232	994375
M49	M49 591	SpyoM01001427	n/a
M12	MGAS2096	MGAS2096_Spy1050	4065274
Gene name = putative cyclomaltodextrin glucanotransferase (amyA); Locus tag = Spy_1302; GeneID = 901394; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 43 and 44			
M1	MGAS5005	MGAS5005_Spy_1065	3571845
M28	MGAS6180	M28_1046	3573776
M2	MGAS10270	MGAS10270_Spy1121	4062598
M4	MGAS10750	MGAS10750_Spy1158	4066697
M4	MGAS10750	MGAS10750_Spy1157	4066696
Gene name = hypothetical protein; Locus tag = Spy_1355; GeneID = 901430 Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 45 and 46			
M1	MGAS5005	MGAS5005_Spy_1104	3571806
M1	*S. pyogenes* SSI-1	SPs0830	1065983
M28	MGAS6180	M28_1096	3574917
M2	MGAS10270	MGAS10270_Spy1161	4063249
M6	MGAS10394	M6_Spy1076	2940706
M12	MGAS9429	MGAS9429_Spy1148	4060735
M3	MGAS315	SpyM3_1030	1009345
M4	MGAS10750	MGAS10750_Spy1203	4067008
M5	Manfredo	SpyM50755	4964203
M18	MGAS8232	SpyM18_1367	993838
M49	M49 591	SpyoM01000531	n/a
M12	MGAS2096	MGAS2096_Spy1166	4065126
Gene name = putative acetyl transferase; Locus tag = Spy_1356; GeneID = 901431 Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 47 and 48			
M1	MGAS5005	MGAS5005_Spy_1105	3571807
M1	*S. pyogenes* SSI-1	SPs0829	1065974
M28	MGAS6180	M28_1097	3574918
M2	MGAS10270	MGAS10270_Spy1162	4063250
M6	MGAS10394	M6_Spy1077	2940707
M12	MGAS9429	MGAS9429_Spy1149	4060736
M3	MGAS315	SpyM3_1031	1009346
M4	MGAS10750	MGAS10750_Spy1204	4067009
M5	Manfredo	SpyM50754	4964294
M18	MGAS8232	SpyM18_1368	993773
M49	M49 591	SpyoM01000532	n/a
M12	MGAS2096	MGAS2096_Spy1167	4065127
Gene name = putative penicillin-binding protein 1A (pbp1A); Locus tag = Spy_1649; GeneID = 901903; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 49 and 50			
M1	MGAS5005	MGAS5005_Spy_1355	3571548
M1	*S. pyogenes* SSI-1	SPs0472	1065774
M28	MGAS6180	M28_1396	3574116
M2	MGAS10270	MGAS10270_Spy1472	4063605
M6	MGAS10394	M6_Spy1401	2940852
M12	MGAS9429	MGAS9429_Spy1351	4061788
M3	MGAS315	SpyM3_1390	1009705
M4	MGAS10750	MGAS10750_Spy1464	4067496
M5	Manfredo	SpyM50436	4964314
M18	MGAS8232	SpyM18_1661	994224
M49	M49 591	SpyoM01000630	n/a
M12	MGAS2096	MGAS2096_Spy1377	4065206
Gene name = putative ABC transporter protein; Locus tag = Spy_1674 GeneID = 901921; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 51 and 52			
M1	MGAS5005	MGAS5005_Spy_1373	3571527
M1	*S. pyogenes* SSI-1	SPs0406	1066926
M28	MGAS6180	M28_1416	3574136
M2	MGAS10270	MGAS10270_Spy1491	4064106
M6	MGAS10394	M6_Spy1421	2942110
M12	MGAS9429	MGAS9429_Spy1371	4061817
M3	MGAS315	SpyM3_1430	1009775
M4	MGAS10750	MGAS10750_Spy1483	4067476
M5	Manfredo	SpyM50417	4964572
M18	MGAS8232	SpyM18_1685	993969
M49	M49 591	SpyoM01001413	n/a
M12	MGAS2096	MGAS2096_Spy1396	4066317
Gene name = putative transcriptional regulator; Locus tag = Spy_1733 GeneID = 901968; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 53 and 54			
M1	MGAS5005	MGAS5005_Spy_1474	3571435
M1	*S. pyogenes* SSI-1	SPs0361	1066905
M28	MGAS6180	M28_1463	3574184
M2	MGAS10270	MGAS10270_Spy1541	4062758
M6	MGAS10394	M6_Spy1468	2942200
M12	MGAS9429	MGAS9429_Spy1476	4061642
M3	MGAS315	SpyM3_1506	1009821
M4	MGAS10750	MGAS10750_Spy1533	4067450

TABLE 5-continued

Serotype	Strain	Locus tag	GeneID
M5	Manfredo	SpyM50371	4962971
M18	MGAS8232	SpyM18_1741	994566
M49	M49 591	SpyoM01000766	n/a
M12	MGAS2096	MGAS2096_Spy1499	4064613
Gene name = putative ABC transporter; Locus tag = Spy_1784; GeneID = 902015 Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 55 and 56			
M1	MGAS5005	MGAS5005_Spy_1518	3571363
M1	*S. pyogenes* SSI-1	SPs0316	1066465
M28	MGAS6180	M28_1508	3574229
M2	MGAS10270	MGAS10270_Spy1586	4063757
M6	MGAS10394	M6_Spy1511	2941566
M12	MGAS9429	MGAS9429_Spy1520	4060951
M3	MGAS315	SpyM3_1550	1009865
M4	MGAS10750	MGAS10750_Spy1578	4067379
M5	Manfredo	SpyM50327	4962953
M18	MGAS8232	SpyM18_1856	993954
M49	M49 591	SpyoM01000777	n/a
M12	MGAS2096	MGAS2096_Spy1545	4065737
Gene name = streptococcal iron acquisition protein (siaA), also known as htsA Locus tag = Spy_1795; GeneID = 902024; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 57 and 58			
M1	MGAS5005	MGAS5005_Spy_1528	3571373
M1	*S. pyogenes* SSI-1	SPs0307	1066589
M28	MGAS6180	M28_1518	3574239
M2	MGAS10270	MGAS10270_Spy1596	4063652
M6	MGAS10394	M6_Spy1521	2941369
M12	MGAS9429	MGAS9429_Spy1532	4060830
M3	MGAS315	SpyM3_1560	1009875
M4	MGAS10750	MGAS10750_Spy1587	4067388
M5	Manfredo	SpyM50318	4962943
M18	MGAS8232	SpyM18_1867	993699
M49	M49 591	SpyoM01000537	n/a
M12	MGAS2096	MGAS2096_Spy1555	4065747
Gene name = DNA polymerase III subunit epsilon (dnaQ); Locus tag = Spy_1864 GeneID = 902074; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 59 and 60			
M1	MGAS5005	MGAS5005_Spy_1582	3571310
M1	*S. pyogenes* SSI-1	SPs0259	1065779
M28	MGAS6180	M28_1570	3574272
M2	MGAS10270	MGAS10270_Spy1649	4064346
M6	MGAS10394	M6_Spy1594	2941328
M12	MGAS9429	MGAS9429_Spy1587	4061431
M3	MGAS315	SpyM3_1608	1009923
M4	MGAS10750	MGAS10750_Spy1640	4066776
M5	Manfredo	SpyM50268	4962913
M18	MGAS8232	SpyM18_1928	994533
M12	MGAS2096	MGAS2096_Spy1607	4065973
Gene name = hypothetical protein; Locus tag = Spy_1865; GeneID = 902075 Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 61 and 62			
M1	MGAS5005	MGAS5005_Spy_1583	3571311
M1	*S. pyogenes* SSI-1	SPs0258	1065783
M28	MGAS6180	M28_1571	3574273
M2	MGAS10270	MGAS10270_Spy1650	4064347
M6	MGAS10394	M6_Spy1595	2941329
M12	MGAS9429	MGAS9429_Spy1588	4061432
M3	MGAS315	SpyM3_1609	1009924
M4	MGAS10750	MGAS10750_Spy1641	4066777
M5	Manfredo	SpyM50267	4964089
M18	MGAS8232	SpyM18_1929	995043
M12	MGAS2096	MGAS2096_Spy1608	4065974
Gene name = DNA-directed RNA polymerase subunit delta (rpoE); Locus tag = Spy_1895; GeneID = 902099; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 63 and 64			
M1	MGAS5005	MGAS5005_Spy_1611	3571270
M1	*S. pyogenes* SSI-1	SPs0233	1066365
M28	MGAS6180	M28_1600	3574304
M2	MGAS10270	MGAS10270_Spy1679	4064179
M6	MGAS10394	M6_Spy1619	2941986
M12	MGAS9429	MGAS9429_Spy1614	4062113
M3	MGAS315	SpyM3_1633	1009948
M4	MGAS10750	MGAS10750_Spy1666	4066764
M5	Manfredo	SpyM50243	4962899
M18	MGAS8232	SpyM18_1960	994734
M49	M49 591	SpyoM01001243	n/a
M12	MGAS2096	MGAS2096_Spy1634	4066193
Gene name = putative tagatose 6-phosphate kinase (lacC.2); Locus tag = Spy_1921 GeneID = 901604; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 65 and 66			
M1	MGAS5005	MGAS5005_Spy_1636	3571268
M1	*S. pyogenes* SSI-1	SPs1655	1066377
M28	MGAS6180	M28_1626	3574354
M2	MGAS10270	MGAS10270_Spy1705	4062540
M6	MGAS10394	M6_Spy1645	2941717
M12	MGAS9429	MGAS9429_Spy1639	4061438
M3	MGAS315	SpyM3_1657	1009972
M4	MGAS10750	MGAS10750_Spy1733	4067200
M5	Manfredo	SpyM51611	4964245
M18	MGAS8232	SpyM18_1989	994273
M49	M49 591	SpyoM01000235	n/a
M12	MGAS2096	MGAS2096_Spy1661	4064633
Gene name = putative ABC transporter protein; Locus tag = Spy_2031 GeneID = 901684; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 67 and 68			
M1	MGAS5005	MGAS5005_Spy_1727	3571167
M1	*S. pyogenes* SSI-1	SPs1732	1065123
M28	MGAS6180	M28_1711	3574440
M2	MGAS10270	MGAS10270_Spy1793	4063167
M6	MGAS10394	M6_Spy1727	2940883
M12	MGAS9429	MGAS9429_Spy1732	4061116
M3	MGAS315	SpyM3_1735	1010050
M4	MGAS10750	MGAS10750_Spy1818	4067042
M5	Manfredo	SpyM51690	4963859
M18	MGAS8232	SpyM18_2089	994103
M49	M49 591	SpyoM01001110	n/a
M12	MGAS2096	MGAS2096_Spy1755	4064574
Gene name = putative ABC transporter-like protein; Locus tag = Spy_2032 GeneID = 901685; Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1); SEQ I.D. Nos. 69 and 70			
M1	MGAS5005	MGAS5005_Spy_1728	3571168
M1	*S. pyogenes* SSI-1	SPs1733	1066253
M28	MGAS6180	M28_1712	3574441
M2	MGAS10270	MGAS10270_Spy1794	4063168
M6	MGAS10394	M6_Spy1728	2941283
M12	MGAS9429	MGAS9429_Spy1733	4061117
M3	MGAS315	SpyM3_1736	1010051
M4	MGAS10750	MGAS10750_Spy1819	4067043

TABLE 5-continued

Serotype	Strain	Locus tag	GeneID
M5	Manfredo	SpyM51691	4963860
M18	MGAS8232	SpyM18_2090	994763
M49	M49 591	SpyoM01001109	n/a
M12	MGAS2096	MGAS2096_Spy1756	4064575
Gene name = hypothetical protein; Locus tag = Spy_2060; GeneID = 901709 Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1), SEQ I.D. Nos. 71 and 72			
M1	MGAS5005	MGAS5005_Spy_1754	3571117
M1	*S. pyogenes* SSI-1	SPs1757	1066220
M28	MGAS6180	M28_1740	3574488
M2	MGAS10270	MGAS10270_Spy1823	4062697
M6	MGAS10394	M6_Spy1754	2940874
M12	MGAS9429	MGAS9429_Spy1764	4061237
M3	MGAS315	SpyM3_1759	1010074
M4	MGAS10750	MGAS10750_Spy1848	4066689
M5	Manfredo	SpyM51716	4964340
M18	MGAS8232	SpyM18_2121	993712
M49	M49 591	SpyoM01000774	n/a
M12	MGAS2096	MGAS2096_Spy1789	4065148
Gene name = hypothetical protein; Locus tag = Spy_2063; GeneID = 901710 Reference sequence from = *Streptococcus pyogenes* M1GAS (strain SF370, serotype M1) SEQ I.D. Nos. 73 and 74			
M1	MGAS5005	MGAS5005_Spy_1756	3571119
M1	*S. pyogenes* SSI-1	SPs1758	1065113
M28	MGAS6180	M28_1742	3574452
M2	MGAS10270	MGAS10270_Spy1825	4062699
M6	MGAS10394	M6_Spy1756	2940724
M12	MGAS9429	MGAS9429_Spy1766	4061239
M3	MGAS315	SpyM3_1761	1010076
M4	MGAS10750	MGAS10750_Spy1850	4066691
M5	Manfredo	SpyM51717	4963879
M18	MGAS8232	SpyM18_2124	994392
M49	M49 591	SpyoM01000772	n/a
M12	MGAS2096	MGAS2096_Spy1791	4065150
Gene name = hypothetical protein; Locus tag = SpyM3_1257; GeneID = 1009572 Reference sequence from = *Streptococcus pyogenes* MGAS315 (strain MGAS315, serotype M3); SEQ I.D. Nos. 75 and 76			
M1	*S. pyogenes* SSI-1	SPs0606	1066746
M1	*S. pyogenes* SSI-1	SPs0414	1066929
M28	MGAS6180	M28_1277	3573985
M2	MGAS10270	MGAS10270_Spy1353	4063770
M6	MGAS10394	M6_Spy0026	2940912
M3	MGAS315	SpyM3_1452	1009767
Gene name = hypothetical protein; Locus tag = SpyM3_1326; GeneID = 1009641 Reference sequence from = *Streptococcus pyogenes* MGAS315 (strain MGAS315, serotype M3); SEQ I.D. Nos. 77 and 78			
M1	MGAS5005	MGAS5005_Spy_1022	3571880
M1	*S. pyogenes* SSI-1	SPs0535	1066759
M2	MGAS10270	MGAS10270_Spy1825	4062961
M4	MGAS10750	MGAS10750_Spy1861	4066847
M49	M49 591	SpyoM01000031	n/a
Gene name = hypothetical protein; Locus tag = SpyM18_1298; GeneID = 994620 Reference sequence from = *Streptococcus pyogenes* MGAS8232 (strain MGAS8232, serotype M18); SEQ I.D. Nos. 79 and 80			
M1	*S. pyogenes* SSI-1	SPs0887	1066078
M28	MGAS6180	M28_1020	3573750
M6	MGAS10394	M6_Spy1017	2941548
M3	MGAS315	SpyM3_0966	1009281
Gene name = hypothetical protein; Locus tag = SpyM18_1299; GeneID = 993960; Reference sequence from = *Streptococcus pyogenes* MGAS8232 (strain MGAS8232, serotype M18); SEQ I.D. Nos. 81 and 82			
M1	MGAS5005	MGAS5005_Spy_1213	3571681
M1	*S. pyogenes* SSI-1	SPs0886	1066065
M28	MGAS6180	M28_1021	3573751
M6	MGAS10394	M6_Spy1018	2942036
M3	MGAS315	SpyM3_0967	1009282
M5	Manfredo	SpyM50478	4963038

SEQUENCE LISTING

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<160> NUMBER OF SEQ ID NOS: 85

<210> SEQ ID NO 1
<211> LENGTH: 421
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 1

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Lys Lys Leu Leu Ala Ser Lys Gly Val Asp Gln Val Phe Val Ala Pro
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Gly Asn Asp Gly Met Thr Leu Asp Gly Leu Asp Leu Val Asn Ile Val
        35                  40                  45
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Val Ser Glu His Ser Arg Leu Ile Ala Phe Ala Lys Glu Asn Glu Ile
    50                  55                  60

Ser Trp Ala Phe Ile Gly Pro Asp Asp Ala Leu Ala Ala Gly Ile Val
65                  70                  75                  80

Asp Asp Phe Asn Ser Ala Gly Leu Arg Ala Phe Gly Pro Thr Lys Ala
                85                  90                  95

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

Lys Tyr Asn Val Pro Thr Ala Ala Tyr Gly Thr Phe Ser Asp Phe Glu
        115                 120                 125

Lys Ala Lys Ala Tyr Ile Glu Glu Gln Gly Ala Pro Ile Val Val Lys
    130                 135                 140

Ala Asp Gly Leu Ala Leu Gly Lys Gly Val Val Val Ala Glu Thr Val
145                 150                 155                 160

Glu Gln Ala Val Glu Ala Ala Gln Glu Met Leu Leu Asp Asn Lys Phe
                165                 170                 175

Gly Asp Ser Gly Ala Arg Val Val Ile Glu Glu Phe Leu Asp Gly Glu
            180                 185                 190

Glu Phe Ser Leu Phe Ala Phe Ala Asn Gly Asp Lys Phe Tyr Ile Met
        195                 200                 205

Pro Thr Ala Gln Asp His Lys Arg Ala Phe Asp Gly Asp Lys Gly Pro
    210                 215                 220

Asn Thr Gly Gly Met Gly Ala Tyr Ala Pro Val Pro His Leu Pro Gln
225                 230                 235                 240

Ser Val Val Asp Thr Ala Val Glu Met Ile Val Arg Pro Val Leu Glu
                245                 250                 255

Gly Met Val Ala Glu Gly Arg Pro Tyr Leu Gly Val Leu Tyr Val Gly
            260                 265                 270

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

Phe Gly Asp Pro Glu Thr Gln Ile Ile Leu Pro Arg Leu Thr Ser Asp
    290                 295                 300

Phe Ala Gln Asn Ile Asp Asp Ile Met Met Gly Ile Glu Pro Tyr Ile
305                 310                 315                 320

Thr Trp Gln Lys Asp Gly Val Thr Leu Gly Val Val Val Ala Ser Glu
                325                 330                 335

Gly Tyr Pro Phe Asp Tyr Glu Lys Gly Val Pro Leu Pro Glu Lys Thr
            340                 345                 350

Asp Gly Asp Ile Ile Thr Tyr Tyr Ala Gly Val Lys Phe Ser Glu Asn
        355                 360                 365

Ser Glu Leu Leu Leu Ser Asn Gly Gly Arg Val Tyr Met Leu Val Thr
    370                 375                 380

Thr Glu Asp Ser Val Lys Ala Gly Gln Asp Lys Ile Tyr Thr Gln Leu
385                 390                 395                 400

Ala Gln Gln Asp Thr Thr Gly Leu Phe Tyr Arg Asn Asp Ile Gly Ser
                405                 410                 415

Lys Ala Ile Arg Glu
            420


<210> SEQ ID NO 2
<211> LENGTH: 1266
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<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 2

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ggtctggact tggtgaatat agtagtttcc gaacattcca ggttgattgc ctttgctaag     180

gagaatgaga tttcttgggc ctttattggt cctgatgatg cgctagcagc tggtatcgtt     240

gatgatttca acagtgctgg actcagagct tttggtccaa caaaggcagc agcggagcta     300

gagtggtcaa aagactttgc caaggaaatc atggtcaaat acaatgtccc aacagcagcc     360

tatggcacat tttcagactt tgaaaaagcc aaagcctaca tcgaagagca gggcgcacct     420

atcgtggtca aggctgatgg cttggcgcta ggtaagggtg tggtcgtggc tgaaaccgtt     480

gagcaggcgg tagaggcggc gcaagagatg cttctggaca ataagtttgg cgattcagga     540

gcgcgtgtgg ttatcgagga attcttggat ggcgaggagt tttccctctt tgcctttgct     600

aatggcgata agttctacat catgccgaca gctcaggatc acaagcgtgc ctttgacgga     660

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gaagggcgtc cttatctagg tgtcctctat gtggggctta tcctgacagc tgatggacct     840

aaggttatcg agttcaactc acgtttcggt gaccctgaaa ctcagattat cctccctcgc     900

ctgacttctg atttcgctca gaatattgac gatatcatga tgggcattga gccttacatc     960

acttggcaga aggacggtgt gactttgggt gttgtcgttg cctcagaagg ctatccattc    1020

gattatgaga aaggtgtgcc actgcctgaa aagaccgacg gcgatatcat cacctactac    1080

gcaggagtta agttttcgga aaatagcgag ctacttctct caaacggagg acgtgtctat    1140

atgctcgtca ccacagaaga cagcgtcaaa gcagggcagg acaaaatcta tacccaactg    1200

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gaataa                                                              1266


<210> SEQ ID NO 3
<211> LENGTH: 281
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 3

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Thr Val Leu Val Ala Cys Ser Glu Lys Gln Asp Asp Lys Asn Thr Leu
            20                  25                  30

Thr Ile Gly Val Met Thr Lys Thr Glu Ser Asp Gln Ala Arg Trp Asp
        35                  40                  45

Lys Val Glu Glu Leu Leu Lys Lys Asp Asn Ile Thr Leu Lys Tyr Lys
    50                  55                  60

Glu Phe Thr Asp Tyr Ser Gln Pro Asn Lys Ala Val Ala Asn Gly Glu
65                  70                  75                  80

Val Asp Ile Asn Ala Phe Gln His Tyr Asn Phe Leu Asn Asn Trp Asn
                85                  90                  95

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

Pro Ile Asn Leu Phe Ser Gly Thr Ser Gln Asp Gly Lys Ala Lys Tyr
        115                 120                 125

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

Asp Ala Thr Asn Glu Ser Arg Ala Leu Tyr Val Leu Gln Ser Ala Gly
145                 150                 155                 160

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

Ile Ser Glu Asn Lys Lys Lys Leu Asp Ile Lys Glu Leu Asp Ala Ser
            180                 185                 190

Gln Thr Ala Arg Ala Leu Val Ser Ala Asp Ala Ala Val Val Asn Asn
        195                 200                 205

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

Glu Lys Ala Asp Asp Asn Ser Lys Gln Trp Ile Asn Ile Ile Ala Gly
225                 230                 235                 240

Gln Lys Asp Trp Glu Lys Ser Glu Lys Ala Asp Ala Ile Lys Lys Leu
                245                 250                 255

Ile Lys Ala Tyr Gln Thr Asp Glu Val Lys Lys Val Val Glu Lys Thr
            260                 265                 270

Ser Asn Gly Ile Asp Val Ser Val Trp
        275                 280

<210> SEQ ID NO 4
<211> LENGTH: 846
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 4

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gcttgttctg aaaaacaaga tgataaaaac actttaacta ttggggtgat gacaaaaaca     120

gaatctgatc aagcgagatg ggataaagtt gaagaattat tgaaaaaaga caatatcact     180

ttgaagtaca aagaatttac agattactcg caacctaata aggcagttgc taatggtgaa     240

gtcgatatta atgccttcca acactataat ttcttaaata actggaataa ggaaaataag     300

gaacatttgg tggccattgc tgatacctat atcagcccaa ttaacctttt ctctggaacc     360

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gcagtaccaa atgatgcgac caatgaaagc cgtgccctct atgtgctgca atcagctggc     480

ctcattaaat tgaatgtgtc tggtgatcaa ttagcaacca ttgccaatat ctcagagaac     540

aaaaagaaat tagatatcaa ggaattagat gctagccaaa cggcacgtgc tttagtatct     600

gctgatgcag ctgttgtcaa taatagttac gctgttcctg caaaaattga ctacaaaacc     660

tctcttttca aagaaaaagc agatgacaat tcaaaacagt ggattaacat tattgcaggt     720

caaaaagatt gggaaaaatc agagaaggct gatgctatta aaaaactcat caaggcctac     780

caaactgatg aggtgaagaa agtcgtggaa aaaacttcaa atggtataga tgtatccgta     840

tggtaa                                                                 846

<210> SEQ ID NO 5
<211> LENGTH: 196
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<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 5

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Asp Ile Tyr Ser Arg Leu Leu Lys Asp Arg Ile Ile Met Leu Thr Gly
            20                  25                  30

Pro Val Glu Asp Asn Met Ala Asn Ser Val Ile Ala Gln Leu Leu Phe
        35                  40                  45

Leu Asp Ala Gln Asp Asn Thr Lys Asp Ile Tyr Leu Tyr Val Asn Thr
    50                  55                  60

Pro Gly Gly Ser Val Ser Ala Gly Leu Ala Ile Val Asp Thr Met Asn
65                  70                  75                  80

Phe Ile Lys Ala Asp Val Gln Thr Ile Val Met Gly Met Ala Ala Ser
                85                  90                  95

Met Gly Thr Val Ile Ala Ser Ser Gly Thr Lys Gly Lys Arg Phe Met
            100                 105                 110

Leu Pro Asn Ala Glu Tyr Met Ile His Gln Pro Met Gly Gly Thr Gly
        115                 120                 125

Gly Gly Thr Gln Gln Thr Asp Met Ala Ile Ala Ala Glu His Leu Leu
    130                 135                 140

Lys Thr Arg His Arg Leu Glu Lys Ile Leu Ala Gln Asn Ala Gly Lys
145                 150                 155                 160

Thr Ile Lys Gln Ile His Lys Asp Ala Glu Arg Asp Tyr Trp Met Ser
                165                 170                 175

Ala Glu Glu Thr Leu Ala Tyr Gly Phe Ile Asp Glu Ile Met Glu Asn
            180                 185                 190

Asn Glu Leu Lys
        195


<210> SEQ ID NO 6
<211> LENGTH: 591
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 6

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cgtttattaa aagaccgtat tatcatgtta acagggcctg tcgaagacaa catggccaac    120

tctgtcatag cgcagctctt attccttgac gcgcaagaca acactaaaga tatctaccta    180

tatgtcaaca caccaggtgg ctctgtctca gcaggcttgg ctattgtcga taccatgaac    240

tttatcaagg ccgatgtgca aactattgtc atgggtatgg cagcttctat ggggacagtc    300

attgcttcat caggaacaaa aggcaaacgc tttatgttac caaatgcaga gtatatgatc    360

caccagccaa tgggtggtac aggtggtggc acgcaacaaa cggatatggc tatcgcagca    420

gaacatctct taaaaacacg tcaccgttta gaaaaaatct tagcgcaaaa tgctggaaaa    480

acgattaaac aaatccataa agatgctgag cgtgattatt ggatgagtgc tgaagaaacc    540

ttggcttacg gtttcattga tgaaatcatg gaaaacaacg aactaaaata a             591


<210> SEQ ID NO 7
<211> LENGTH: 91
<212> TYPE: PRT
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<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 7

Met Phe Gln Lys Gln Glu Arg Ile Gly Leu Val Val Tyr Leu Tyr Tyr
1               5                   10                  15

Asn Arg Asp Ala Arg Lys Leu Ser Lys Phe Gly Asp Leu Tyr Tyr His
            20                  25                  30

Ser Lys Arg Ser Arg Tyr Leu Ile Ile Tyr Ile Asn Lys Asn Asp Leu
        35                  40                  45

Asp Thr Lys Leu Glu Glu Met Arg Arg Leu Lys Cys Val Lys Asp Ile
    50                  55                  60

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

His Arg Asp Glu Thr Asn Asn His Gln Lys Gly
                85                  90


<210> SEQ ID NO 8
<211> LENGTH: 276
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 8

atgtttcaaa aacaagaacg tattggactc gtcgtttacc tgtattataa ccgagatgcc      60

agaaagttat caaaatttgg tgatttatat taccattcca agcgctctcg ttacctcatt     120

atttatatta ataaaaatga tttagacaca aaattagaag aaatgagacg tttgaaatgt     180

gttaaagaca ttagaccatc agcttttgat gatattgacc gccaatttgt aggtaacctt     240

catcgcgacg aaacaaacaa ccatcaaaag ggttaa                               276


<210> SEQ ID NO 9
<211> LENGTH: 184
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 9

Met Lys Trp Ser Gly Phe Met Lys Thr Lys Ser Lys Arg Phe Leu Asn
1               5                   10                  15

Leu Ala Thr Leu Cys Leu Ala Leu Leu Gly Thr Thr Leu Leu Met Ala
            20                  25                  30

His Pro Val Gln Ala Glu Val Ile Ser Lys Arg Asp Tyr Met Thr Arg
        35                  40                  45

Phe Gly Leu Gly Asp Leu Glu Asp Asp Ser Ala Asn Tyr Pro Ser Asn
    50                  55                  60

Leu Glu Ala Arg Tyr Lys Gly Tyr Leu Glu Gly Tyr Glu Lys Gly Leu
65                  70                  75                  80

Lys Gly Asp Asp Ile Pro Glu Arg Pro Lys Ile Gln Val Pro Glu Asp
                85                  90                  95

Val Gln Pro Ser Asp His Gly Asp Tyr Arg Asp Gly Tyr Glu Glu Gly
            100                 105                 110

Phe Gly Glu Gly Gln His Lys Arg Asp Pro Leu Glu Thr Glu Ala Glu
        115                 120                 125

Asp Asp Ser Gln Gly Gly Arg Gln Glu Gly Arg Gln Gly His Gln Glu
    130                 135                 140

Gly Ala Asp Ser Ser Asp Leu Asn Val Glu Glu Ser Asp Gly Leu Ser
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145                 150                 155                 160

Val Ile Asp Glu Val Val Gly Val Ile Tyr Gln Ala Phe Ser Thr Ile
                165                 170                 175

Trp Thr Tyr Leu Ser Gly Leu Phe
            180


<210> SEQ ID NO 10
<211> LENGTH: 555
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 10

atgaaatgga gtggttttat gaaaacaaaa tcaaaacgct ttttaaacct agcaaccctt      60

tgcttggccc tactaggaac aactttgcta atggcacatc ccgtacaggc ggaggtgata     120

tcaaaaagag actatatgac tcgcttcggg ttaggcgatt tagaagatga ttcagctaac     180

tatccttcaa atttagaagc tagatataaa ggatatttag agggatatga aaaaggctta     240

aaaggagatg atatacccga acggcccaag attcaggttc ctgaggatgt tcagccatct     300

gaccatggcg actatagaga tggttatgag gaaggatttg gagaaggaca acataaacgt     360

gatccattag aaacagaagc agaagatgat tctcaaggag gacgtcaaga aggacgtcaa     420

ggacatcaag aaggagcaga ttctagtgat ttgaacgttg aagaaagcga cggtttgtct     480

gttattgatg aagtagttgg agtaatttat caagcattta gtactatttg gacatactta     540

agcggtttgt tctaa                                                      555


<210> SEQ ID NO 11
<211> LENGTH: 260
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 11

Met Asp Ile Asn Leu Leu Gln Ala Leu Leu Ile Gly Leu Trp Thr Ala
1               5                   10                  15

Phe Cys Phe Ser Gly Met Leu Leu Gly Ile Tyr Thr Asn Arg Cys Ile
            20                  25                  30

Ile Leu Ser Phe Gly Val Gly Ile Ile Leu Gly Asp Leu Pro Thr Ala
        35                  40                  45

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

Gly Ala Gly Gly Thr Val Pro Pro Asn Pro Ile Gly Pro Gly Ile Phe
65                  70                  75                  80

Gly Thr Leu Met Ala Ile Thr Ser Ala Gly Lys Val Thr Pro Glu Ala
                85                  90                  95

Ala Leu Ala Leu Ser Thr Pro Ile Ala Val Ala Ile Gln Phe Leu Gln
            100                 105                 110

Thr Phe Ala Tyr Thr Ala Phe Ala Gly Ala Pro Glu Thr Ala Lys Lys
        115                 120                 125

Gln Leu Gln Lys Gly Asn Ile Arg Gly Phe Lys Phe Ala Ala Asn Gly
    130                 135                 140

Thr Ile Trp Ala Phe Ala Phe Ile Gly Leu Gly Leu Gly Leu Leu Gly
145                 150                 155                 160

Ala Leu Ser Met Asp Thr Leu Leu His Leu Val Asp Tyr Ile Pro Pro
                165                 170                 175
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Val Leu Leu Asn Gly Leu Thr Val Ala Gly Lys Met Leu Pro Ala Ile
            180                 185                 190

Gly Phe Ala Met Ile Leu Ser Val Met Ala Lys Lys Glu Leu Ile Pro
        195                 200                 205

Phe Val Leu Ile Gly Tyr Val Cys Ala Ala Tyr Leu Gln Ile Pro Thr
    210                 215                 220

Ile Gly Ile Ala Ile Ile Gly Ile Ile Phe Ala Leu Asn Glu Phe Tyr
225                 230                 235                 240

Asn Lys Pro Lys Gln Val Asp Ala Thr Thr Val Gln Gly Gly Gln Gln
                245                 250                 255

Asp Asp Trp Ile
            260


<210> SEQ ID NO 12
<211> LENGTH: 783
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 12

atggatatca atttgttaca ggcactttta attggtcttt ggacagcctt ttgtttcagc     60

ggaatgttac ttggcatcta caccaaccgt tgtattattc tgtcttttgg tgtagggatt    120

atcttaggtg acttgccaac tgcacttagc atgggagcta tctccgaatt agcttatatg    180

ggatttggag tgggtgccgg tggtaccgtt cctcctaatc ctatcggccc tggtatcttt    240

ggtaccttga tggctattac cagtgctggt aaagtcaccc cagaagcggc actagcctta    300

tcaacaccaa tcgcagttgc catccaattc cttcaaacat tcgcctatac agcttttgct    360

ggcgctcccg aaaccgctaa aaaacaattg caaaaaggca atattagagg cttcaaattc    420

gctgccaacg gcactatctg ggctttcgct tttatcggat taggccttgg tttattaggt    480

gccttgtcaa tggatactct ccttcacttg gttgattata tcccacctgt cttgctcaat    540

ggattgactg tcgctggtaa aatgttacct gctatcggat ttgccatgat cttatctgtt    600

atggccaaga aagaattgat tccttttgta ctaattggtt atgtttgtgc agcctacctc    660

caaattccaa ccattggtat cgccattatt ggtatcattt tcgccttgaa tgaattttac    720

aacaaaccta aacaagtcga tgcaacaact gtccaaggag gccaacaaga tgactggatc    780

taa                                                                   783


<210> SEQ ID NO 13
<211> LENGTH: 162
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 13

Met Thr Gln Pro Asn Ile Ile Met Thr Arg Val Asp Glu Arg Leu Ile
1               5                   10                  15

His Gly Gln Gly Gln Leu Trp Val Lys Phe Leu Asn Cys Asn Thr Val
            20                  25                  30

Ile Val Ala Asn Asp Ala Val Ser Glu Asp Lys Ile Gln Gln Ser Leu
        35                  40                  45

Met Lys Thr Val Ile Pro Ser Ser Ile Ala Ile Arg Phe Phe Ser Ile
    50                  55                  60

Gln Lys Val Ile Asp Ile Ile His Lys Ala Ser Pro Ala Gln Ser Ile
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65 70 75 80

Phe Ile Val Val Lys Asp Leu Gln Asp Ala Lys Leu Leu Val Glu Gly
85 90 95

Gly Val Pro Ile Thr Glu Ile Asn Ile Gly Asn Ile His Lys Thr Asp
100 105 110

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

Ser Ala Ile Arg Cys Leu Ala His Asp His His Val Val Phe Asn Thr
130 135 140

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

Tyr Ile

<210> SEQ ID NO 14
<211> LENGTH: 489
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 14

atgacacaac caaacattat catgacgcga gttgatgagc gtttgattca cggacagggg 60

caattatggg tcaaattcct caactgcaac accgttatcg tcgctaacga tgcggtttct 120

gaagataaga ttcaacaatc cctcatgaaa acagttattc catccagtat tgccattcgt 180

tttttctcca ttcaaaaagt gattgacatc attcataaag caagtcctgc tcaaagtatc 240

ttcatcgtgg tcaaagattt gcaagatgcc aaactcctag ttgaaggggg tgttcccatc 300

acagaaatca atatcggtaa tattcataaa actgatgata aggttgcgat tacccagttt 360

atttcgctgg gagaaacaga caagtctgct attcgttgct tagcccatga ccaccacgtg 420

gtttttaaca ccaaaacaac tccagctggc aatagcgcct ctgacgttga catcttagat 480

tatatttaa 489

<210> SEQ ID NO 15
<211> LENGTH: 337
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 15

Met Glu Glu Glu Ile Ala Leu Leu Glu Asn His Met Thr Glu Pro Asp
1 5 10 15

Phe Trp Asn Asp Asn Ile Ala Ala Gln Lys Thr Ser Gln Glu Leu Asn
20 25 30

Glu Leu Lys Gly Lys Tyr Asp Thr Phe His Asn Met Gln Glu Leu Ser
35 40 45

Asp Glu Thr Glu Leu Leu Leu Glu Met Leu Asp Glu Asp Asp Ser Leu
50 55 60

Lys Glu Glu Leu Glu Glu Asn Leu Met Gln Leu Asp Lys Ile Met Gly
65 70 75 80

Ala Tyr Glu Met Thr Leu Leu Leu Ser Glu Pro Tyr Asp His Asn Asn
85 90 95

Ala Ile Leu Glu Ile His Pro Gly Ser Gly Gly Thr Glu Ala Gln Asp
100 105 110

Trp Gly Asp Leu Leu Leu Arg Met Tyr Thr Arg Phe Gly Asn Ala Asn
115 120 125

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Gly Phe Lys Ile Glu Val Leu Asp Tyr Gln Ala Gly Asp Glu Ala Gly
    130                 135                 140

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

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

Asp Ser Ala Lys Arg Arg His Thr Ser Phe Ala Ser Val Glu Val Met
            180                 185                 190

Pro Glu Leu Asp Asp Thr Ile Glu Val Glu Val Arg Asp Asp Asp Ile
        195                 200                 205

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

Lys Val Ser Thr Gly Val Arg Leu Thr His Ile Pro Thr Gly Ile Val
225                 230                 235                 240

Val Ser Ser Thr Val Asp Arg Thr Gln Tyr Gly Asn Arg Asp Arg Ala
                245                 250                 255

Met Lys Met Leu Gln Ala Lys Leu Tyr Gln Leu Glu Gln Glu Lys Lys
            260                 265                 270

Ala Gln Glu Val Asp Ala Leu Lys Gly Asp Lys Lys Glu Ile Thr Trp
        275                 280                 285

Gly Ser Gln Ile Arg Ser Tyr Val Phe Thr Pro Tyr Thr Met Val Lys
    290                 295                 300

Asp His Arg Thr Asn Phe Glu Leu Ala Gln Val Asp Lys Val Met Asp
305                 310                 315                 320

Gly Glu Ile Asn Gly Phe Ile Asp Ala Tyr Leu Lys Trp Arg Ile Glu
                325                 330                 335

Asp


<210> SEQ ID NO 16
<211> LENGTH: 1014
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 16

ttggaagagg agattgctct tcttgaaaat cacatgactg agccagactt ttggaatgac      60

aatattgcag cgcaaaagac atctcaagaa ctaaatgagt taaaaggtaa gtatgatact     120

ttccataata tgcaagaatt atctgacgaa acagaactct tacttgagat gcttgacgaa     180

gatgattctt tgaaagaaga attagaagaa aatctaatgc agctagataa gataatgggt     240

gcttatgaaa tgacgcttct cttatctgaa ccctatgacc acaataatgc tatcttagaa     300

atccatcctg gttcaggagg aactgaagcg caagattggg gagatttact cttacgaatg     360

tatacccgtt ttggcaatgc taatggtttc aaaatagaag tattggatta tcaagcagga     420

gatgaagctg gtattaaatc ggttaccctc tcttttgaag gccccaatgc ttatggtttg     480

ttgaaatcag aaatgggagt tcatcgcctc gttcgtatat caccttttga ttcggctaaa     540

cgtcgtcata cctcatttgc ttcagttgaa gtgatgccag agttagatga tacgattgaa     600

gtagaagtac gtgatgatga cattaaaatg gatactttcc gttccggagg agctggtggt     660

cagaatgtca ataaagtatc aacaggtgtt cgtttgacgc atattccaac tggaattgtg     720

gtatcgtcta ccgttgaccg tactcaatat ggaaaccgcg atcgcgctat gaagatgttg     780
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caggctaagc tatatcagtt agaacaagaa aagaaagcac aagaagtaga tgctctcaag     840

ggtgataaaa aagaaatcac ttggggaagt cagattcgtt cttatgtttt caccccttat     900

acgatggtga aggatcatcg tactaacttt gagcttgctc aggtagataa ggttatggat     960

ggagagatca atggctttat tgatgcctac cttaagtggc gcattgaaga ctaa          1014


<210> SEQ ID NO 17
<211> LENGTH: 230
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 17

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

Thr Thr Ala Leu Arg Asp Val Asn Val Ser Val Asn Gln Gly Glu Phe
            20                  25                  30

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

Leu Leu Tyr Arg Glu Glu Gln Leu Thr Thr Gly Lys Leu Tyr Val Gly
    50                  55                  60

Glu Phe Asn Leu Thr Lys Leu Lys Ala Arg Asp Val Pro Ile Leu Arg
65                  70                  75                  80

Arg His Ile Gly Val Val Phe Gln Asp Tyr Lys Leu Leu Pro Arg Lys
                85                  90                  95

Thr Val Phe Glu Asn Val Ala Tyr Ala Met Glu Val Ile Gly Glu Lys
            100                 105                 110

Arg Arg His Ile Lys Lys Arg Val Pro Glu Val Leu Asp Leu Val Gly
        115                 120                 125

Leu Lys His Lys Met Arg Ser Phe Pro Ser Gln Leu Ser Gly Gly Glu
    130                 135                 140

Gln Gln Arg Val Ala Ile Ala Arg Ala Ile Val Asn Asn Pro Lys Leu
145                 150                 155                 160

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

Glu Ile Met Gln Leu Leu Glu Arg Ile Asn Val Gln Gly Thr Thr Ile
            180                 185                 190

Leu Met Ala Thr His Asn Ser His Ile Val Asn Thr Phe Arg His Arg
        195                 200                 205

Val Val Ala Ile Glu Asp Gly Arg Ile Val Arg Asp Glu Glu Lys Gly
    210                 215                 220

Asp Tyr Gly Tyr Asp Asp
225                 230


<210> SEQ ID NO 18
<211> LENGTH: 693
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 18

atggcactaa tagaaatgtc tggtgttact aaaaaatacc gccgctcaac gaccgccctc      60

agagacgtca atgtttctgt taaccaaggt gagtttgttt atctcgtagg cccatcaggt     120

gctggtaaat caacttttat caaactcctt taccgtgaag aacaactgac aactggtaag     180

ctatatgtgg gtgaattcaa tttaactaag ctaaaagcac gtgatgttcc gattcttcgt     240
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cgtcacatcg gagtagtttt tcaagattac aaactgctac caagaaaaac agtctttgaa    300

aatgtagctt acgccatgga agttattggt gaaaagcgcc gccacattaa aaaacgcgtg    360

ccagaggtac tcgatttagt tggcttgaaa cataagatgc gttcttttcc aagtcagcta    420

tcaggagggg agcagcaacg tgtggccatt gcgcgtgcga ttgttaacaa ccctaaatta    480

ttgattgcag atgaaccgac agggaattta gatcctgaga tttcatggga aattatgcag    540

ttacttgaac gtattaatgt tcagggaaca actatcttaa tggcgacaca caacagtcat    600

attgtgaata cattccgtca tcgtgttgtt gctattgaag atggtcgcat agtacgtgat    660

gaagaaaaag gagattatgg ttacgatgat tag                                 693
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<210> SEQ ID NO 19
<211> LENGTH: 2045
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 19

Met Arg Lys Val Lys Lys Val Phe Val Ser Ser Cys Met Leu Leu Thr
1               5                   10                  15

Val Gly Leu Gly Val Ala Val Pro Thr Gly Phe Ser Gln Ser Asn Gly
            20                  25                  30

Val Met Val Val Lys Ala Ala Glu Val Pro Ala Thr Asp Leu Ser Arg
        35                  40                  45

Gln Ala Ser Asp Ser Glu Arg Val Asp Glu Ser Ser Leu Leu Gln Lys
    50                  55                  60

Glu Asn Leu Ser Val Asp Ser Phe Lys Leu Glu Asn Leu Asn Gly Trp
65                  70                  75                  80

Glu Ala Glu Asn Asp Thr Ala Gly Asn Leu Gly Lys Phe Lys Asp Pro
                85                  90                  95

Asp Ser Ser Gly Tyr Gln Asn Ile Leu Thr Ser Ser Gly Lys Asn Ile
            100                 105                 110

Ser Val Ala Val Ala Pro Lys Gly Ser Gly Lys Met Asn Ile Lys Val
        115                 120                 125

Thr Lys Arg Ser Asn Phe Gln Gly Gly Tyr Tyr Val Gly Gly Leu Arg
    130                 135                 140

Thr Gln Thr Pro Val Leu Lys Leu Asn Asp Val Tyr Arg Tyr Ser Phe
145                 150                 155                 160

Thr Thr Lys Lys Leu Ser Gly Asn Ser Ser Glu Phe Lys Thr Arg Val
                165                 170                 175

Lys Pro Val Glu Ser Asn Asn Lys Leu Gly Lys Glu Leu Val Ile Arg
            180                 185                 190

Val Asp Asn Lys Asn Val Ser Thr Lys His Asp Trp Leu Pro Asp Ile
        195                 200                 205

Ser Asp Gly Thr His Thr Val Asp Phe Thr Gly Leu Asp Lys Lys Leu
    210                 215                 220

Ser Val Ala Phe Arg Phe Ser Pro Arg Gln Thr Ser Asn Val Val Tyr
225                 230                 235                 240

Glu Phe Ser Asn Ile Asn Ile Lys Asn Ile Ser Pro Ala Ser Val Pro
                245                 250                 255

Ala Ile Pro Ser Lys Val Leu Glu Gly Thr Ser Val Leu Ser Gly Thr
            260                 265                 270
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```
Ala Ile Ser Ser Gly Asp Thr Leu Glu Lys Arg Lys Ser Phe Asp Gly
        275                 280                 285

Asp Ile Leu Arg Val Tyr Lys Asp Ser Lys Ile Ile Ala Arg Thr Val
    290                 295                 300

Ile Lys Gly Asn Lys Trp Asp Val Lys Leu Ser Lys Pro Leu Ile Ala
305                 310                 315                 320

Gly Glu Lys Leu Asp Phe Glu Ile Leu His Pro Arg Ser Gln Asn Val
                325                 330                 335

Ser Lys Lys Ile Ser Lys Gln Val Glu Ala Lys Pro Phe Asp Pro Ala
            340                 345                 350

Ser Tyr Lys Glu Lys Val Ile Ala Lys Leu Lys Pro Val Tyr Glu Ala
        355                 360                 365

Thr Ser Glu Lys Ile Thr Asn Asp Ala Trp Leu Asp Glu Asn Ala Lys
    370                 375                 380

Asp Leu Gln Lys Gln Lys Leu Glu Glu Gln Tyr Ile Ser Gly Lys Val
385                 390                 395                 400

Ala Ile Ser Glu Ala Gly Thr Lys Gln Glu Ala Ile Asp Ala Ala Tyr
                405                 410                 415

Asn Lys Tyr Ser Ser Gln Thr Asp Pro Asp Ser Leu Pro Ser Gln Tyr
            420                 425                 430

Lys Gln Gly Asn Lys Glu Asn Glu Gln Glu Lys Gly Arg Gln Asp Leu
        435                 440                 445

Ile Gln Thr Arg Asp Leu Thr Leu Lys Ala Ile Gln Glu Asp Lys Trp
    450                 455                 460

Leu Thr Glu Gln Glu Lys Thr Ile Gln Lys Glu Glu Ala Leu Lys Ala
465                 470                 475                 480

Phe Glu Thr Gly Ile Glu Ser Val Asn Gln Thr Val Ser Leu Glu Gln
                485                 490                 495

Leu Lys Gln Arg Leu Ile Val Tyr Lys Ala Ser Glu Lys Asp Ser Glu
            500                 505                 510

Lys Lys Glu Tyr Pro Glu Ser Ile Pro Asn Gln His Ile Pro Gly Lys
        515                 520                 525

Glu Lys Glu Val Lys Ala Ala Lys Gln Glu Glu Leu Lys Lys Leu His
    530                 535                 540

Asp Thr Thr Leu Glu Lys Ile Asn Gln Asp Lys Trp Leu Thr Pro Asp
545                 550                 555                 560

Gln Gln Ala Glu Gln Leu Lys Gln Ala Glu Val Thr Phe Lys Lys Gly
                565                 570                 575

Gln Glu Ala Ile Lys Ser Ala Gln Thr Leu Thr Gln Leu Glu Thr Asp
            580                 585                 590

Leu Ala Asp Tyr Val Ser Glu Asn Glu Gly Lys Gly Asn Ser Ile Pro
        595                 600                 605

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

Val Lys Leu Lys Glu Ala His Glu Ala Thr Lys Gln Ala Ile Glu Lys
625                 630                 635                 640

Asp Pro Trp Leu Ser Pro Glu Gln Lys Lys Ala Gln Lys Glu Lys Ala
                645                 650                 655

Lys Ala Arg Leu Asp Glu Gly Leu Lys Ala Leu Lys Ala Ala Asp Ser
            660                 665                 670

Leu Glu Ile Leu Lys Val Thr Glu Glu Ala Phe Val Asp Lys Glu Lys
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        675                 680                 685

Asn Pro Asp Ser Ile Pro Asn Gln His Lys Ala Gly Thr Ala Asp Gln
    690                 695                 700

Ala Arg Lys Gln Ala Leu Asp Ser Leu Asp Lys Glu Val Gln Lys Glu
705                 710                 715                 720

Leu Glu Ser Ile Asp Asn Asp Asn Thr Leu Thr Thr Asp Glu Lys Ala
                725                 730                 735

Ala Ala Lys Lys Lys Val Asn Asp Ala Tyr Asp Val Ala Lys Gln Thr
            740                 745                 750

Ala Met Glu Ala Asn Ser Tyr Glu Asp Leu Thr Thr Ile Lys Asp Glu
        755                 760                 765

Phe Leu Ser Asn Leu Pro His Lys Gln Gly Thr Pro Leu Lys Asp Gln
    770                 775                 780

Gln Ser Asp Ala Ile Ala Glu Leu Glu Lys Lys Gln Gln Glu Ile Glu
785                 790                 795                 800

Lys Ala Ile Glu Gly Asp Lys Thr Leu Pro Arg Asp Glu Lys Glu Lys
                805                 810                 815

Gln Ile Ala Asp Ser Lys Glu Arg Leu Lys Ser Asp Thr Gln Lys Val
            820                 825                 830

Lys Asp Ala Lys Asn Ala Asp Ala Ile Lys Lys Ala Phe Glu Glu Gly
        835                 840                 845

Lys Val Asn Ile Pro Gln Ala His Ile Pro Gly Asp Leu Asn Lys Asp
    850                 855                 860

Lys Glu Lys Leu Leu Ala Glu Leu Lys Gln Lys Ala Asp Asp Thr Glu
865                 870                 875                 880

Lys Ala Ile Asp Val Asp Lys Thr Leu Thr Glu Asp Glu Lys Lys Glu
                885                 890                 895

Gln Lys Val Lys Thr Lys Ala Glu Leu Glu Lys Ala Lys Thr Asp Val
            900                 905                 910

Lys Asn Thr Gln Thr Arg Glu Glu Leu Asp Lys Lys Val Pro Glu Leu
        915                 920                 925

Lys Lys Ala Ile Glu Asp Thr His Val Lys Gly Asn Leu Glu Gly Val
    930                 935                 940

Lys Asn Lys Ala Ile Glu Asp Leu Lys Lys Ala His Thr Glu Thr Val
945                 950                 955                 960

Ala Lys Ile Asn Gly Asp Asp Thr Leu Asp Lys Ala Thr Lys Glu Ala
                965                 970                 975

Gln Val Lys Glu Ala Asp Lys Ala Leu Ala Ala Gly Lys Asp Ala Ile
            980                 985                 990

Thr Lys Ala Asp Asp Ala Asp Lys  Val Ser Thr Ala Val  Thr Glu His
        995                 1000                 1005

Thr Pro  Lys Ile Lys Ala Ala  His Lys Thr Gly Asp  Leu Lys Lys
    1010                 1015                 1020

Ala Gln  Val Asp Ala Asn Thr  Ala Leu Asp Lys Ala  Ala Glu Lys
    1025                 1030                 1035

Glu Arg  Gly Glu Ile Asn Lys  Asp Ala Thr Leu Thr  Thr Glu Asp
    1040                 1045                 1050

Lys Ala  Lys Gln Leu Lys Glu  Val Glu Thr Ala Leu  Thr Lys Ala
    1055                 1060                 1065

Lys Asp  Asn Val Lys Ala Ala  Lys Thr Ala Asp Ala  Ile Asn Asp
    1070                 1075                 1080
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Ala Arg  Asp Lys Gly Val Ala  Thr Ile Asp Ala Val  His Lys Ala
    1085                 1090                 1095

Gly Gln  Asp Leu Gly Ala Arg  Lys Ser Gly Gln Val  Ala Lys Leu
    1100                 1105                 1110

Glu Glu  Ala Ala Lys Ala Thr  Lys Asp Lys Ile Ser  Ala Asp Pro
    1115                 1120                 1125

Thr Leu  Thr Ser Lys Glu Lys  Glu Glu Gln Ser Lys  Ala Val Asp
    1130                 1135                 1140

Ala Glu  Leu Lys Lys Ala Ile  Glu Ala Val Asn Ala  Ala Asp Thr
    1145                 1150                 1155

Ala Asp  Lys Val Asp Asp Ala  Leu Gly Glu Gly Val  Thr Asp Ile
    1160                 1165                 1170

Lys Asn  Gln His Lys Ser Gly  Asp Ser Ile Asp Ala  Arg Arg Glu
    1175                 1180                 1185

Ala His  Gly Lys Glu Leu Asp  Arg Val Ala Gln Glu  Thr Lys Gly
    1190                 1195                 1200

Ala Ile  Glu Lys Asp Pro Thr  Leu Thr Thr Glu Glu  Lys Ala Lys
    1205                 1210                 1215

Gln Val  Lys Asp Val Asp Ala  Ala Lys Glu Arg Gly  Met Ala Lys
    1220                 1225                 1230

Leu Asn  Glu Ala Lys Asp Ala  Asp Ala Leu Asp Lys  Ala Tyr Gly
    1235                 1240                 1245

Glu Gly  Val Thr Asp Ile Lys  Asn Gln His Lys Ser  Gly Asp Pro
    1250                 1255                 1260

Val Asp  Ala Arg Arg Gly Leu  His Asn Lys Ser Ile  Asp Glu Val
    1265                 1270                 1275

Ala Gln  Ala Thr Lys Asp Ala  Ile Thr Ala Asp Thr  Thr Leu Thr
    1280                 1285                 1290

Glu Ala  Glu Lys Glu Thr Gln  Arg Gly Asn Val Asp  Lys Glu Ala
    1295                 1300                 1305

Thr Lys  Ala Lys Glu Glu Leu  Ala Lys Ala Lys Asp  Ala Asp Ala
    1310                 1315                 1320

Leu Asp  Lys Ala Tyr Gly Asp  Gly Val Thr Ser Ile  Lys Asn Gln
    1325                 1330                 1335

His Lys  Ser Gly Lys Gly Leu  Asp Val Arg Lys Asp  Glu His Lys
    1340                 1345                 1350

Lys Ala  Leu Glu Ala Val Ala  Lys Arg Val Thr Ala  Glu Ile Glu
    1355                 1360                 1365

Ala Asp  Pro Thr Leu Thr Pro  Glu Val Arg Glu Gln  Gln Lys Ala
    1370                 1375                 1380

Glu Val  Gln Lys Glu Leu Glu  Leu Ala Thr Asp Lys  Ile Ala Glu
    1385                 1390                 1395

Ala Lys  Asp Ala Asp Glu Ala  Asp Lys Ala Tyr Gly  Asp Gly Val
    1400                 1405                 1410

Thr Ala  Ile Glu Asn Ala His  Val Ile Gly Lys Gly  Ile Glu Ala
    1415                 1420                 1425

Arg Lys  Asp Leu Ala Lys Lys  Asp Leu Ala Glu Ala  Ala Ala Lys
    1430                 1435                 1440

Thr Lys  Ala Leu Ile Ile Glu  Asp Lys Thr Leu Thr  Asp Asp Gln
    1445                 1450                 1455
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Arg Lys  Glu Gln Leu Leu Gly  Val Asp Thr Glu Tyr  Ala Lys Gly
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Ile Glu  Asn Ile Asp Ala Ala  Lys Asp Ala Ala Gly  Val Asp Lys
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Ala Tyr  Ser Asp Gly Val Arg  Asp Ile Leu Ala Gln  Tyr Lys Glu
    1490                 1495                 1500

Gly Gln  Asn Leu Asn Asp Arg  Arg Asn Ala Ala Lys  Glu Phe Leu
    1505                 1510                 1515

Leu Lys  Glu Ala Asp Lys Val  Thr Lys Leu Ile Asn  Asp Asp Pro
    1520                 1525                 1530

Thr Leu  Thr His Asp Gln Lys  Val Asp Gln Ile Asn  Lys Val Glu
    1535                 1540                 1545

Gln Ala  Lys Leu Asp Ala Ile  Lys Ser Val Asp Asp  Ala Gln Thr
    1550                 1555                 1560

Ala Asp  Ala Ile Asn Asp Ala  Leu Gly Lys Gly Ile  Glu Asn Ile
    1565                 1570                 1575

Asn Asn  Gln Tyr Gln His Gly  Asp Gly Val Asp Val  Arg Lys Ala
    1580                 1585                 1590

Thr Ala  Lys Gly Asp Leu Glu  Lys Glu Ala Ala Lys  Val Lys Ala
    1595                 1600                 1605

Leu Ile  Ala Lys Asp Pro Thr  Leu Thr Gln Ala Asp  Lys Asp Lys
    1610                 1615                 1620

Gln Thr  Ala Ala Val Asp Ala  Ala Lys Asn Thr Ala  Ile Ala Ala
    1625                 1630                 1635

Val Asp  Lys Ala Thr Thr Thr  Glu Gly Ile Asn Gln  Glu Leu Gly
    1640                 1645                 1650

Lys Gly  Ile Thr Ala Ile Asn  Lys Ala Tyr Arg Pro  Gly Glu Gly
    1655                 1660                 1665

Val Lys  Ala Arg Lys Glu Ala  Ala Lys Ala Asp Leu  Glu Lys Glu
    1670                 1675                 1680

Ala Ala  Lys Val Lys Ala Leu  Ile Thr Asn Asp Pro  Thr Leu Thr
    1685                 1690                 1695

Lys Ala  Asp Lys Ala Lys Gln  Thr Glu Ala Val Ala  Lys Ala Leu
    1700                 1705                 1710

Lys Ala  Ala Ile Ala Ala Val  Asp Lys Ala Thr Thr  Ala Glu Gly
    1715                 1720                 1725

Ile Asn  Gln Glu Leu Gly Lys  Gly Ile Thr Ala Ile  Asn Lys Ala
    1730                 1735                 1740

Tyr Arg  Pro Gly Glu Gly Val  Lys Ala Arg Lys Glu  Ala Ala Lys
    1745                 1750                 1755

Ala Asp  Leu Glu Arg Glu Ala  Ala Lys Val Arg Glu  Ala Ile Ala
    1760                 1765                 1770

Asn Asp  Pro Thr Leu Thr Lys  Ala Asp Lys Ala Lys  Gln Thr Glu
    1775                 1780                 1785

Ala Val  Ala Lys Ala Leu Lys  Ala Ala Ile Ala Ala  Val Asp Lys
    1790                 1795                 1800

Ala Thr  Thr Ala Glu Gly Ile  Asn Gln Glu Leu Gly  Lys Gly Ile
    1805                 1810                 1815

Thr Ala  Ile Asn Lys Ala Tyr  Arg Pro Gly Glu Gly  Val Glu Ala
    1820                 1825                 1830

His Lys  Glu Ala Ala Lys Ala  Asn Leu Glu Lys Val  Ala Lys Glu
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1835 1840 1845

Thr Lys Ala Leu Ile Ser Gly Asp Arg Tyr Leu Ser Glu Thr Glu
1850 1855 1860

Lys Ala Val Gln Lys Gln Ala Val Glu Gln Ala Leu Ala Lys Ala
1865 1870 1875

Leu Gly Gln Val Glu Ala Ala Lys Thr Val Glu Ala Val Lys Leu
1880 1885 1890

Ala Glu Asn Leu Gly Thr Val Ala Ile Arg Ser Ala Tyr Val Ala
1895 1900 1905

Gly Leu Ala Lys Asp Thr Asp Gln Ala Thr Ala Ala Leu Asn Glu
1910 1915 1920

Ala Lys Gln Ala Ala Ile Glu Ala Leu Lys Gln Ala Ala Ala Glu
1925 1930 1935

Thr Leu Ala Lys Ile Thr Thr Asp Ala Lys Leu Thr Glu Ala Gln
1940 1945 1950

Lys Ala Glu Gln Ser Glu Asn Val Ser Leu Ala Leu Lys Thr Ala
1955 1960 1965

Ile Ala Thr Val Arg Ser Ala Gln Ser Ile Ala Ser Val Lys Glu
1970 1975 1980

Ala Lys Asp Lys Gly Ile Thr Ala Ile Arg Ala Ala Tyr Val Pro
1985 1990 1995

Asn Lys Ala Val Ala Lys Ser Ser Ser Ala Asn His Leu Pro Lys
2000 2005 2010

Ser Gly Asp Ala Asn Ser Ile Val Leu Val Gly Leu Gly Val Met
2015 2020 2025

Ser Leu Leu Leu Gly Met Val Leu Tyr Ser Lys Lys Lys Glu Ser
2030 2035 2040

Lys Asp
2045

<210> SEQ ID NO 20
<211> LENGTH: 6138
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 20

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gtgccggcga cagatttatc acgtcaggcg tctgattcgg agagggtaga tgaatcgtct 180

ttattgcaga aagaaaactt atcagtagat tcatttaaat tagaaaattt aaatggatgg 240

gaagctgaaa atgatacagc aggtaatttg gggaaattta aagatccaga tagttcgggc 300

tatcaaaata ttttgacatc atctggaaag aatatcagtg tagctgttgc tcccaaaggt 360

tcaggtaaaa tgaacattaa agtaactaaa agatcaaatt ttcagggtgg atattatgta 420

ggtggtctta gaactcaaac tccggtattg aagttaaatg atgtttatcg atattctttt 480

acaactaaaa aattatcagg aaattcttca gagttcaaaa cgagagttaa gcccgttgaa 540

tctaataata aactagggaa agagcttgtt attagggtgg ataataaaaa tgtatctact 600

aagcatgatt ggcttccaga catctctgat ggaactcata ctgtggactt cactggtctt 660

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gaaaaaagaa aatcgtttga tggcgatatc ctaagagttt ataaagatag caaaatcatt    900

gctagaacag taataaaagg caataagtgg gatgttaaac tttcaaagcc tcttattgca    960

ggtgaaaaat tagattttga gattttgcat ccgagatctc aaaacgttag taaaaaaatt   1020

tcaaaacaag tcgaagctaa accatttgat ccagcttcct ataaagaaaa agttatagcc   1080

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gaaaatgcga aggatttgca aaaacaaaaa ttagaagaac aatatatttc tggaaaagta   1200

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caagaaaaag ggcgtcaaga tttaatccag actcgtgatc tgacgttgaa agccattcaa   1380

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cctaatcagc atattccagg gaaagaaaaa gaagttaaag ctgctaaaca agaagaactt   1620

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gatccatggt tgagtccgga acagaaaaaa gctcaaaaag aaaaagccaa agcaagacta   1980

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<210> SEQ ID NO 21
<211> LENGTH: 1210
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 21

Met Ile Ser Phe Ala Pro Phe Leu Ser Pro Glu Ala Ile Lys His Leu
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Gln Glu Asn Glu Arg Cys Arg Asp Gln Ser Gln Lys Arg Thr Ala Gln
            20                  25                  30

Gln Ile Glu Ala Ile Tyr Thr Ser Gly Gln Asn Ile Leu Val Ser Ala
        35                  40                  45

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

Lys Ile Leu Arg Gly Val Ser Ile Asp Arg Leu Phe Ile Ser Thr Phe
65                  70                  75                  80

Thr Val Lys Ala Ala Thr Glu Leu Arg Glu Arg Ile Glu Asn Lys Leu
                85                  90                  95

Tyr Ser Gln Ile Ala Gln Thr Thr Asp Phe Gln Met Lys Val Tyr Leu
            100                 105                 110

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

Ala Phe Ala Gln Lys Val Val Ser Arg Tyr Gly Tyr Ser Ile Gly Ile
    130                 135                 140

Ser Ser Gln Phe Arg Ile Met Gln Asp Lys Ala Glu Gln Asp Val Leu
145                 150                 155                 160

Lys Gln Glu Val Phe Ser Lys Leu Phe Asn Glu Phe Met Asn Gln Lys
                165                 170                 175

Glu Ala Pro Val Phe Arg Ala Leu Val Lys Asn Phe Ser Gly Asn Cys
            180                 185                 190

Lys Asp Thr Ser Ala Phe Arg Glu Leu Val Tyr Thr Cys Tyr Ser Phe
        195                 200                 205
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Ser Gln Ser Thr Glu Asn Pro Lys Ile Trp Leu Gln Glu Asn Phe Leu
    210                 215                 220

Ser Ala Ala Lys Thr Tyr Gln Arg Leu Glu Asp Ile Pro Asp His Asp
225                 230                 235                 240

Ile Glu Leu Leu Leu Leu Ala Met Gln Asp Thr Ala Asn Gln Leu Arg
                245                 250                 255

Asp Val Thr Asp Met Glu Asp Tyr Gly Gln Leu Thr Lys Ala Gly Ser
            260                 265                 270

Arg Ser Ala Lys Tyr Thr Lys His Leu Thr Ile Ile Glu Lys Leu Ser
        275                 280                 285

Asp Trp Val Arg Asp Phe Lys Cys Leu Tyr Gly Lys Ala Gly Leu Asp
    290                 295                 300

Arg Leu Ile Arg Asp Val Thr Gly Leu Ile Pro Ser Gly Asn Asp Val
305                 310                 315                 320

Thr Val Ser Lys Val Lys Tyr Pro Val Phe Lys Thr Leu His Gln Lys
                325                 330                 335

Leu Lys Gln Phe Arg His Leu Glu Thr Ile Leu Met Tyr Gln Lys Asp
            340                 345                 350

Cys Phe Ser Leu Leu Glu Gln Leu Gln Asp Phe Val Leu Ala Phe Ser
        355                 360                 365

Glu Ala Tyr Leu Ala Val Lys Ile Gln Glu Ser Ala Phe Glu Phe Ser
    370                 375                 380

Asp Ile Ala His Phe Ala Ile Lys Ile Leu Glu Glu Asn Thr Asp Ile
385                 390                 395                 400

Arg Gln Ser Tyr Gln Gln His Tyr His Glu Val Met Val Asp Glu Tyr
                405                 410                 415

Gln Asp Asn Asn His Met Gln Glu Arg Leu Leu Thr Leu Leu Ser Asn
            420                 425                 430

Gly His Asn Arg Phe Met Val Gly Asp Ile Lys Gln Ser Ile Tyr Arg
        435                 440                 445

Phe Arg Gln Ala Asp Pro Gln Ile Phe Asn Gln Lys Phe Arg Asp Tyr
    450                 455                 460

Gln Lys Lys Pro Glu Gln Gly Lys Val Ile Leu Leu Lys Glu Asn Phe
465                 470                 475                 480

Arg Ser Gln Ser Glu Val Leu Asn Val Ser Asn Ala Val Phe Ser His
                485                 490                 495

Leu Met Asp Glu Ser Val Gly Asp Val Leu Tyr Asp Glu Gln His Gln
            500                 505                 510

Leu Ile Ala Gly Ser His Ala Gln Thr Val Pro Tyr Leu Asp Arg Arg
        515                 520                 525

Ala Gln Leu Leu Leu Tyr Asn Ser Asp Lys Asp Asp Gly Asn Ala Pro
    530                 535                 540

Ser Asp Ser Glu Gly Ile Ser Phe Ser Glu Val Thr Ile Val Ala Lys
545                 550                 555                 560

Glu Ile Ile Lys Leu His Asn Asp Lys Gly Val Pro Phe Glu Asp Ile
                565                 570                 575

Thr Leu Leu Val Ser Ser Arg Thr Arg Asn Asp Ile Ile Ser His Thr
            580                 585                 590

Phe Asn Gln Tyr Gly Ile Pro Ile Ala Thr Asp Gly Gly Gln Gln Asn
        595                 600                 605
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Tyr Leu Lys Ser Val Glu Val Met Val Met Leu Asp Thr Leu Arg Thr
    610                 615                 620

Ile Asn Asn Pro Arg Asn Asp Tyr Ala Leu Val Ala Leu Leu Arg Ser
625                 630                 635                 640

Pro Met Phe Ala Phe Asp Glu Asp Asp Leu Ala Arg Ile Ala Leu Gln
                645                 650                 655

Lys Asp Asn Glu Leu Asp Lys Asp Cys Leu Tyr Asp Lys Ile Gln Arg
            660                 665                 670

Ala Val Ile Gly Arg Gly Ala His Pro Glu Leu Ile His Asp Thr Leu
        675                 680                 685

Leu Gly Lys Leu Asn Val Phe Leu Lys Thr Leu Lys Ser Trp Arg Arg
    690                 695                 700

Tyr Ala Lys Leu Gly Ser Leu Tyr Asp Leu Ile Trp Lys Ile Phe Asn
705                 710                 715                 720

Asp Arg Phe Tyr Phe Asp Phe Val Ala Ser Gln Ala Lys Ala Glu Gln
                725                 730                 735

Ala Gln Ala Asn Leu Tyr Ala Leu Ala Leu Arg Ala Asn Gln Phe Glu
            740                 745                 750

Lys Ser Gly Tyr Lys Gly Leu Tyr Arg Phe Ile Lys Met Ile Asp Lys
        755                 760                 765

Val Leu Glu Thr Gln Asn Asp Leu Ala Asp Val Glu Val Ala Thr Pro
    770                 775                 780

Lys Gln Ala Val Asn Leu Met Thr Ile His Lys Ser Lys Gly Leu Gln
785                 790                 795                 800

Phe Pro Tyr Val Phe Ile Leu Asn Cys Asp Lys Arg Phe Ser Met Thr
                805                 810                 815

Asp Ile His Lys Ser Phe Ile Leu Asn Arg Gln His Gly Ile Gly Ile
            820                 825                 830

Lys Tyr Leu Ala Asp Ile Lys Gly Leu Leu Gly Glu Thr Thr Leu Asn
        835                 840                 845

Ser Val Lys Val Ser Met Glu Thr Leu Pro Tyr Gln Leu Asn Lys Gln
    850                 855                 860

Glu Leu Arg Leu Ala Thr Leu Ser Glu Glu Met Arg Leu Leu Tyr Val
865                 870                 875                 880

Ala Met Thr Arg Ala Glu Lys Lys Val Tyr Phe Ile Gly Lys Ala Ser
                885                 890                 895

Lys Ser Lys Ser Gln Glu Ile Thr Asp Pro Lys Lys Leu Gly Lys Leu
            900                 905                 910

Leu Pro Leu Ala Leu Arg Glu Gln Leu Leu Thr Phe Gln Asp Trp Leu
        915                 920                 925

Leu Ala Ile Ala Asp Ile Phe Ser Thr Glu Asp Leu Tyr Phe Asp Val
    930                 935                 940

Arg Phe Ile Glu Asp Ser Asp Leu Thr Gln Glu Ser Val Gly Arg Leu
945                 950                 955                 960

Gln Thr Pro Gln Leu Leu Asn Pro Asp Asp Leu Lys Asp Asn Arg Gln
                965                 970                 975

Ser Glu Thr Ile Ala Arg Ala Leu Asp Met Leu Glu Ala Val Ser Gln
            980                 985                 990

Leu Asn Ala Asn Tyr Glu Ala Ala  Ile His Leu Pro Thr  Val Arg Thr
        995                 1000                1005

Pro Ser  Gln Leu Lys Ala Thr  Tyr Glu Pro Leu Leu  Glu Pro Ile
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    1010                1015                1020

Gly Val  Asp Ile Ile Glu Lys  Ser Ser Arg Ser Leu  Ser Asp Phe
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Thr Leu  Pro His Phe Ser Lys  Lys Ala Lys Val Glu  Ala Ser His
    1040                1045                1050

Ile Gly  Ser Ala Leu His Gln  Leu Met Gln Val Leu  Pro Leu Ser
    1055                1060                1065

Lys Pro  Ile Asn Gln Gln Thr  Leu Leu Asp Ala Leu  Arg Gly Ile
    1070                1075                1080

Asp Ser  Asn Glu Glu Val Lys  Thr Ala Leu Asp Leu  Lys Lys Ile
    1085                1090                1095

Glu Ser  Phe Phe Cys Asp Thr  Ser Leu Gly Gln Phe  Phe Gln Thr
    1100                1105                1110

Tyr Gln  Lys His Leu Tyr Arg  Glu Ala Pro Phe Ala  Ile Leu Lys
    1115                1120                1125

Leu Asp  Pro Ile Ser Gln Glu  Glu Tyr Val Leu Arg  Gly Ile Ile
    1130                1135                1140

Asp Ala  Tyr Phe Leu Phe Asp  Asp His Ile Val Leu  Val Asp Tyr
    1145                1150                1155

Lys Thr  Asp Lys Tyr Lys Gln  Pro Ile Glu Leu Lys  Lys Arg Tyr
    1160                1165                1170

Gln Gln  Gln Leu Glu Leu Tyr  Ala Glu Ala Leu Thr  Gln Thr Tyr
    1175                1180                1185

Lys Leu  Pro Val Thr Lys Arg  Tyr Leu Val Leu Met  Gly Gly Gly
    1190                1195                1200

Lys Pro  Glu Ile Val Glu Val
    1205                1210
```

<210> SEQ ID NO 22
<211> LENGTH: 3633
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 22

```
gtgatttctt ttgccccatt tttaagcccc gaagctatta aacatttgca agaaaacgaa     60

aggtgcagag atcagtctca aaaacgcaca gctcaacaaa ttgaagcaat ttatactagt    120

ggccaaaata tacttgtatc agcttctgct ggttcaggaa aaacctttgt aatggtcgaa    180

cgcatacttg ataaaatttt gagaggtgtt tcaattgatc ggctttttat ctcaaccttt    240

actgttaaag cagctacaga actgcgtgag cggattgaaa acaaattata ctcacaaatt    300

gctcaaacta cagattttca aatgaaagtt tatttaacag aacaattgca atctctttgt    360

caagctgata ttggtactat ggatgctttt gcacagaaag tagtaagtcg ctatggttat    420

agcattggca tttcatccca atttcgtatc atgcaggata aagcagaaca agatgtttta    480

aagcaagagg tgtttagcaa actctttaat gagtttatga atcaaaaaga ggcaccggtg    540

tttagggctc ttgtgaaaaa tttttctggt aactgtaaag acacttcagc ttttagagag    600

ttagtttata cttgttattc ttttagccaa tcgacagaaa acccaaaaat atggttgcaa    660

gaaaatttc taagcgctgc taaaacttac caaagacttg aagatatccc ggatcatgat    720

attgaactct tacttttggc aatgcaagac actgcaaatc agctaagaga tgtgactgat    780

atggaagatt atgggcagct gactaaggca ggtagccgat ctgctaaata cactaaacac    840
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ttaacgatca tagaaaagtt gtctgattgg gtgcgtgatt ttaaatgttt gtatggaaaa 900

gccggattgg atcggttgat cagagatgtg acaggcctta taccatctgg gaatgatgtt 960

acagtctcga aggtaaaata ccctgttttt aagaccttgc atcaaaaatt aaaacaattt 1020

aggcatttag aaacaatttt aatgtatcag aaagactgtt tttccttatt ggaacagtta 1080

caagattttg tgcttgcgtt ttcagaagct tatttagctg tcaaaataca agaaagtgct 1140

tttgaatttt cagatattgc acactttgca atcaaaattt tagaggaaaa tacggatatt 1200

cgccaatcct atcagcaaca ctatcatgag gtgatggttg atgaatatca agataacaat 1260

catatgcaag agcgactcct gaccttacta tcgaacggtc ataatcgctt tatggtagga 1320

gatatcaaac aatcgatcta tcgatttcgg caagccgatc ctcagatttt taatcaaaag 1380

tttagagact atcaaaaaaa acctgagcag gggaaagtga ttttactcaa agaaaacttt 1440

cgtagccaat cagaggtgtt aaatgtcagc aatgctgttt ttagtcactt aatggacgaa 1500

tcagtaggag acgtcttata cgatgagcaa catcagttaa tagcaggtag tcatgctcaa 1560

acagtcccct atctagaccg tcgtgctcag ttattgctat ataatagcga taaagatgat 1620

ggcaacgccc cttcagatag tgagggtatt tcatttagtg aggttacaat tgttgccaaa 1680

gaaattatta agcttcacaa tgataagggt gtcccttttg aagacattac gttactcgtt 1740

tcttcaagaa caagaaatga tatcatttct catacattca atcaatatgg tattcctata 1800

gcaacagatg gtgggcagca aaactatctt aaatctgttg aagtgatggt tatgttagat 1860

acattacgca ccattaataa cccaagaaat gattatgccc ttgtggcttt actgcgctca 1920

ccgatgtttg cctttgatga ggatgattta gcaagaatag cacttcaaaa agacaatgag 1980

ctagataaag attgcctata tgacaagata caaagggctg tgattggaag aggtgctcat 2040

cctgaattga ttcacgatac cttgcttggc aagttaaatg tttttttaaa gacgttgaaa 2100

agctggcgtc gatacgctaa gctagggtcg ttgtatgact tgatttggaa aatttttaat 2160

gatcgttttt attttgattt tgtagctagt caagcaaaag cagaacaagc acaagctaat 2220

ctatacgcat tagctctacg tgctaatcag tttgaaaaat cgggctataa agggctatac 2280

cgttttatta aaatgattga taaggtactt gagacgcaaa atgacttagc tgatgtggaa 2340

gtggctactc ctaaacaagc tgttaattta atgaccattc acaagtctaa aggtttacaa 2400

tttccgtatg tatttatcct taattgtgac aagcgcttct caatgacaga tattcataaa 2460

tcatttattc tgaatcggca gcacggtatc ggtatcaagt accttgcaga tatcaaaggt 2520

ttacttggtg aaacaacact caattctgtt aaagtaagca tggaaacctt accttatcaa 2580

ttgaacaaac aagagttgcg cttagcaact ttatcagaag aaatgcgctt actgtatgtt 2640

gctatgacac gagctgaaaa aaaagtttat tttattggta aagctagtaa gagcaaaagt 2700

caagaaatca cagatcctaa aaagttaggc aaacttttgc cgctggcttt acgagaacag 2760

ttattgacat tccaagattg gctattagca atagcagata tattttcaac tgaagatctt 2820

tattttgatg ttcgctttat tgaagatagt gatttgacac aagagtcagt cggacgactt 2880

caaacaccac agttattaaa tccagatgat cttaaagata atcgtcaatc agaaacaatt 2940

gcacgggctt tagatatgtt agaagcagtg tctcaattga atgccaatta tgaagcagct 3000

attcatttgc caacagttcg aacgcctagc caacttaagg caacttacga gcctttatta 3060

gaacccattg gtgtagatat tatagagaaa tcttctcgat cgctatctga ttttactttg 3120

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```
ccacattttt caaaaaaagc aaaagttgaa gcaagtcata ttggatcagc tcttcatcag   3180

ttgatgcagg tgctcccttt gtcaaaaccg ataaatcaac aaacgctttt agacgcttta   3240

agaggaattg atagtaacga agaggtaaaa acagctcttg atctcaaaaa aatagagtcg   3300

ttcttttgtg atacaagcct aggccaattt tttcagactt accaaaaaca cttgtatcga   3360

gaagcgccat ttgctatttt aaaacttgac cctatcagtc aagaagagta tgtcctacgt   3420

ggtattatag atgcctactt tttgtttgat gatcatattg tattagtgga ctataaaaca   3480

gataaataca agcagcccat tgagttaaaa aagcgttacc aacaacagtt ggagttatat   3540

gcagaagctc tcactcaaac gtataaactt cctgtgacta agcgctatct tgttttaatg   3600

ggaggtggaa agccagaaat tgtcgaagtt taa                                3633
```

<210> SEQ ID NO 23
<211> LENGTH: 397
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 23

```
Met Pro Ser Glu Phe Gln Lys Ala Leu Pro Ile Leu Thr Lys Ile Lys
1               5                   10                  15

Glu Ala Gly Tyr Glu Ala Tyr Phe Val Gly Gly Ser Val Arg Asp Val
            20                  25                  30

Leu Leu Glu Arg Pro Ile His Asp Val Asp Ile Ala Thr Ser Ser Tyr
        35                  40                  45

Pro Glu Glu Thr Lys Ala Ile Phe Asn Arg Thr Val Asp Val Gly Ile
    50                  55                  60

Glu His Gly Thr Val Leu Val Leu Glu Asn Gly Gly Glu Tyr Glu Ile
65                  70                  75                  80

Thr Thr Phe Arg Thr Glu Asp Ile Tyr Val Asp Tyr Arg Arg Pro Ser
                85                  90                  95

Gln Val Ser Phe Val Arg Ser Leu Glu Glu Asp Leu Lys Arg Arg Asp
            100                 105                 110

Phe Thr Val Asn Ala Leu Ala Leu Asp Glu Asn Gly Gln Val Ile Asp
        115                 120                 125

Lys Phe Arg Gly Leu Ile Asp Leu Lys Gln Lys Arg Leu Arg Ala Val
    130                 135                 140

Gly Lys Ala Glu Glu Arg Phe Glu Glu Asp Ala Leu Arg Ile Met Arg
145                 150                 155                 160

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

Phe Glu Ala Met Arg Ser His Ser Pro Leu Leu Glu Lys Ile Ser Val
            180                 185                 190

Glu Arg Ser Phe Thr Glu Phe Asp Lys Leu Leu Met Ala Pro His Trp
        195                 200                 205

Arg Lys Gly Ile Ser Ala Met Ile Ala Cys Gln Ala Tyr Asp Tyr Leu
    210                 215                 220

Pro Gly Leu Lys Gln Gln Glu Ala Gly Leu Asn His Leu Ile Val Ser
225                 230                 235                 240

Leu Lys Asp Asn Phe Thr Phe Ser Asp Tyr His Gln Ala Trp Ala Tyr
                245                 250                 255

Val Met Ile Ser Leu Ala Ile Glu Asp Pro Lys Ser Phe Leu Lys Ala
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            260                 265                 270

Trp Lys Thr Ser Asn Asp Phe Gln Arg Tyr Val Thr Lys Leu Ile Ala
        275                 280                 285

Leu Tyr Arg Ile Arg Gln Glu Arg Ser Phe Glu Lys Leu Asp Ile Tyr
    290                 295                 300

Gln Tyr Gly Lys Lys Met Ala Ser Leu Val Glu Asp Leu Arg Lys Ala
305                 310                 315                 320

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

Leu Val Ile His Asp Lys His Asp Ile Val Leu Asn Gly Ser His Leu
            340                 345                 350

Ile Lys Asp Phe Gly Met Lys Ser Gly Pro Gln Leu Gly Leu Met Leu
        355                 360                 365

Glu Lys Val Glu Leu Ala Ile Val Glu Gly Arg Leu Asp Asn Asp Phe
    370                 375                 380

Thr Thr Ile Glu Ala Phe Val Arg Glu Glu Leu Ala Thr
385                 390                 395


<210> SEQ ID NO 24
<211> LENGTH: 1194
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 24

atgccttctg agtttcagaa ggctttaccc atattgacta aaataaaaga agctggttat      60

gaagcctatt ttgtgggagg aagcgtcaga gatgttttac tcgagcgtcc cattcatgat     120

gtagatattg caactagttc ctatcctgaa gagactaaag cgatttttaa cagaactgtc     180

gatgttggca ttgaacatgg tacagtgctc gtgcttgaaa atggcggtga gtatgaaatt     240

acaaccttta ggacagaaga tatctatgtt gattatcgcc gtcctagtca ggtttctttt     300

gtgcgctctt tagaggaaga cttaaaacga agagacttta ccgtcaatgc cttggccttg     360

gatgaaaatg gtcaagttat tgataaattt agaggactca ttgatttaaa gcaaaaacgg     420

ttacgagcag tgggtaaagc agaggaacgt tttgaagaag atgcactacg cattatgaga     480

ggctttcgat ttgcggcgag tctggatttt gacattgaag ctataacttt tgaagctatg     540

aggagccatt cacctctatt ggaaaagatt tctgtggaac gttcttttac tgaatttgat     600

aaattattga tggcaccgca ctggcgaaaa gggatttctg ccatgattgc ttgtcaggct     660

tacgactatt taccaggctt gaagcagcag gaagcaggct tgaatcatct gatagtttct     720

ttgaaagata actttacctt tagtgattat caccaagctt gggcttatgt gatgattagt     780

ttagccattg aggatcctaa aagcttccta aaagcatgga agacttcaaa tgattttcag     840

cgttatgtca caaagttgat tgctctttat agaattcgtc aggaaagatc ttttgaaaaa     900

ttggatattt accagtacgg caagaaaatg gcgagtctag tggaagacct ccgaaaagct     960

caaagcttat ccgttgacat ggatcgtatt aatactttag atcaggcact ggttattcat    1020

gacaaacacg atatcgtcct taatggttct cacctgatta aggattttgg gatgaaatca    1080

ggtcctcagc tagggcttat gcttgagaaa gttgaattag cgattgtaga ggggcgccta    1140

gataatgatt tcactacaat tgaagcattt gttagagagg aattagcaac atga          1194


<210> SEQ ID NO 25
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<211> LENGTH: 425
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 25

Met Thr Tyr Glu Glu Thr Leu Glu Trp Ile His Asp His Leu Val Phe
1               5                   10                  15

Gly Ile Lys Pro Gly Leu Lys Arg Met Leu Trp Val Leu Gly Gln Leu
            20                  25                  30

Gly Asn Pro Gln Lys Asn Val Lys Gly Val His Ile Val Gly Thr Asn
        35                  40                  45

Gly Lys Gly Ser Thr Val Asn His Leu Gln His Ile Phe Thr Thr Ala
    50                  55                  60

Gly Tyr Glu Val Gly Thr Phe Thr Ser Pro Tyr Ile Met Asp Phe Lys
65                  70                  75                  80

Glu Arg Ile Ser Ile Asn Gly Arg Met Ile Ser Glu Lys Asp Leu Val
                85                  90                  95

Ile Ala Ala Asn Arg Ile Arg Pro Leu Thr Glu Arg Leu Val Gln Glu
            100                 105                 110

Thr Asp Phe Gly Glu Val Thr Glu Phe Glu Val Ile Thr Leu Ile Met
        115                 120                 125

Phe Leu Tyr Phe Gly Asp Met His Pro Val Asp Ile Ala Ile Ile Glu
    130                 135                 140

Ala Gly Leu Gly Gly Leu Tyr Asp Ser Thr Asn Val Phe Gln Ala Met
145                 150                 155                 160

Val Val Val Cys Pro Ser Ile Gly Leu Asp His Gln Ala Ile Leu Gly
                165                 170                 175

Glu Thr Tyr Ala Asn Ile Ala Ala Gln Lys Ala Gly Val Leu Glu Gly
            180                 185                 190

Gly Glu Thr Leu Val Phe Ala Val Glu Asn Pro Ser Ala Arg Glu Val
        195                 200                 205

Phe Leu Thr Lys Ala Glu Gln Val Gly Ala Ser Ile Trp Glu Trp Gln
    210                 215                 220

Glu Gln Phe Gln Met Ala Glu Asn Ala Ser Gly Tyr Arg Phe Thr Ser
225                 230                 235                 240

Pro Leu Gly Val Ile Ser Asp Ile His Ile Ala Met Pro Gly His His
                245                 250                 255

Gln Val Ser Asn Ala Ala Leu Ala Ile Met Thr Cys Leu Thr Leu Gln
            260                 265                 270

Asp Arg Tyr Pro Arg Leu Thr Pro Asp His Ile Arg Glu Gly Leu Ala
        275                 280                 285

Asn Ser Leu Trp Leu Gly Arg Thr Glu Leu Leu Ala Pro Asn Leu Met
    290                 295                 300

Ile Asp Gly Ala His Asn Asn Glu Ser Val Ala Ala Leu Val Ala Val
305                 310                 315                 320

Leu Lys Asn Asn Tyr Asn Asp Lys Lys Leu His Ile Leu Phe Gly Ala
                325                 330                 335

Ile Asp Thr Lys Pro Ile Ala Asp Met Leu Val Ala Leu Glu Gln Ile
            340                 345                 350

Gly Asp Leu Gln Val Thr Ser Phe His Tyr Pro Asn Ala Tyr Pro Leu
        355                 360                 365

Glu Lys Tyr Pro Glu Arg Phe Gly Arg Val Ala Asp Phe Lys Asp Phe
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    370                 375                 380

Leu Ala Leu Arg Lys His Ala Lys Ala Asp Asp Phe Phe Val Ile Thr
385                 390                 395                 400

Gly Ser Leu Tyr Phe Ile Ser Glu Ile Arg Gln Tyr Trp Glu Lys His
                405                 410                 415

Ile Glu Lys Ser Val Leu Leu Thr His
            420                 425


<210> SEQ ID NO 26
<211> LENGTH: 1278
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 26

atgacttatg aagagactct agaatggatt catgatcact tagttttcgg catcaagcca      60

ggcttaaaac gtatgctttg ggttcttgga cagttaggaa atccccaaaa aaatgtcaag     120

ggagtgcata tcgttggaac taacggaaaa ggttccacgg tcaatcattt acaacacatc     180

tttacgacag ctggttatga agtggggacc tttacctctc cttatattat ggatttcaaa     240

gaacgtatta gcataaatgg tcgaatgatt tcagaaaaag atttggttat tgctgctaat     300

cgtattcgtc ctttgacaga gcgtctagtt caagagactg attttggaga ggtaactgaa     360

tttgaagtga ttactttgat catgttcctc tattttggtg acatgcatcc tgtagatatt     420

gctattattg aagcaggcct tggcggtctt tatgattcga ccaatgtttt tcaagcaatg     480

gttgtggtct gtccctcaat tggtttagat caccaagcta ttttgggcga gacttacgct     540

aatattgccg cccaaaaagc tggtgtttta gaagggggcg agacccttgt tttgccgtt     600

gaaaacccgt cagctcgaga ggttttttta acaaaagctg agcaggttgg tgcttcaatc     660

tgggaatggc aagagcagtt tcaaatggct gagaacgcat ctggctatcg ttttactagt     720

cctttaggag ttatttcaga tattcacatc gctatgccag gacaccacca agtgtctaat     780

gcagctttag ctattatgac ttgcttaacc ttgcaagacc gctatcctag gctaactcca     840

gatcatataa gggaaggtct agcaaatagt ttgtggctag gccgtaccga attattagca     900

ccaaatctaa tgattgatgg ggctcataac aatgaaagcg ttgctgcttt ggtagccgtc     960

ttaaaaaata actacaatga taaaaagctt catattttgt ttggtgcgat cgacaccaag    1020

cctattgcag atatgttggt tgctcttgag caaataggtg acttgcaggt tactagcttt    1080

cattacccta acgcctatcc attggaaaaa tacccagaac gttttggtag ggttgctgat    1140

ttcaaagatt tcttggcctt gcgtaagcat gctaaagcag atgacttttt cgtgattaca    1200

gggtcactat attttatttc agaaattaga cagtattggg aaaaacatat tgaaaaaagc    1260

gttcttttaa cccattaa                                                  1278


<210> SEQ ID NO 27
<211> LENGTH: 357
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 27

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

Ile Leu Thr Ser Leu Ser Phe Ile Leu Gln Lys Lys Ser Gly Ser Gly
            20                  25                  30
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Ser Gln Ser Asp Lys Leu Val Ile Tyr Asn Trp Gly Asp Tyr Ile Asp
        35                  40                  45

Pro Ala Leu Leu Lys Lys Phe Thr Lys Glu Thr Gly Ile Glu Val Gln
    50                  55                  60

Tyr Glu Thr Phe Asp Ser Asn Glu Ala Met Tyr Thr Lys Ile Lys Gln
65                  70                  75                  80

Gly Gly Thr Thr Tyr Asp Ile Ala Val Pro Ser Asp Tyr Thr Ile Asp
                85                  90                  95

Lys Met Ile Lys Glu Asn Leu Leu Asn Lys Leu Asp Lys Ser Lys Leu
            100                 105                 110

Val Gly Met Asp Asn Ile Gly Lys Glu Phe Leu Gly Lys Ser Phe Asp
        115                 120                 125

Pro Gln Asn Asp Tyr Ser Leu Pro Tyr Phe Trp Gly Thr Val Gly Ile
    130                 135                 140

Val Tyr Asn Asp Gln Leu Val Asp Lys Ala Pro Met His Trp Glu Asp
145                 150                 155                 160

Leu Trp Arg Pro Glu Tyr Lys Asn Ser Ile Met Leu Ile Asp Gly Ala
                165                 170                 175

Arg Glu Met Leu Gly Val Gly Leu Thr Thr Phe Gly Tyr Ser Val Asn
            180                 185                 190

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

Leu Thr Pro Asn Val Lys Ala Ile Val Ala Asp Glu Met Lys Gly Tyr
    210                 215                 220

Met Ile Gln Gly Asp Ala Ala Ile Gly Ile Thr Phe Ser Gly Glu Ala
225                 230                 235                 240

Ser Glu Met Leu Asp Ser Asn Glu His Leu His Tyr Ile Val Pro Ser
                245                 250                 255

Glu Gly Ser Asn Leu Trp Phe Asp Asn Leu Val Leu Pro Lys Thr Met
            260                 265                 270

Lys His Glu Lys Glu Ala Tyr Ala Phe Leu Asn Phe Ile Asn Arg Pro
        275                 280                 285

Glu Asn Ala Ala Gln Asn Ala Ala Tyr Ile Gly Tyr Ala Thr Pro Asn
    290                 295                 300

Lys Lys Ala Lys Ala Leu Leu Pro Asp Glu Ile Lys Asn Asp Pro Ala
305                 310                 315                 320

Phe Tyr Pro Thr Asp Asp Ile Ile Lys Lys Leu Glu Val Tyr Asp Asn
                325                 330                 335

Leu Gly Ser Arg Trp Leu Gly Ile Tyr Asn Asp Leu Tyr Leu Gln Phe
            340                 345                 350

Lys Met Tyr Arg Lys
        355


<210> SEQ ID NO 28
<211> LENGTH: 1074
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 28

atgcgtaaac tttattcctt tctagcagga gttttgggtg ttattgttat tttaacaagt      60

ctttctttca tcttgcagaa aaaatcgggt tctggtagtc aatcggataa attagttatt     120
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tataactggg gagattacat tgatccagct ttgctcaaaa aattcaccaa agaaacgggc    180

attgaagtgc agtatgaaac tttcgattcc aatgaagcca tgtacactaa aatcaagcag    240

ggcggaacca cttacgacat tgctgttcct agtgattaca ccattgataa aatgatcaaa    300

gaaaacctac tcaataagct tgataagtca aaattagttg gcatggataa tatcgggaaa    360

gaatttttag ggaaaagctt tgacccacaa aacgactatt ctttgcctta tttctgggga    420

accgttggga ttgtttataa tgatcaatta gttgataagg cgcctatgca ctgggaagat    480

ctgtggcgtc cagaatataa aaatagtatt atgctgattg atggagcgcg tgaaatgcta    540

ggggttggtt taacaacttt tggttatagt gtgaattcta aaaatctaga gcagttgcag    600

gcagccgaga gaaaactgca gcagttgacg ccgaatgtta aagccattgt agcagatgag    660

atgaaaggct acatgattca aggtgacgct gctattggaa ttaccttttc tggtgaagcc    720

agtgagatgt tagatagtaa cgaacacctt cactacatcg tgccttcaga agggtctaac    780

ctttggtttg ataatttggt actaccaaaa accatgaaac acgaaaaaga agcttatgct    840

tttttgaact ttatcaatcg tcctgaaaat gctgcgcaaa atgctgcata tattggttat    900

gcgacaccaa ataaaaaagc caaggcctta cttccagatg agataaaaaa tgatcctgct    960

ttttatccaa cagatgacat tatcaaaaaa ttggaagttt atgacaattt agggtcaaga   1020

tggttgggga tttataatga tttatacctc caatttaaaa tgtatcgcaa ataa         1074


<210> SEQ ID NO 29
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 29

Met Ala Phe Glu Lys Glu Ile Lys Leu Lys Asp Cys Lys Tyr Leu Tyr
1               5                   10                  15

Thr Ile Ser Pro Asn Ile Lys Lys Tyr Thr Leu Arg Asp Thr Thr Phe
            20                  25                  30

Ser Gln Thr Lys Val Gly His Tyr Gln Leu Ile Arg Leu Leu Glu Lys
        35                  40                  45

Ile Pro Asn Ser Gly Asp Gly Phe Pro Leu Lys Ile Thr Ile Asn Lys
    50                  55                  60

Glu Leu Thr Gly Phe Lys Leu Ala Ile Thr Asp Gln Ser Gly Leu Arg
65                  70                  75                  80

Leu Val Asn Ile Phe Lys Thr Lys Asp Asn Gln Ile Leu Gln Asp Lys
                85                  90                  95

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

Thr Val Val
        115


<210> SEQ ID NO 30
<211> LENGTH: 348
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 30

atggcttttg aaaaagaaat taagcttaaa gactgtaaat acctttatac aatcagtcca     60

aacattaaaa aatataccct aagagatact acatttagtc aaactaaagt agggcactac    120
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caattaatac gtttactcga aaaaatacct aattcagggg atggtttccc tttaaaaatc    180

actattaata aagaactcac agggtttaaa ttagctatca ccgatcagtc tggtcttaga    240

ttagttaata tttttaaaac aaaagataat caaatccttc aagataaatt ttatttcttg    300

atggacagcc ttgtagaacg tgaaattttt agcaaaacag tcgtctaa                 348


<210> SEQ ID NO 31
<211> LENGTH: 375
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 31

Met Thr Tyr Phe Asp Asn Ala Ala Thr Thr Pro Leu Ser Pro Asn Val
1               5                   10                  15

Ile Arg Ala Met Thr Ala Ala Met Gln Asp Asn Phe Gly Asn Pro Ser
            20                  25                  30

Ser Ile His Phe Tyr Gly Arg Arg Ala Asn Lys Ile Leu Arg Glu Cys
        35                  40                  45

Arg Gln Ala Ile Ala Arg Asn Leu Gly Ala Ser Glu Gln Gln Ile Ile
    50                  55                  60

Val Thr Ser Gly Gly Thr Glu Ser Asn Asn Met Ala Ile Lys Gly Tyr
65                  70                  75                  80

Ala Leu Ala His Gln Ala Lys Gly Lys His Leu Ile Thr Thr Thr Ile
                85                  90                  95

Glu His His Ser Val Leu His Thr Met Ala Tyr Leu Glu Glu Arg Phe
            100                 105                 110

Gly Phe Glu Val Thr Tyr Leu Pro Cys Gln Asn Gly Gln Ile Asn Leu
        115                 120                 125

Ser Asp Leu Lys Gln Ala Leu Arg Asp Asp Thr Ile Leu Val Ser Ile
    130                 135                 140

Met Tyr Ala Asn Asn Glu Thr Gly Asp Leu Leu Pro Ile Lys Asp Ile
145                 150                 155                 160

Gly Asn Leu Leu Lys Asp His Gln Ala Ala Phe His Val Asp Ala Val
                165                 170                 175

Gln Ala Val Gly Lys Leu Lys Ile Ile Pro Ser Glu Leu Gly Ile Asp
            180                 185                 190

Phe Leu Ser Ala Ser Ala His Lys Phe His Gly Pro Lys Gly Cys Gly
        195                 200                 205

Phe Leu Tyr Ser Asn Gly Gln Pro Ile Asp Pro Leu Leu His Gly Gly
    210                 215                 220

Asp Gln Glu Gly Lys Arg Arg Ala Ser Thr Glu Asn Met Leu Gly Ile
225                 230                 235                 240

Ile Gly Met Ala Gln Ala Leu Thr Asp Ala Met Thr Cys Leu Asp Gln
                245                 250                 255

Ser Thr Asp His Ile Ile Ser Leu Arg His His Leu Ile Ser Leu Leu
            260                 265                 270

Glu Gly Leu Pro Tyr Tyr Ile Asn Gln Gly Thr His Tyr Leu Pro His
        275                 280                 285

Val Leu Asn Ile Gly Phe Leu Gly Tyr Gln Asn Thr Ile Leu Leu Thr
    290                 295                 300

Gln Leu Asp Leu Ala Gly Ile Ala Val Ser Thr Gly Ser Ala Cys Thr
305                 310                 315                 320
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Ala Gly Ala Val Asn Pro Ser His Val Leu Ala Ala Tyr Tyr Gly Asp
                325                 330                 335

Asp Ser Ser Arg Leu Lys Glu Ser Ile Arg Ile Ser Phe Ser Asp Gln
            340                 345                 350

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

Leu Gly Gly Thr Asp Gly Phe
    370                 375


<210> SEQ ID NO 32
<211> LENGTH: 1128
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 32

atgacttact ttgataacgc cgccaccaca ccacttagtc ctaatgtgat tagggcgatg      60

acagcagcta tgcaagataa ctttggtaac ccctctagta ttcatttcta cggtcgccga     120

gccaataaaa tccttcgtga atgccgacaa gctatcgcta gaaacttggg ggcaagtgaa     180

cagcaaatta tagtaacgtc cggtggaact gaaagcaata atatggccat aaaaggctat     240

gctttagctc atcaagcaaa gggcaaacat ctcatcacaa ctactattga gcaccactct     300

gtgcttcata ccatggccta tctcgaagag cgatttggtt ttgaggtcac ttatttgcct     360

tgtcaaaatg gacaaataaa tttatctgac ttaaaacaag ccttgagaga tgacaccatt     420

ttggtaagca taatgtatgc caataacgaa acaggtgacc tgttacctat taaggacatt     480

gggaatctgc tcaaagacca tcaagctgct tttcatgttg atgccgttca agctgttggc     540

aaactcaaga ttattcctag cgaacttggg attgactttt tatctgcttc tgctcacaaa     600

tttcatggtc ctaaaggatg cggcttttta tacagtaacg gacaaccaat cgaccctctt     660

cttcacgggg gtgatcaaga aggaaagcga cgcgcaagta ctgaaaatat gttaggtatt     720

attggtatgg cacaagcttt gactgatgct atgacttgtc ttgaccaatc aactgatcac     780

attattagtt tacgtcatca cttgattagc ctcctagaag gactacccta ctatattaat     840

caaggtactc attatcttcc tcatgttctc aatattggat ttttaggcta ccaaaatact     900

attttactaa cacaacttga cttagcaggc attgcagtat caactggttc tgcttgtact     960

gctggagctg ttaatccaag tcatgtttta gctgcgtact atggggatga ctcttctcgt    1020

ttaaaagaat caattcgtat cagtttttca gatcaaaata gcattgaaga tgttaatcaa    1080

ttagctcaaa cattaaaaaa tattttagga ggaacagatg gcttttga                 1128


<210> SEQ ID NO 33
<211> LENGTH: 575
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 33

Met Ile Lys Thr Asp His His Leu Leu Lys Arg Val Leu Gln Asp Leu
1               5                   10                  15

Leu Lys Lys Pro Leu Pro Val Cys Ile Leu Val Ile Ala Ser Phe Val
            20                  25                  30

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

Asp Met Ser Leu Ser Val Asn Ser Trp Gln Thr Leu Lys Trp Leu Leu
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    50                  55                  60

Gly Gln Met Leu Val Ile Ile Val Val Asn Thr Leu Ile Gln Trp Val
65                  70                  75                  80

Met Pro Leu Val Tyr Ser Arg Leu Leu Tyr Gln Tyr Ser Gln Gln Leu
                85                  90                  95

Lys Asp Lys Leu Leu Glu Lys Ile His Arg Leu Pro Phe Ala Tyr Leu
            100                 105                 110

Asp Arg Gln Thr Ile Gly Asp Leu Val Ser Arg Val Ile Thr Asp Thr
        115                 120                 125

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

Gly Leu Leu Thr Ile Leu Cys Thr Ile Ile Ala Met Ala Gln Ile Asp
145                 150                 155                 160

Trp Leu Met Leu Ile Leu Val Leu Val Leu Thr Pro Ser Ser Leu Phe
                165                 170                 175

Leu Ala Arg Phe Ile Ala Gln Lys Ser Phe His Tyr Ala Gln Ala Gln
            180                 185                 190

Thr Lys Ser Arg Gly Asn Leu Ala Gln Phe Thr Glu Glu Ile Leu Arg
        195                 200                 205

Gln Glu Gly Leu Val Gln Leu Phe Asn Ala Gln Glu Gln Ser Ile Cys
    210                 215                 220

Asp Tyr His Val Leu Asn Lys Thr Tyr Cys Glu Ala Ser Gln Lys Ala
225                 230                 235                 240

Ile Phe Tyr Ala Ser Thr Val Asn Pro Ala Thr Arg Phe Ile Asn Ser
                245                 250                 255

Val Ile Tyr Ala Leu Leu Ala Gly Leu Gly Ala Val Arg Ile Met Ala
            260                 265                 270

Gly Leu Phe Ser Val Gly Gln Leu Thr Thr Phe Leu Asn Val Val Val
        275                 280                 285

Gln Tyr Thr Lys Pro Phe Asn Asp Ile Ser Ser Val Leu Ala Glu Ile
    290                 295                 300

Gln Ser Ser Leu Ala Cys Ala Gln Arg Leu Tyr Asp Leu Leu Asp Ile
305                 310                 315                 320

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

Lys Gly Gln Ile Asp Phe Glu Glu Val Ser Phe Ser Tyr Gln Lys Asp
            340                 345                 350

Arg Pro Leu Leu Lys Asp Ile Asn Phe Ser Val Pro Ala Gly Ser Lys
        355                 360                 365

Val Ala Ile Val Gly Pro Thr Gly Ala Gly Lys Ser Thr Leu Ile Asn
    370                 375                 380

Leu Leu Met Arg Phe Tyr Glu Leu Asp Ala Gly Ser Ile Lys Leu Asp
385                 390                 395                 400

Lys Val Pro Ile Lys Cys Tyr Ala Lys Glu Glu Leu Arg Ser Ile Thr
                405                 410                 415

Gly Ile Val Leu Gln Glu Thr Trp Leu Lys Asp Ala Thr Val His Glu
            420                 425                 430

Leu Ile Ala Tyr Gly Ser Glu Glu Ala Ser Arg Asp Glu Val Val Ala
        435                 440                 445

Ala Ala Lys Ala Ala His Ala His Phe Phe Ile Met Gln Leu Pro Lys
    450                 455                 460
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Thr Tyr Asp Thr Tyr Leu Ser Ala Ser Asp Asp Ala Leu Ser Gln Gly
465                 470                 475                 480

Gln Leu Gln Leu Leu Ala Ile Ala Arg Met Phe Leu Lys Lys Pro Lys
                485                 490                 495

Val Leu Val Leu Asp Glu Ala Thr Ser Ser Ile Asp Ile Arg Thr Glu
            500                 505                 510

Ala Val Ile Gln Glu Ala Leu Lys Glu Leu Met Arg Gly Arg Thr Ser
        515                 520                 525

Phe Ile Ile Ala His Arg Leu Ser Thr Ile Gln Ser Ala Asp Leu Ile
    530                 535                 540

Leu Val Met Asp Gln Gly Arg Leu Val Glu Trp Gly Thr His Ala Ser
545                 550                 555                 560

Leu Met Ser Lys Asn Gly Cys Tyr Val Arg Leu Gln Lys Ile Glu
                565                 570                 575


<210> SEQ ID NO 34
<211> LENGTH: 1728
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 34

atgattaaaa cagatcatca cctcctaaag cgagtgcttc aggatttgtt aaaaaaacct     60

ctacctgttt gtattctcgt gatcgctagt tttgtacaag ttggtttaag tgtttacttg    120

cctgttctta tcggtaaagc cgttgatatg agtttgtcag tcaattcttg gcaaacttta    180

aaatggctgt tggggcaaat gttagttatt attgtggtca acacattgat tcaatgggtg    240

atgcctcttg tctatagtcg tttgctatat caatatagcc agcaattgaa agataagctt    300

ttggaaaaaa ttcatcgtct tcctttgca tatctagatc gtcaaaccat tggagatttg    360

gttagtcgag tgataaccga cactgagcaa ctgatcaatg gtctacaaat ggtttttaac    420

cagtttatac ttggactatt gacgattctg tgtaccatta tagctatggc acagattgac    480

tggctcatgt taatcttggt tttggtgtta acaccaagct ccctcttttt agctcgtttt    540

attgctcaaa agagttttca ttatgcacaa gcacagacca aaagcagagg aaatttagct    600

cagtttactg aagaaatcct tcgtcaagaa ggtttggttc aactgtttaa tgctcaagag    660

cagtctatct gtgattatca tgttttaaat aaaacctatt gcgaggcttc acaaaaagcc    720

attttttacg cctcaacagt caatccagcc actcgcttta ttaatagtgt catttatgct    780

ttactggcag gtttaggggc tgttcgtatc atggctggac ttttttcagt aggtcagcta    840

accacttttt taaatgttgt tgtccaatat accaaacctt tcaacgatat ttcatctgtc    900

ttggcagaga tacagagttc tttagcttgt gcgcaaaggc tttatgacct tttagatatt    960

gaaataaaag agcaagagca ctttctaaca tttaaggcat cagcggttaa ggggcaaatt   1020

gactttgaag aagtaagttt ttcttatcaa aaagacaggc ccttactgaa agatattaat   1080

ttttctgttc ctgcgggttc caaggtagcg attgtagggc ctacaggtgc aggtaaatca   1140

actttaatca atttactcat gcgcttttat gaacttgatg ctggtagcat caagttagat   1200

aaagttccta ttaagtgtta tgctaaggaa gaacttaggt ccattactgg catagtattg   1260

caagaaacct ggttgaaaga tgcgactgtt catgagttga ttgcttacgg cagtgaagag   1320

gctagccgtg atgaagtagt ggcagcagcc aaagcagctc atgcacactt ctttattatg   1380
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caacttccta agacttatga tacttactta agtgcttctg atgatgcttt gtcccaaggg   1440

cagctccagt tattagctat tgccagaatg tttttgaaaa aaccaaaagt cttggttcta   1500

gatgaagcca cctcctctat tgatattaga acagaagctg ttattcaaga ggcactaaaa   1560

gaactcatga gaggaaggac cagctttatc attgcccatc gtttatcaac gattcaatca   1620

gctgatttga ttcttgttat ggatcaaggt cgattggttg agtggggaac acatgccagc   1680

ttaatgtcaa aaaacggctg ttatgttaga ttacaaaaga tagaataa                1728


<210> SEQ ID NO 35
<211> LENGTH: 456
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 35

Met Ser Lys Ile Val Val Val Gly Ala Asn His Ala Gly Thr Ala Cys
1               5                   10                  15

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

Phe Asp Gln Asn Ser Asn Ile Ser Phe Leu Gly Cys Gly Met Ala Leu
        35                  40                  45

Trp Ile Gly Glu Gln Ile Ala Gly Pro Glu Gly Leu Phe Tyr Ser Asp
    50                  55                  60

Lys Glu Glu Leu Glu Ser Leu Gly Ala Lys Val Tyr Met Glu Ser Pro
65                  70                  75                  80

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

Gly Lys Asn His Val Glu Thr Tyr Asp Lys Leu Ile Phe Ala Thr Gly
            100                 105                 110

Ser Gln Pro Ile Leu Pro Pro Ile Lys Gly Ala Glu Ile Lys Glu Gly
        115                 120                 125

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

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

Lys Arg Val Ala Val Val Gly Ala Gly Tyr Ile Gly Val Glu Leu Ala
                165                 170                 175

Glu Ala Phe Gln Arg Lys Gly Lys Glu Val Val Leu Ile Asp Val Val
            180                 185                 190

Asp Thr Cys Leu Ala Gly Tyr Tyr Asp Arg Asp Leu Thr Asp Leu Met
        195                 200                 205

Ala Lys Asn Met Glu Glu His Gly Ile Gln Leu Ala Phe Gly Glu Thr
    210                 215                 220

Val Lys Glu Val Ala Gly Asn Gly Lys Val Glu Lys Ile Ile Thr Asp
225                 230                 235                 240

Lys Asn Glu Tyr Asp Val Asp Met Val Ile Leu Ala Val Gly Phe Arg
                245                 250                 255

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

Ala Phe Leu Val Asn Lys Arg Gln Glu Thr Ser Ile Pro Gly Val Tyr
        275                 280                 285

Ala Ile Gly Asp Cys Ala Thr Ile Tyr Asp Asn Ala Thr Arg Asp Thr
    290                 295                 300
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Asn Tyr Ile Ala Leu Ala Ser Asn Ala Val Arg Thr Gly Ile Val Ala
305                 310                 315                 320

Ala His Asn Ala Cys Gly Thr Asp Leu Glu Gly Ile Gly Val Gln Gly
                325                 330                 335

Ser Asn Gly Ile Ser Ile Tyr Gly Leu His Met Val Ser Thr Gly Leu
            340                 345                 350

Thr Leu Glu Lys Ala Lys Arg Leu Gly Phe Asp Ala Ala Val Thr Glu
        355                 360                 365

Tyr Thr Asp Asn Gln Lys Pro Glu Phe Ile Glu His Gly Asn Phe Pro
    370                 375                 380

Val Thr Ile Lys Ile Val Tyr Asp Lys Asp Ser Arg Arg Ile Leu Gly
385                 390                 395                 400

Ala Gln Met Ala Ala Arg Glu Asp Val Ser Met Gly Ile His Met Phe
                405                 410                 415

Ser Leu Ala Ile Gln Glu Gly Val Thr Ile Glu Lys Leu Ala Leu Thr
            420                 425                 430

Asp Ile Phe Phe Leu Pro His Phe Asn Lys Pro Tyr Asn Tyr Ile Thr
        435                 440                 445

Met Ala Ala Leu Gly Ala Lys Asp
    450                 455
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<210> SEQ ID NO 36
<211> LENGTH: 1371
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 36

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atgagtaaaa tcgttgttgt tggtgcaaac catgctggta cggcctgtat caagactatg     60

ttaacaaact acggtgatgc taatgagatt gttgtatttg accaaaactc aaatatttca    120

tttttaggct gtggtatggc actttggatt ggtgagcaaa ttgctggacc agaaggactt    180

ttctattcag ataaagaaga attagagtct ttaggggcta aagtttacat ggaatcacct    240

gttcaatcaa tcgactacga tgccaaaaca gtgacagcgc ttgttgatgg taaaaaccac    300

gtggaaactt acgacaagtt gatttttgca actggctcac aacctatctt accaccgatt    360

aaaggtgccg aaatcaaaga aggatcactt gaatttgaag caactcttga aaatcttcaa    420

tttgtgaagt tataccaaaa ctcagctgat gtgattgcaa agcttgaaaa caaagacatt    480

aaacgtgtag ccgtagttgg tgctggttac attggtgttg agttagctga agctttccaa    540

cgcaaaggca aagaagtggt tctgattgat gtcgtggaca cttgcttggc aggttattac    600

gaccgtgatt tgactgactt aatggctaaa aacatggaag aacatggtat tcaactagcc    660

tttggtgaaa cagttaaaga agtagctggt aatggtaagg ttgaaaagat cattactgac    720

aaaaatgagt acgatgtgga tatggttatc ctcgccgttg gtttccgtcc aaacacaact    780

cttggaaatg gtaagattga tcttttccgt aatggtgctt tccttgtcaa taaacgccaa    840

gaaacttcta ttccaggtgt ttatgctatc ggtgactgtg caactatcta cgataatgct    900

actcgcgata caaactacat tgctttagct tcaaatgccg tccgtacagg aattgtagca    960

gcacataacg cttgtggtac agaccttgaa ggtattggcg ttcaaggctc aaacggtatt   1020

tccatttacg gattgcacat ggtttcaact ggtttgacac ttgaaaaagc aaaacgtctt   1080

ggttttgatg ctgcagtgac tgagtatact gataaccaaa aacctgaatt tatcgaacac   1140
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ggtaacttcc cagtaaccat taagattgtt tacgataaag actcacgtcg tatcttgggt   1200

gctcaaatgg cagcccgtga agatgtgtca atgggaattc acatgttctc acttgctatc   1260

caagaaggcg taaccattga aaagttggca ttaactgata ttttcttctt accacatttc   1320

aacaaacctt acaactacat cacaatggca gcacttggtg ccaaagacta g            1371


<210> SEQ ID NO 37
<211> LENGTH: 232
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 37

Met Phe Ser Gly His Gln Leu Lys Thr Ala Arg Leu Ser Lys Gly Ile
1               5                   10                  15

Thr Gln Ser Glu Leu Gly Arg Leu Leu His Val Asn Lys Met Thr Ile
            20                  25                  30

Ser Asn Trp Glu Lys Gly Lys Asn Ile Pro Asn Glu Lys His Leu Asn
        35                  40                  45

Ala Leu Leu His Leu Phe Asn Val Thr Ser Asp Tyr Phe Asp Pro Asn
    50                  55                  60

Tyr Arg Leu Leu Thr Pro Tyr Asn Gln Leu Thr Ile Ser Asn Lys Glu
65                  70                  75                  80

Lys Val Ile Gly Tyr Ser Glu Arg Leu Leu Asn His Gln Ile Asp Lys
                85                  90                  95

Lys Ser Lys Asp Leu Ile Asp Lys Pro Ser Gln Leu Tyr Ala Tyr Arg
            100                 105                 110

Val Tyr Glu Ser Leu Ser Ala Gly Thr Gly Tyr Ser Tyr Phe Gly Asp
        115                 120                 125

Gly Asn Phe Asp Val Val Phe Tyr Asp Glu Gln Leu Glu Tyr Asp Phe
    130                 135                 140

Ala Ser Trp Val Phe Gly Asp Ser Met Glu Pro Thr Tyr Leu Asn Gly
145                 150                 155                 160

Glu Val Val Leu Ile Lys Gln Asn Ser Phe Asp Tyr Asp Gly Ala Ile
                165                 170                 175

Tyr Ala Val Glu Trp Asp Gly Gln Thr Tyr Ile Lys Lys Val Phe Arg
            180                 185                 190

Glu Asp Glu Gly Leu Arg Leu Val Ser Leu Asn Lys Lys Tyr Ser Asp
        195                 200                 205

Lys Phe Ala Pro Tyr Ser Glu Glu Pro Arg Ile Ile Gly Lys Ile Ile
    210                 215                 220

Ala Asn Phe Arg Pro Leu Glu Ile
225                 230


<210> SEQ ID NO 38
<211> LENGTH: 699
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 38

atgttttctg gacatcaact aaaaacagca cgattatcaa agggaataac tcaatcagaa     60

ttgggaagat tgttgcatgt caataaaatg acaatatcta attgggaaaa aggtaagaat    120

ataccaaatg aaaaacattt aaatgcctta ttgcatctat tcaatgtgac atctgattat    180
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ttcgacccaa actatagatt gctaacgcct tataaccagc tgacaatatc taataaagaa    240

aaagtaattg gctattcaga gcgattgtta aatcatcaaa tagacaaaaa atctaaagat    300

ctcatagata aaccatcaca attatatgct tatcgggtct atgaaagttt atctgctggt    360

actggttact cctattttgg tgatggtaac tttgatgttg tcttttacga tgaacaatta    420

gaatacgatt ttgcgtcttg ggtttttgga gattctatgg agccaactta tttaaatggt    480

gaagttgttc ttataaaaca aaatagtttt gattacgatg gagcaattta tgcagtcgaa    540

tgggatgggc aaacatatat caaaaaggta tttcgtgaag atgagggatt acgtctagtg    600

tccttaaata aaaaatattc tgataagttt gctccctata gcgaagaacc tcgcattatt    660

ggcaaaatta tcgctaattt taggccctta gaaatttaa                           699


<210> SEQ ID NO 39
<211> LENGTH: 306
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 39

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

Lys Thr Leu His Gln Lys Ala Lys Ala Leu Leu Thr Gln Glu Glu Leu
            20                  25                  30

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

Asp Ile Tyr Leu Pro Leu Ile Asn Leu Ile Gln Val Tyr Lys Ile Ala
    50                  55                  60

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

Gln Leu Arg Pro Phe Ile Ile Gly Ile Ser Gly Ser Val Ala Val Gly
                85                  90                  95

Lys Ser Thr Thr Ser Arg Leu Leu Gln Leu Leu Leu Ser Arg Thr His
            100                 105                 110

Pro Asn Ser Gln Val Glu Leu Val Thr Thr Asp Gly Phe Leu Tyr Pro
        115                 120                 125

Asn Gln Phe Leu Ile Glu Gln Gly Leu Leu Asn Arg Lys Gly Phe Pro
    130                 135                 140

Glu Ser Tyr Asn Met Glu Leu Leu Leu Asp Phe Leu Asp Ser Ile Lys
145                 150                 155                 160

Asn Gly Gln Thr Ala Phe Ala Pro Val Tyr Ser His Asp Ile Tyr Asp
                165                 170                 175

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

Val Glu Gly Ile Asn Val Phe Gln Asn Gln Gln Asn Asn Arg Leu Tyr
        195                 200                 205

Met Ser Asp Tyr Phe Asp Phe Ser Ile Tyr Ile Asp Ala Asp Ser Ser
    210                 215                 220

His Ile Glu Thr Trp Tyr Ile Glu Arg Phe Leu Ser Ile Leu Lys Leu
225                 230                 235                 240

Ala Lys Arg Asp Pro His Asn Tyr Tyr Ala Gln Tyr Ala Gln Leu Pro
                245                 250                 255

Arg Ser Glu Ala Ile Ala Phe Ala Arg Asn Val Trp Lys Thr Val Asn
            260                 265                 270
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Leu Glu Asn Leu Glu Lys Phe Ile Glu Pro Thr Arg Asn Arg Ala Glu
        275   280   285

Leu Ile Leu His Lys Ser Ala Asp His Lys Ile Asp Glu Ile Tyr Leu
    290   295   300

Lys Lys
305

<210> SEQ ID NO 40
<211> LENGTH: 921
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 40

atgtcaaatg aatttattaa ctttgaaaaa atttctagag agtcttggaa aacattacat 60

caaaaggcaa aagctctcct cacacaagag gaacttaaaa gtattactag cttaaatgat 120

aacatcagta ttaacgatgt cattgatatc taccttccat taattaatct gatccaggtt 180

tacaaaattg cgcaagaaaa tctttctttt tctaaaagcc tttttctaaa aaaagacatt 240

caattaaggc cttttattat tggaatttct ggttcagtag ctgttggtaa atcaacaact 300

agtcgtcttt tacaactttt attatcacga acgcacccca atagtcaagt cgaactggta 360

acgactgatg gtttttata tcctaatcag tttcttattg aacaaggact gttaaatcgt 420

aaaggatttc cagaatctta taacatggaa cttctcttag attttctaga ttccatcaaa 480

aatggtcaaa ctgcttttgc acccgtctat tctcatgata tttacgatat tatcccaaat 540

caaaaacaat catttaataa ccctgacttc cttatcgtcg aaggtattaa cgtttttcaa 600

aatcaacaaa acaatcgttt atatatgagt gattactttg atttttctat ttatattgat 660

gcagacagca gtcacatcga aacctggtac attgaacggt ttctaagcat tttaaaatta 720

gcaaaacgtg accctcataa ttattatgcc caatatgcac aattacctcg atctgaggct 780

atagcatttg cgcgcaacgt ttggaaaacc gttaatttag aaaatcttga aaaattcatt 840

gaacctacac gtaaccgtgc tgaattaatt ttacataaaa gtgctgatca taaaattgat 900

gaaatttacc tcaaaaagtg a 921

<210> SEQ ID NO 41
<211> LENGTH: 1036
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 41

Met Phe Ala Gln Leu Asp Thr Lys Thr Val Tyr Ser Phe Met Asp Ser
1   5   10   15

Leu Ile Asp Leu Asn His Tyr Phe Glu Arg Ala Lys Gln Phe Gly Tyr
            20   25   30

His Thr Ile Gly Ile Met Asp Lys Asp Asn Leu Tyr Gly Ala Tyr His
        35   40   45

Phe Ile Lys Gly Cys Gln Lys Asn Gly Leu Gln Pro Val Leu Gly Leu
    50   55   60

Glu Ile Glu Ile Leu Tyr Gln Glu Arg Gln Val Leu Leu Asn Leu Ile
65   70   75   80

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

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Lys Met Ser Gly Lys Leu His Met Asp Tyr Phe Cys Gln His Leu Glu
            100                 105                 110

Gly Ile Ala Val Ile Ile Pro Ser Lys Gly Trp Ser Asp Thr Leu Val
        115                 120                 125

Val Pro Phe Asp Tyr Tyr Ile Gly Val Asp Gln Tyr Thr Asp Leu Ser
    130                 135                 140

His Met Asp Ser Lys Arg Gln Leu Ile Pro Leu Arg Thr Val Arg Tyr
145                 150                 155                 160

Phe Ala Gln Asp Asp Met Glu Thr Leu His Met Leu His Ala Ile Arg
                165                 170                 175

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

Leu Ala Asp Cys Gln Gln Leu Thr Ala Phe Tyr Gln Thr His Cys Pro
        195                 200                 205

Gln Ala Leu Gln Asn Leu Glu Asp Leu Val Ser Gly Ile Tyr Tyr Asp
    210                 215                 220

Phe Asp Thr Asn Leu Lys Leu Pro His Phe Asn Arg Asp Lys Ser Ala
225                 230                 235                 240

Lys Gln Glu Leu Gln Asp Leu Thr Glu Ala Gly Leu Lys Glu Lys Gly
                245                 250                 255

Leu Trp Lys Glu Pro Tyr Gln Ser Arg Leu Leu His Glu Leu Val Ile
            260                 265                 270

Ile Ser Asp Met Gly Phe Asp Asp Tyr Phe Leu Ile Val Trp Asp Leu
        275                 280                 285

Leu Arg Phe Gly Arg Ser Lys Gly Tyr Tyr Met Gly Met Gly Arg Gly
    290                 295                 300

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

Asp Pro Val Gln His Asp Leu Leu Phe Glu Arg Phe Leu Asn Lys Glu
                325                 330                 335

Arg Tyr Ser Met Pro Asp Ile Asp Ile Asp Leu Pro Asp Ile Tyr Arg
            340                 345                 350

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

Ala Gln Ile Val Thr Phe Ser Thr Phe Gly Pro Lys Gln Ala Ile Arg
    370                 375                 380

Asp Val Phe Lys Arg Phe Gly Val Pro Glu Tyr Glu Leu Thr Asn Leu
385                 390                 395                 400

Thr Lys Lys Ile Gly Phe Lys Asp Ser Leu Ala Thr Val Tyr Glu Lys
                405                 410                 415

Ser Ile Ser Phe Arg Gln Val Ile Asn Ser Arg Thr Glu Phe Gln Lys
            420                 425                 430

Ala Phe Ala Ile Ala Lys Arg Ile Glu Gly Asn Pro Arg Gln Thr Ser
        435                 440                 445

Ile His Ala Ala Gly Ile Val Met Ser Asp Asp Ala Leu Thr Asn His
    450                 455                 460

Ile Pro Leu Lys Ser Gly Asp Asp Met Met Ile Thr Gln Tyr Asp Ala
465                 470                 475                 480

His Ala Val Glu Ala Asn Gly Leu Leu Lys Met Asp Phe Leu Gly Leu
                485                 490                 495

Arg Asn Leu Thr Phe Val Gln Lys Met Gln Glu Lys Val Ala Lys Asp
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            500                 505                 510

Tyr Gly Cys Gln Ile Asp Ile Thr Ala Ile Asp Leu Glu Asp Pro Gln
        515                 520                 525

Thr Leu Ala Leu Phe Ala Lys Gly Asp Thr Lys Gly Ile Phe Gln Phe
    530                 535                 540

Glu Gln Asn Gly Ala Ile Asn Leu Leu Lys Arg Ile Lys Pro Gln Arg
545                 550                 555                 560

Phe Glu Glu Ile Val Ala Thr Thr Ser Leu Asn Arg Pro Gly Ala Ser
                565                 570                 575

Asp Tyr Thr Thr Asn Phe Ile Lys Arg Arg Glu Gly Gln Glu Lys Ile
            580                 585                 590

Asp Leu Ile Asp Pro Val Ile Ala Pro Ile Leu Glu Pro Thr Tyr Gly
        595                 600                 605

Ile Met Leu Tyr Gln Glu Gln Val Met Gln Ile Ala Gln Val Tyr Ala
    610                 615                 620

Gly Phe Thr Leu Gly Lys Ala Asp Leu Leu Arg Arg Ala Met Ser Lys
625                 630                 635                 640

Lys Asn Leu Gln Glu Met Gln Lys Met Glu Glu Asp Phe Ile Ala Ser
                645                 650                 655

Ala Lys His Leu Gly Arg Ala Glu Glu Thr Ala Arg Gly Leu Phe Lys
            660                 665                 670

Arg Met Glu Lys Phe Ala Gly Tyr Gly Phe Asn Arg Ser His Ala Phe
        675                 680                 685

Ala Tyr Ser Ala Leu Ala Phe Gln Leu Ala Tyr Phe Lys Ala His Tyr
    690                 695                 700

Pro Ala Val Phe Tyr Asp Ile Met Met Asn Tyr Ser Ser Ser Asp Tyr
705                 710                 715                 720

Ile Thr Asp Ala Leu Glu Ser Asp Phe Gln Val Ala Gln Val Thr Ile
                725                 730                 735

Asn Ser Ile Pro Tyr Thr Asp Lys Ile Glu Ala Ser Lys Ile Tyr Met
            740                 745                 750

Gly Leu Lys Asn Ile Lys Gly Leu Pro Arg Asp Phe Ala Tyr Trp Ile
        755                 760                 765

Ile Glu Gln Arg Pro Phe Asn Ser Val Glu Asp Phe Leu Thr Arg Thr
    770                 775                 780

Pro Glu Lys Tyr Gln Lys Lys Val Phe Leu Glu Pro Leu Ile Lys Ile
785                 790                 795                 800

Gly Leu Phe Asp Cys Phe Glu Pro Asn Arg Lys Lys Ile Leu Asp Asn
                805                 810                 815

Leu Asp Gly Leu Leu Val Phe Val Asn Glu Leu Gly Ser Leu Phe Ser
            820                 825                 830

Asp Ser Ser Phe Ser Trp Val Asp Thr Lys Asp Tyr Ser Val Thr Glu
        835                 840                 845

Lys Tyr Ser Leu Glu Gln Glu Ile Val Gly Val Gly Met Ser Lys His
    850                 855                 860

Pro Leu Ile Asp Ile Ala Glu Lys Ser Thr Gln Thr Phe Thr Pro Ile
865                 870                 875                 880

Ser Gln Leu Val Lys Glu Ser Glu Ala Val Val Leu Ile Gln Ile Asp
                885                 890                 895

Ser Ile Arg Ile Ile Arg Thr Lys Thr Ser Gly Gln Gln Met Ala Phe
            900                 905                 910
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Leu Ser Val Asn Asp Thr Lys Lys Lys Leu Asp Val Thr Leu Phe Pro
915 920 925

Gln Glu Tyr Ala Ile Tyr Lys Asp Gln Leu Lys Glu Gly Glu Phe Tyr
930 935 940

Tyr Leu Lys Gly Arg Ile Lys Glu Arg Asp His Arg Leu Gln Met Val
945 950 955 960

Cys Gln Gln Val Gln Met Ala Ile Ser Gln Lys Tyr Trp Leu Leu Val
965 970 975

Glu Asn His Gln Phe Asp Ser Gln Ile Ser Glu Ile Leu Gly Ala Phe
980 985 990

Pro Gly Thr Thr Pro Val Val Ile His Tyr Gln Lys Asn Lys Glu Thr
995 1000 1005

Ile Ala Leu Thr Lys Ile Gln Val His Val Thr Glu Asn Leu Lys
1010 1015 1020

Glu Lys Leu Arg Pro Phe Val Leu Lys Thr Val Phe Arg
1025 1030 1035

<210> SEQ ID NO 42
<211> LENGTH: 3111
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 42

atgtttgctc aacttgatac taaaactgta tactcattta tggatagttt aattgactta 60

aatcattatt ttgaacgagc aaagcaattt ggttaccaca ccataggaat catggataag 120

gataatcttt atggtgctta ccattttatt aaaggttgtc aaaaaaatgg actgcagcca 180

gttttaggtt tggaaataga gattctctat caagagcggc aggtgctcct taacttaatc 240

gcccagaata cacaaggcta tcatcagctt ttaaaaattt ccacggcaaa aatgtctggc 300

aagcttcata tggattactt ctgccaacat ttggaaggga tagcggttat tattcctagt 360

aagggttgga gcgatacatt agtggtccct tttgactact atatcggtgt tgatcagtat 420

actgatttat ctcatatgga ttctaagagg cagcttatac ccctaaggac agttcgttat 480

tttgcgcaag atgatatgga aaccctgcac atgttgcatg ccattcgaga taacctcagt 540

ctggcagaga cccctgtggt agaaagtgat caagagttag cagattgtca acaactaacc 600

gccttctatc aaacacactg ccctcaagct ctacagaatt tagaagactt agtgtcagga 660

atctattatg atttcgatac aaatttaaaa ttgcctcatt ttaatagaga taagtctgcc 720

aagcaagaat tgcaagactt gactgaggct ggtttgaagg aaaaaggatt gtggaaagag 780

ccttatcaat cgcgcttact acatgaattg gtcattattt ctgacatggg ctttgatgat 840

tattttttga ttgtgtggga tttacttcgc tttggacgca gtaaaggcta ttatatggga 900

atgggacgtg gctcggcggc aggtagtcta gtggcttatg ctctgaacat tacagggatt 960

gatccagttc aacatgattt gctatttgag cgctttttaa acaaagaacg ttatagcatg 1020

cctgatattg atatcgatct tccagatatt taccgttcag aatttctacg gtatgtccga 1080

aatcgttatg gtagcgacca ttcggcgcaa attgtgacct tttcaacctt tggccctaaa 1140

caggctattc gtgatgtttt caaacggttc ggggttccag aatacgaact gactaatctc 1200

actaaaaaaa ttggttttaa agatagcttg gctactgtct atgaaaagtc aatctctttt 1260

aggcaggtta ttaatagtag aactgaattt caaaaggctt ttgccattgc caagcgtatc 1320

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gaaggaaatc caagacaaac gtccattcac gcagctggta ttgtgatgag tgatgatgcc 1380

ttgaccaatc atattcctct aaaatcgggc gatgacatga tgatcaccca gtatgatgct 1440

catgcggtcg aagctaatgg cctgttaaaa atggattttt tggggttaag aaatttgacc 1500

tttgttcaaa aaatgcaaga gaaggttgct aaagactacg ggtgtcagat tgatattaca 1560

gccattgatt tagaagaccc gcaaacgttg gcactttttg ctaaagggga taccaaggga 1620

attttccaat ttgaacaaaa tggtgctatt aatcttttaa aacggattaa gccacaacgt 1680

tttgaagaaa ttgttgccac taccagtcta aatagaccag gggcaagtga ctataccact 1740

aatttcatta aacgaagaga aggacaagaa aaaattgatt tgattgatcc tgtgattgct 1800

cccattttag agccaactta cggtattatg ctttatcaag aacaagttat gcagattgca 1860

caggtttatg ctggttttac gttaggcaag gccgacttgt taaggcgtgc catgtctaaa 1920

aaaaatctac aagaaatgca aaaaatggaa gaagacttta ttgcttctgc taagcaccta 1980

gggagagctg aagaaacagc tagaggactt tttaaacgga tggaaaaatt tgcaggttat 2040

ggttttaacc gcagccatgc ctttgcctat tcagctttag cttttcaatt ggcttatttc 2100

aaagcccatt acccggctgt tttttacgat atcatgatga attattctag cagtgactat 2160

atcacagatg ctctagaatc agattttcaa gtagcgcaag ttaccattaa tagtattcct 2220

tacactgata aaattgaagc tagcaagatt tacatggggc tgaaaaatat taaggggttg 2280

ccaagggatt ttgcttattg gattatcgag caaagaccat ttaatagcgt agaggatttt 2340

ctcactagaa ctccagaaaa atatcaaaaa aaggttttcc ttgagcctct gataaaaata 2400

ggtctgtttg attgctttga gcctaaccgt aaaaaaattc tggacaattt ggatggttta 2460

ctggtatttg ttaatgagct tggttctctt ttttcagatt cttcctttag ttgggtagat 2520

acgaaagatt actcagtaac tgaaaaatat tctttggaac aggagatcgt tggagttggc 2580

atgagcaagc atcctttaat tgatattgct gagaaaagta cccaaacttt tactcctatt 2640

tcacagttag tcaaagaaag cgaagcagtc gtactgattc aaatagatag cattaggatc 2700

attagaacca aaacaagtgg gcagcaaatg gctttttttaa gtgtgaatga cactaagaaa 2760

aagctcgatg tcacactttt tccacaagag tatgccattt ataaagacca attaaaagaa 2820

ggagaattct attacttaaa aggtagaata aaagaaagag accatcgact gcagatggtg 2880

tgtcagcaag tgcaaatggc tattagtcaa aaatattggt tattagttga aaaccatcag 2940

tttgattccc aaatttctga gattttaggt gcctttccag gaacgactcc agttgttatt 3000

cactatcaaa aaaataagga aacaattgca ttaactaaga ttcaggttca tgtaacagag 3060

aatttaaagg aaaaacttcg tccttttgtt ctgaaaacgg tttttcgata a 3111

<210> SEQ ID NO 43
<211> LENGTH: 711
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 43

Met Arg Glu Leu His Ile Lys Thr Tyr Lys Leu Leu Thr Lys Ser Ala
1 5 10 15

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

Asn Ala Ser Val Thr Asn Lys Ala Asp Phe Ser Thr Asp Thr Ile Tyr

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        35                  40                  45

Gln Ile Val Thr Asp Arg Phe Asn Asp Gly Asn Thr Ser Asn Asn Gly
    50                  55                  60

Lys Thr Asp Val Phe Asp Lys Asn Asp Leu Lys Lys Tyr His Gly Gly
65                  70                  75                  80

Asp Trp Gln Gly Ile Ile Ala Lys Ile Lys Asp Gly Tyr Leu Thr Asp
                85                  90                  95

Met Gly Ile Ser Ala Ile Trp Ile Ser Ser Pro Val Glu Asn Ile Asp
            100                 105                 110

Ser Ile Asp Pro Ser Asn Gly Ser Ala Ala Tyr His Gly Tyr Trp Ala
        115                 120                 125

Lys Asp Phe Phe Lys Thr Asn Gln His Phe Gly Thr Glu Ala Asp Phe
    130                 135                 140

Gln Gln Leu Val Lys Val Ala His Gln His His Ile Lys Val Val Ile
145                 150                 155                 160

Asp Phe Ala Pro Asn His Thr Ser Thr Ala Glu Lys Glu Gly Thr Thr
                165                 170                 175

Phe Lys Glu Asp Gly Ala Leu Tyr Lys Asn Gly Lys Leu Val Gly Lys
            180                 185                 190

Phe Ser Asp Asp Lys Asp Lys Ile Phe Asn His Glu Ser Trp Thr Asp
        195                 200                 205

Phe Ser Thr Tyr Glu Asn Ser Ile Tyr His Ser Met Tyr Gly Leu Ala
    210                 215                 220

Asp Leu Asn Asn Ile Asn Pro Lys Val Asp Gln Tyr Met Lys Glu Ala
225                 230                 235                 240

Ile Asp Lys Trp Leu Asp Leu Gly Val Asp Gly Ile Arg Val Asp Ala
                245                 250                 255

Val Lys His Met Ser Gln Gly Trp Gln Lys Asn Trp Leu Ser His Ile
            260                 265                 270

Tyr Glu Lys His Asn Val Phe Val Phe Gly Glu Trp Phe Ser Gly His
        275                 280                 285

Thr Asp Asp Asp Tyr Asp Met Thr Thr Phe Ala Asn Asn Ser Gly Met
    290                 295                 300

Gly Leu Leu Asp Phe Arg Phe Ala Asn Ala Ile Arg Gln Leu Tyr Thr
305                 310                 315                 320

Gly Phe Ser Thr Phe Thr Met Arg Asp Phe Tyr Lys Val Leu Glu Asn
                325                 330                 335

Arg Asp Gln Val Thr Asn Glu Val Thr Asp Gln Val Thr Phe Ile Asp
            340                 345                 350

Asn His Asp Met Glu Arg Phe Ala Thr Lys Val Ala Asn Asn Gln Thr
        355                 360                 365

Ala Val Asn Gln Ala Tyr Ala Leu Leu Leu Thr Ser Arg Gly Val Pro
    370                 375                 380

Asn Ile Tyr Tyr Gly Thr Glu Gln Tyr Ala Thr Gly Asp Lys Asp Pro
385                 390                 395                 400

Asn Asn Arg Gly Asp Met Pro Ser Phe Asn Lys Glu Ser Gln Ala Tyr
                405                 410                 415

Lys Val Ile Ser Lys Leu Ala Pro Leu Arg Lys Gln Asn Gln Ala Leu
            420                 425                 430

Ala Tyr Gly Thr Thr Glu Gln Arg Trp Ile Ser Asp His Val Leu Val
        435                 440                 445
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Phe Glu Arg Lys Phe Gly Asn His Val Ala Leu Val Ala Ile Asn Arg
    450                 455                 460

Asp Gln Thr Asn Gly Tyr Thr Ile Thr Asn Ala Lys Thr Ala Leu Pro
465                 470                 475                 480

Gln Asn Ser Tyr Lys Asp Lys Leu Glu Gly Leu Leu Gly Gly Gln Glu
                485                 490                 495

Leu Ile Val Gly Ala Asp Gly Thr Ile Ser Ser Phe Glu Leu Gly Ala
            500                 505                 510

Gly Gln Val Ala Val Trp Thr Tyr Glu Gly Glu Asp Lys Thr Pro Gln
        515                 520                 525

Leu Gly Asp Val Asp Ala Ser Val Gly Ile Ala Gly Asn Lys Ile Thr
    530                 535                 540

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

Glu Ile Ser Ala Glu Ile Leu Ser Trp Ser Asp Thr Leu Ile Thr Leu
                565                 570                 575

Lys Val Pro Thr Val Pro Ala Asn Tyr Tyr Asn Ile Ser Val Thr Thr
            580                 585                 590

Ala Asp Lys Gln Thr Ser Asn Ser Tyr Gln Ala Phe Glu Val Leu Thr
        595                 600                 605

Asp Lys Gln Ile Pro Val Arg Leu Leu Ile Asn Asp Phe Lys Thr Val
    610                 615                 620

Pro Gly Glu Gln Leu Tyr Leu Met Gly Asp Val Phe Glu Met Gly Ala
625                 630                 635                 640

Asn Asp Ala Lys Asn Ala Val Gly Pro Leu Phe Asn Asn Thr Gln Thr
                645                 650                 655

Ile Ala Lys Tyr Pro Asn Trp Phe Phe Asp Thr His Leu Pro Ile Asn
            660                 665                 670

Lys Glu Ile Ala Val Lys Leu Val Lys Lys Asp Ser Ile Gly Asn Val
        675                 680                 685

Leu Trp Thr Ser Pro Glu Thr Tyr Ser Ile Lys Thr Gly His Glu Ala
    690                 695                 700

Gln Thr Ile Thr Ile Lys Lys
705                 710
```

<210> SEQ ID NO 44
<211> LENGTH: 2136
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 44

```
atgagagaat tacatatcaa aacttataag ttattaacga aaagtgctgt tttacttggc     60

ttaatttcat ttccactaac tgtttctgct gccgataatg cttctgtcac caacaaagca    120

gatttttcaa cagatacgat ttatcagatt gtaacagatc gttttaacga tggtaatacc    180

tctaataatg gtaagactga tgtttttgat aaaaatgacc ttaaaaaata ccatggaggt    240

gattggcaag gaatcatcgc caagattaag gatggttacc tgacagatat ggggatttct    300

gccatttgga tttcttctcc tgttgaaaat atcgacagta ttgatccttc taatggaagt    360

gctgcatatc atgggtattg ggctaaggac ttctttaaaa caaaccagca ttttggcact    420

gaagcagact ttcaacaact agtcaaagta gctcatcaac accatattaa ggtagttatt    480
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gattttgctc ctaatcatac gtctacagcc gaaaaagaag gcacaacttt caaagaagat 540

ggcgctttat ataaaaacgg taaattagtt ggtaaatttt cagatgataa agacaagatt 600

tttaatcatg aatcttggac cgattttagt acttatgaaa attctattta tcattcaatg 660

tacggactag ctgatttaaa taacattaat ccgaaagttg accagtacat gaaagaagct 720

attgataaat ggttagacct gggtgttgat ggtatccgag ttgacgctgt taaacatatg 780

tcacaaggtt ggcaaaaaaa ttggttgagt catatctatg aaaaacataa tgtctttgtt 840

ttcggggaat ggttctcggg acataccgac gatgattatg atatgacgac atttgctaac 900

aatagtggga tggggctttt agattttaga tttgccaatg ctattagaca gttgtataca 960

ggtttttcaa cgtttaccat gcgagatttt tacaaggttc ttgaaaatag agatcaggtg 1020

actaatgaag tgacagacca ggtgaccttt attgataatc atgatatgga acgcttcgca 1080

acaaaagtgg ctaataatca aactgctgtt aatcaagcct atgctttgct tttaacatct 1140

agaggtgtgc ctaatattta ttatggtaca gagcagtatg caacaggtga taaagatcct 1200

aataatcgtg gtgatatgcc aagttttaat aaagagtcac aagcctataa agtgattagt 1260

aagctagctc ctttaagaaa acaaaatcaa gctttagctt atggaacaac tgaacaacgt 1320

tggattagtg atcatgtttt ggtatttgag cgtaaatttg gtaatcatgt cgcactagtg 1380

gctattaata gagatcaaac gaatggttat acaattacta atgctaaaac agccttgccc 1440

caaaatagct acaaggacaa attagaaggt cttcttggcg gtcaagaatt aatagttgga 1500

gcagatggca ctattagtag ctttgaactt ggagcggggc aagtcgctgt atggacttat 1560

gaaggagagg acaagacacc acaacttgga gatgtcgatg cttcagtggg tattgctgga 1620

aataagatta ctatttcagg tcaaggtttt ggtaattcta aaggtcaagt gacttttgga 1680

gaaatctctg ctgagatcct ttcttggtca gataccctta tcaccttaaa agtaccgacg 1740

gttccagcaa attattataa catttcagtg acaactgccg ataagcaaac cagcaatagt 1800

taccaagcct ttgaagtatt gactgataaa caaattcctg ttcgtttact catcaatgat 1860

tttaagacag taccagggga acaactatat ctcatgggtg atgtttttga gatgggggca 1920

aatgacgcta agaatgctgt tggtcctcta tttaataaca ctcagaccat tgccaagtac 1980

ccaaactggt tctttgatac tcatctacca atcaataaag aaatagcagt caaacttgtt 2040

aaaaaagata gtattgggaa tgttttatgg acaagtcctg agacttatag tataaagaca 2100

ggtcatgaag cacaaaccat tactataaaa aaataa 2136

<210> SEQ ID NO 45
<211> LENGTH: 427
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 45

Met Ser Lys His Gln Asp Ile Leu Asp Tyr Leu Glu Lys Leu Ala Ile
1   5   10   15

Gly Lys Lys Val Ser Val Arg Ser Ile Ser Asn His Leu Lys Val Ser
            20   25   30

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

Val Glu Thr Lys Pro Arg Ser Gly Thr Val Arg Ile Glu Lys Lys Gly
    50   55   60

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Arg Val Arg Ile Asp Arg Leu Thr Tyr Ser Glu Ile Ala Arg Ile Ser
65                  70                  75                  80

Asp Ser Glu Val Leu Ala Gly His Ala Gly Leu Gly His Glu Phe Ser
                85                  90                  95

Arg Phe Ser Ile Gly Ala Met Thr Gln Gln Asn Ile Arg Arg Tyr Leu
            100                 105                 110

Val Lys Gly Gly Leu Leu Ile Val Gly Asp Arg Glu Thr Ile Gln Leu
        115                 120                 125

Leu Ala Leu Glu Asn His Asn Ala Ile Leu Val Thr Gly Gly Phe Pro
    130                 135                 140

Val Ser Lys Arg Val Ile Glu Met Ala Asn Asn Gln Arg Ile Pro Val
145                 150                 155                 160

Met Val Thr His Tyr Asp Thr Phe Thr Val Ala Thr Met Ile Asn His
                165                 170                 175

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

Val Met Ile Pro Ile Thr Asp Tyr Gly Tyr Leu Cys Glu Asp Ser Ser
        195                 200                 205

Val Glu Glu Phe Asn Thr Leu Ile Lys Lys Thr Arg Gln Val Arg Phe
    210                 215                 220

Pro Val Leu Asp Tyr Lys Arg Lys Val Ile Gly Val Val Ser Met Arg
225                 230                 235                 240

Asp Val Val Asp Gln Leu Pro Thr Thr Lys Leu Thr Lys Val Met Ser
                245                 250                 255

Lys Asn Pro Ile Thr Ala Arg Pro Asn Thr Ser Leu Ala Asn Ile Ser
            260                 265                 270

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

Glu Asn Asn Leu Leu Gly Met Ile Thr Arg Arg Gln Ala Met Glu Asn
    290                 295                 300

Leu Pro Asn His Gln Pro Asn Asn Pro Tyr Thr Tyr Ser Glu Gln Ile
305                 310                 315                 320

Leu Ser Asn Leu Glu Glu Thr Val Asp Tyr Tyr Gln Val Val Val Glu
                325                 330                 335

Pro Thr Met Ile Asp Ser Ala Gly Asn Met Ser Asn Gly Val Ile Ser
            340                 345                 350

Glu Phe Leu Lys Glu Ile Ser Ile Arg Ala Leu Thr Lys Lys His Gln
        355                 360                 365

Lys Asn Ile Ile Ile Glu Gln Met Met Val Tyr Phe Leu His Ala Ile
    370                 375                 380

Gln Ile Glu Asp Glu Leu Lys Ile Tyr Pro Lys Ile Ile Thr Glu Asn
385                 390                 395                 400

Arg Arg Ser Ser Thr Ile Asp Ile Glu Ile Phe Val Asp Asp Gln Val
                405                 410                 415

Ile Ala Lys Ala Ile Ile Thr Thr Lys Ile Asn
            420                 425
```

<210> SEQ ID NO 46
<211> LENGTH: 1284
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 46

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atgagcaaac atcaagatat tttagattat ttagaaaaac ttgctattgg taaaaaagtg     60

agtgttagaa gcatttcaaa ccacttaaaa gtaagcgatg gaacagccta ccgtgctatt    120

aaagaggcag aaaatcgagg tattgtcgaa accaaaccaa gaagtggaac tgttcgtatt    180

gaaaaaaaag gacgggttcg tattgaccgt ctgacctatt ccgaaattgc tcggatcagt    240

gattcggaag tgctagcggg acatgctggt ttaggacatg aatttagtag gttttcaatt    300

ggtgctatga ctcaacaaaa tattcgtcgt tacttggtca aaggagggtt attaatagtt    360

ggggatcgtg aaacgattca actcttagct cttgaaaacc ataatgccat tttggtgacg    420

ggcggatttc cagtatccaa acgtgttatt gaaatggcaa ataaccaacg aatcccagtt    480

atggtaactc attatgatac ctttactgtg gcaacaatga ttaatcacgc gctatctaat    540

attcgtatta aaacagatct caaaacagtt gaacaggtaa tgatacctat tacagattat    600

ggttaccttt gcgaagacag ctctgttgaa gaattcaata cattaataaa aaaaacacga    660

caagtcaggt ttcctgtatt agattataaa agaaaagtga ttggtgtagt tagtatgcgt    720

gatgtggtgg atcagttgcc aacaactaag cttaccaagg tcatgtctaa aaatccaata    780

acggctagac caaatactag tcttgctaat attagccaga aaatgatctt tgaagattta    840

aacatgttac ctgtcactga cgaagaaaac aatttacttg gtatgattac tcgtagacaa    900

gcaatggaaa atttgccaaa tcaccaacca aataacccct atacttatag tgagcaaata    960

ctttctaacc ttgaagaaac ggttgattat tatcaagtag tagttgagcc aacaatgatt   1020

gatagtgctg gtaacatgtc aaacggtgtt atttcagagt tcttaaagga aattagtatc   1080

agagccctca cgaaaaagca ccaaaaaaat atcattatcg aacaaatgat ggtatacttt   1140

ttacatgcta ttcaaattga ggatgaatta aaaatatatc ctaaaatcat tactgaaaat   1200

agacgaagca gcaccattga tattgaaatt tttgtggatg atcaagtgat tgctaaagct   1260

attattacaa cgaaaataaa ttag                                          1284
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<210> SEQ ID NO 47
<211> LENGTH: 180
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 47

Met Asp Ile Trp Thr Lys Leu Ala Val Phe Ala Phe Phe Glu Thr Pro
1               5                   10                  15

Lys Val Ile Leu Arg Pro Phe Arg Tyr Glu Asp His Trp Asp Phe Tyr
            20                  25                  30

Ser Met Val Asn Asp Thr Lys Asn Leu Tyr Tyr Val Phe Pro Glu Gln
        35                  40                  45

Lys Thr Lys Ala Ala Ser Asp Tyr Leu Leu Val His Ser Phe Ile Lys
    50                  55                  60

Phe Pro Leu Gly Gln Trp Ala Ile Glu Asp Lys Ala Thr His Gln Val
65                  70                  75                  80

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

Asp Ile Gly Tyr Phe Leu Asn Tyr Ala Phe Trp Gly Gln Gly Ile Met
            100                 105                 110

Thr Glu Val Val Ile Lys Leu Val Tyr Leu Ser Phe His Glu Phe Gly
        115                 120                 125
```

-continued

```
Leu Lys Thr Leu Arg Ile Ile Thr His Leu Glu Asn Lys Ala Ser Gln
    130                 135                 140

Lys Val Ala Lys Lys Ala Gly Phe Gln Leu Lys Thr Cys Phe Lys Gly
145                 150                 155                 160

Ser Asp Arg Asn Thr His Lys Ile Cys Ile Tyr Lys Met Tyr Gln Leu
                165                 170                 175

Thr Asn Asp Arg
            180
```

<210> SEQ ID NO 48
<211> LENGTH: 543
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 48

```
atggatattt ggacaaagct tgcagtgttt gctttttttg agactccgaa agtaatatta     60

cggccttttc gctatgaaga tcattgggat ttttacagca tggttaacga cactaaaaac    120

ctttattatg tttttccaga acaaaaaact aaggcagcaa gtgactatct tttagtacat    180

agttttataa agtttccttt aggtcagtgg gcaatagaag ataaagcaac ccaccaagta    240

ataggttcta ttagaattga gcattatgat gctaaaacgc gttgtgctga tattggctat    300

tttttaaact atgccttttg gggacaagga attatgacag aagtcgtaat aaaacttgtt    360

tatttatctt ttcacgaatt tggtctcaaa acgttgcgta ttataactca tttagaaaat    420

aaggccagcc agaaagtagc taaaaaagca ggttttcaac taaaaacctg ttttaaagga    480

agtgatcgta atactcataa aatctgcatt tataaaatgt accaactaac taatgatagg    540

tga                                                                  543
```

<210> SEQ ID NO 49
<211> LENGTH: 721
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 49

```
Met Ile Thr Ile Lys Asn Pro Lys Ile Leu Lys Trp Leu Lys Tyr Val
1               5                   10                  15

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

Leu Leu Phe Thr Phe Tyr Ile Ser Ser Ala Pro Lys Leu Ser Glu Ala
        35                  40                  45

Gln Leu Lys Ser Thr Asn Ser Ser Leu Val Tyr Asp Gly Asn Asn Asn
    50                  55                  60

Leu Ile Ala Asp Leu Gly Ser Glu Lys Arg Glu Asn Val Thr Ala Asp
65                  70                  75                  80

Ser Ile Pro Ile Asn Leu Val Asn Ala Ile Thr Ser Ile Glu Asp Lys
                85                  90                  95

Arg Phe Phe Asn His Arg Gly Val Asp Leu Tyr Arg Ile Phe Gly Ala
            100                 105                 110

Ala Phe His Asn Leu Thr Ser Gln Thr Thr Gln Gly Gly Ser Thr Leu
        115                 120                 125

Asp Gln Gln Leu Ile Lys Leu Ala Tyr Phe Ser Thr Asn Glu Ser Asp
    130                 135                 140
```

-continued

```
Gln Thr Leu Lys Arg Lys Ala Gln Glu Val Trp Leu Ala Leu Gln Met
145                 150                 155                 160

Glu Arg Lys Tyr Thr Lys Gln Glu Ile Leu Thr Phe Tyr Ile Asn Lys
                165                 170                 175

Val Tyr Met Gly Asn Gly Asn Tyr Gly Met Leu Thr Ala Ala Lys Ser
            180                 185                 190

Tyr Tyr Gly Lys Asp Leu Lys Asp Leu Ser Tyr Ala Gln Leu Ala Leu
        195                 200                 205

Leu Ala Gly Ile Pro Gln Ala Pro Ser Gln Tyr Asp Pro Tyr Leu His
    210                 215                 220

Pro Glu Ala Ala Gln Asn Arg Arg Asn Val Val Leu Gln Gln Met Tyr
225                 230                 235                 240

Met Glu Lys His Leu Thr Lys Ala Glu Tyr Glu Thr Ala Ile Ala Thr
                245                 250                 255

Pro Val Ala Glu Gly Leu Gln Ser Leu Gln Gln Arg Ser Thr Tyr Pro
            260                 265                 270

Lys Tyr Met Asp Asn Tyr Leu Lys Gln Val Ile Glu Glu Val Lys Lys
        275                 280                 285

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

Ile Ile Pro Asp Ala Gln Gln Thr Leu Tyr Asn Ile Tyr His Ser Gly
305                 310                 315                 320

Asp Tyr Val Tyr Tyr Pro Asp Gln Asp Phe Gln Val Ala Ser Thr Ile
                325                 330                 335

Val Asp Val Thr Asn Gly His Val Ile Ala Gln Leu Gly Gly Arg Asn
            340                 345                 350

Gln Asp Glu Asn Val Ser Phe Gly Thr Asn Gln Ala Val Leu Thr Asp
        355                 360                 365

Arg Asp Trp Gly Ser Thr Met Lys Pro Ile Thr Ala Tyr Ala Pro Ala
    370                 375                 380

Ile Glu Ser Gly Val Tyr Thr Ser Thr Ala Gln Ser Thr Asn Asp Ser
385                 390                 395                 400

Val Tyr Tyr Trp Pro Gly Thr Thr Thr Gln Leu Phe Asn Trp Asp Leu
                405                 410                 415

Arg Tyr Asn Gly Trp Met Thr Ile Gln Ala Ala Ile Met Leu Ser Arg
            420                 425                 430

Asn Val Pro Ala Val Arg Ala Leu Glu Ala Ala Gly Leu Asp Tyr Ala
        435                 440                 445

Arg Ser Phe Leu Ser Ser Leu Gly Ile Asn Tyr Pro Glu Met His Tyr
    450                 455                 460

Ser Asn Ala Ile Ser Ser Asn Asn Ser Ser Ser Asp Lys Lys Tyr Gly
465                 470                 475                 480

Ala Ser Ser Glu Lys Met Ala Ala Ala Tyr Ala Ala Phe Ala Asn Gly
                485                 490                 495

Gly Ile Tyr His Lys Pro Arg Tyr Val Asn Lys Val Glu Phe Ser Asp
            500                 505                 510

Gly Thr Ser Lys Thr Phe Asp Glu Lys Gly Lys Arg Ala Met Lys Glu
        515                 520                 525

Thr Thr Ala Tyr Met Met Thr Asp Met Leu Lys Thr Val Leu Thr Tyr
    530                 535                 540

Gly Thr Gly Thr Ala Ala Ala Ile Pro Gly Val Ala Gln Ala Gly Lys
```

-continued

```
545                 550                 555                 560

Thr Gly Thr Ser Asn Tyr Thr Asp Glu Glu Leu Ala Lys Ile Gly Glu
                565                 570                 575

Lys Tyr Gly Leu Tyr Pro Asp Tyr Val Gly Thr Leu Ala Pro Asp Glu
            580                 585                 590

Asn Phe Val Gly Phe Thr Lys Arg Tyr Ala Met Ala Val Trp Thr Gly
        595                 600                 605

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

Ser Asp Val Tyr Arg Ser Met Met Thr Tyr Leu Thr Asn Gly Tyr Ser
625                 630                 635                 640

Glu Asp Trp Thr Met Pro Asn Gly Leu Tyr Arg Ser Gly Gly Phe Leu
                645                 650                 655

Tyr Leu Ser Gly Thr Tyr Ala Ser Asn Thr Asp Tyr Thr Asn Ser Val
            660                 665                 670

Tyr Asn Asn Leu Tyr Ser Asn Asn Thr Thr Thr Ala Ser Ser Gln Thr
        675                 680                 685

Thr Ser Asp Asp Thr Ser Ser Ser Asn Asp Thr Ser Asn Ser Thr Asn
    690                 695                 700

Thr Asp Asn Asn Gly Ser His Pro Ser Thr Asp Asp Lys Lys Thr Thr
705                 710                 715                 720

His


<210> SEQ ID NO 50
<211> LENGTH: 2166
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 50

gtgattacaa ttaaaaatcc aaaaatcctt aagtggctaa agtatgtatt aagtgcaatt      60

cttagcctta ttatccttgt tattattatt ggtggtcttt tgtttacctt ctacattagc     120

agtgctccga aactgtcaga agcccagtta aaatcaacaa actctagctt ggtttatgac     180

ggtaataaca atctgattgc tgatttgggt tctgaaaagc gtgaaaatgt aacagctgat     240

agtatcccta ttaatctagt taatgctatt acctcaattg aagataaacg tttctttaac     300

catcgtggag tagatcttta tcgtattttt ggtgctgcct ttcataatct aacgagtcag     360

accactcaag gggggtcaac gcttgatcag caactcatta aactagccta tttttctact     420

aatgaatctg atcaaacctt aaaacgtaag gctcaagaag tttggcttgc tcttcaaatg     480

gagcgaaaat atactaaaca agaaatcctg actttttaca tcaacaaagt atatatgggt     540

aatggcaact atggtatgct gacagccgct aagtcttatt atggcaagga tcttaaggat     600

ttatcttatg cccaactagc cctattggct ggaatccctc aagctcctag tcaatatgat     660

ccttaccttc atcctgaagc tgctcaaaat cgccgtaacg tcgtgttgca acagatgtac     720

atggaaaaac atctgacgaa agcagaatat gaaactgcca tcgcaactcc cgtcgctgaa     780

ggtctacaat cactccaaca gcgctcaact tatccaaaat atatggataa ttatctaaaa     840

caagttattg aagaagtcaa aaaagaaacg aataaagata tttttaccgc tggtttaaaa     900

gtttatacca atattatccc cgatgcgcag cagactcttt ataatattta tcattctggt     960

gattatgttt actatccaga ccaagatttc caagttgctt caacgattgt tgatgtgaca    1020
```

-continued

```
aatggtcatg ttattgctca gcttggcgga cgtaatcaag atgaaaatgt ttcatttggg   1080

actaaccaag ctgttttaac tgatcgtgac tggggttcta ccatgaagcc aatcacagcc   1140

tatgctcctg ctattgaatc tggtgtttat acttctactg ctcagtcgac taatgactca   1200

gtctattatt ggcctggaac cactacccaa ttgtttaact gggaccttag atataacgga   1260

tggatgacaa tccaagctgc tattatgcta tcgcgaaatg tcccagcagt ccgagcactg   1320

gaagccgcag gacttgacta tgctcgatct ttcttaagca gtttaggtat taactatccc   1380

gaaatgcact actcaaacgc tatctcaagt aataacagta gctcagataa aaaatatggt   1440

gcaagtagtg aaaaaatggc cgctgcatac gctgcttttg caaatggtgg tatttatcat   1500

aaaccaaggt atgtcaataa agtggaattt agtgatggta caagtaaaac ttttgatgaa   1560

aaaggaaaac gtgccatgaa agaaaccacg gcctatatga tgacagatat gttaaaaact   1620

gttctcactt atggtacagg tactgctgct gccattcctg gtgttgcgca agctggtaaa   1680

acagggactt ctaactacac tgatgaggaa ctagctaaaa ttggtgaaaa atacggcctt   1740

tatccagatt atgttggtac attagcgcca gacgaaaact ttgttggctt tactaagcgc   1800

tacgccatgg ctgtttggac aggttacaaa aaccgcttga ccccagtata cggatcaagt   1860

ctagagattg catctgacgt ttatcgtagc atgatgactt acttaacaaa tggttacagt   1920

gaagattgga cgatgccaaa tggtctttat cgcagtggtg gattcctcta cttaagcgga   1980

acctatgcga gcaacaccga ctatactaat tcggtttaca acaatcttta cagcaataac   2040

acgacaacag cttctagcca aacgacttca gatgatacta gtagtagcaa tgatacaagt   2100

aattcaacca atacagacaa caatggcagt catccatcta ccgatgataa aaagacaact   2160

cattaa                                                              2166


<210> SEQ ID NO 51
<211> LENGTH: 244
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 51

Met Ile Glu Phe Lys His Val Ser Lys Leu Tyr Gly Asp Lys Glu Ala
1               5                   10                  15

Leu Ser Asp Leu Asn Val Thr Ile Asn Asp Gly Glu Ile Phe Gly Leu
            20                  25                  30

Ile Gly His Asn Gly Ala Gly Lys Thr Thr Thr Ile Ser Ile Leu Thr
        35                  40                  45

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

Leu Thr Glu Asn Arg Glu Ala Ile Lys Lys Gln Ile Ala Tyr Val Pro
65                  70                  75                  80

Asp Ser Pro Asp Ile Phe Leu Asn Leu Thr Pro Asn Glu Tyr Trp Gln
                85                  90                  95

Phe Leu Ala Lys Ile Tyr Gly Val Ser Asp Glu Asp Arg Glu Glu Arg
            100                 105                 110

Leu Ala Gln Leu Thr Thr Leu Phe Glu Leu Lys Glu Glu Val Asn Gln
        115                 120                 125

Thr Ile Asp Ser Phe Ser His Gly Met Arg Gln Lys Val Ile Val Ile
    130                 135                 140

Gly Ala Leu Val Ser Asn Pro Asn Ile Trp Ile Leu Asp Glu Pro Leu
```

-continued

```
145                 150                 155                 160

Thr Gly Leu Asp Pro Gln Ala Ser Phe Asp Leu Lys Glu Met Met Lys
                165                 170                 175

Ala His Ala Ala Ser Gly His Thr Val Leu Phe Ser Thr His Val Leu
            180                 185                 190

Ser Val Ala Glu Gln Leu Cys Asp Arg Ile Gly Ile Leu Lys Lys Gly
        195                 200                 205

Lys Leu Ile Phe Val Gly Thr Ile Asp Glu Leu Lys Glu His His Pro
    210                 215                 220

Asp Lys Asp Leu Glu Ser Ile Tyr Leu Glu Leu Ala Gly Arg Lys Ala
225                 230                 235                 240

Gln Glu Glu Gly


<210> SEQ ID NO 52
<211> LENGTH: 735
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 52

atgatagaat ttaaacatgt ttcaaagttg tatggcgaca aagaagctct cagcgattta      60

aacgtcacca tcaatgacgg tgaaattttt ggccttatcg gacataatgg tgcaggtaaa     120

accacgacca tcagcatttt gacttctatt atcgaagcga gttatggcga agtatttgtg     180

gatggtcaac ttctgacaga aaatagagaa gctatcaaaa aacaaattgc ttatgtgcca     240

gattctcctg atattttctt gaatctaact ccaaatgagt attggcagtt tttagctaaa     300

atttatgggg tgtcagatga ggacagagaa gaacggttag cacagctgac aacacttttt     360

gaactgaagg aagaagttaa tcaaaccatt gatagtttct cacatgggat gcgccaaaaa     420

gtgattgtga ttggtgctct tgtatcaaat cctaacatct ggattttgga tgaaccatta     480

acaggtttgg atcctcaggc ttcttttgac cttaaagaaa tgatgaaagc tcatgcagct     540

tctggacata cagtcttatt ttcgactcac gtgctatcag tcgctgagca gttatgtgat     600

cgtatcggga ttctaaaaaa agggaaattg atttttgttg gaacgattga tgagttgaaa     660

gaacaccatc ctgacaaaga cttggagagc atctaccttg aactcgctgg gcgtaaggcg     720

caagaagagg ggtga                                                      735


<210> SEQ ID NO 53
<211> LENGTH: 424
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 53

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

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

Ser Thr Gly Glu Leu Ser Lys Thr Phe Lys Asp Phe Ser Thr Ser Ser
        35                  40                  45

Asn Lys Ser Asp Ala Ile Lys Gln Thr Arg Ala Phe Ser Ile Leu Leu
    50                  55                  60

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

-continued

```
Asn Ser Asp Ser Met Ile Leu Val Thr Val Asn Pro Lys Thr Lys Lys
                85                  90                  95

Thr Thr Met Thr Ser Leu Glu Arg Asp Thr Leu Thr Thr Leu Ser Gly
            100                 105                 110

Pro Lys Asn Asn Glu Met Asn Gly Val Glu Ala Lys Leu Asn Ala Ala
        115                 120                 125

Tyr Ala Ala Gly Gly Ala Gln Met Ala Ile Met Thr Val Gln Asp Leu
    130                 135                 140

Leu Asn Ile Thr Ile Asp Asn Tyr Val Gln Ile Asn Met Gln Gly Leu
145                 150                 155                 160

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

Asp Phe Pro Ile Ser Ile Ala Glu Asn Glu Pro Glu Tyr Gln Ala Thr
            180                 185                 190

Val Ala Pro Gly Thr His Lys Ile Asn Gly Glu Gln Ala Leu Val Tyr
        195                 200                 205

Ala Arg Met Arg Tyr Asp Asp Pro Glu Gly Asp Tyr Gly Arg Gln Lys
    210                 215                 220

Arg Gln Arg Glu Val Ile Gln Lys Val Leu Lys Lys Ile Leu Ala Leu
225                 230                 235                 240

Asp Ser Ile Ser Ser Tyr Arg Lys Ile Leu Ser Ala Val Ser Ser Asn
                245                 250                 255

Met Gln Thr Asn Ile Glu Ile Ser Ser Arg Thr Ile Pro Ser Leu Leu
            260                 265                 270

Gly Tyr Arg Asp Ala Leu Arg Thr Ile Lys Thr Tyr Gln Leu Lys Gly
        275                 280                 285

Glu Asp Ala Thr Leu Ser Asp Gly Gly Ser Tyr Gln Ile Val Thr Ser
    290                 295                 300

Asn His Leu Leu Glu Ile Gln Asn Arg Ile Arg Thr Glu Leu Gly Leu
305                 310                 315                 320

His Lys Val Asn Gln Leu Lys Thr Asn Ala Thr Val Tyr Glu Asn Leu
                325                 330                 335

Tyr Gly Ser Thr Lys Ser Gln Thr Val Asn Asn Asn Tyr Asp Ser Ser
            340                 345                 350

Gly Gln Ala Pro Ser Tyr Ser Asp Ser His Ser Ser Tyr Ala Asn Tyr
        355                 360                 365

Ser Ser Gly Val Asp Thr Gly Gln Ser Ala Ser Thr Asp Gln Asp Ser
    370                 375                 380

Thr Ala Ser Ser His Arg Pro Ala Thr Pro Ser Ser Ser Ser Asp Ala
385                 390                 395                 400

Leu Ala Ala Asp Glu Ser Ser Ser Ser Gly Ser Gly Ser Leu Val Pro
                405                 410                 415

Pro Ala Asn Ile Asn Pro Gln Thr
            420
```

<210> SEQ ID NO 54
<211> LENGTH: 1275
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 54

```
atgaaaattg gaaaaaaaat agttttaatg ttcacagcta ttgtgttaac aactgtcttg     60
```

-continued

```
gcattaggtg tctatctaac tagtgcttat accttctcaa caggagaatt atcaaagacc    120

tttaaagatt tttcgacatc ttcaaacaaa agtgatgcca ttaaacaaac aagagctttt    180

tctatcttgt tgatgggtgt tgatacaggc tcttcagagc gtgcctccaa gtgggaagga    240

aacagtgatt cgatgatttt ggttacggtt aatccaaaga ccaagaaaac aactatgact    300

agtttagaac gagatacctt aaccacgtta tctggaccca aaaataatga aatgaatggt    360

gttgaagcta agcttaacgc tgcttatgca gcaggtggcg ctcagatggc tattatgacc    420

gtgcaagatc ttttgaatat caccattgat aactatgttc aaattaatat gcaaggcctt    480

attgatcttg tgaatgcagt tggagggatt acagttacaa atgagtttga ttttcctatc    540

tcgattgctg aaaacgaacc tgaatatcaa gctactgttg cgcctggaac acacaaaatt    600

aacggtgaac aagctttggt ttatgctcgt atgcgttatg atgatcctga gggagattat    660

ggtcgacaaa agcgtcaacg tgaagtcatt caaaaggtat tgaaaaaaat ccttgctctt    720

gatagcatta gctcttatcg gaagatttta tctgctgtaa gtagtaatat gcaaacgaat    780

atcgaaatct cttctcgcac tatccctagt ctattaggtt atcgtgacgc acttagaact    840

attaagactt atcaactaaa aggagaagat gccactttat cagatggtgg atcataccaa    900

attgttacct ctaatcattt gttagaaatc caaaatcgta tccgaacaga attaggactt    960

cataaggtta atcaattaaa aacaaatgct actgtttatg aaaatttgta tgggtcaact   1020

aagtctcaga cagtaaacaa caactatgac tcttcaggcc aggctccatc ttattctgat   1080

agtcatagct cttacgctaa ttattcaagt ggagtagata ccggccagag tgctagtaca   1140

gaccaggact ctactgcttc aagccatagg ccagctacgc cgtcttcttc atcagatgct   1200

ttagcagctg atgagtctag ctcatcaggg tctggatcat tagttcctcc tgctaatatc   1260

aaccctcaga cctaa                                                    1275


<210> SEQ ID NO 55
<211> LENGTH: 300
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 55

Met Thr Gln Gln Ser Met Leu Leu Ser Ile Glu Gln Val Asn Lys Ser
1               5                   10                  15

Tyr Gly Lys Asn Gln Val Leu Ser Asp Ile Ser Phe Asp Ile Tyr Lys
            20                  25                  30

Gly Glu Ile Cys Gly Leu Val Gly Gln Asn Gly Ala Gly Lys Thr Thr
        35                  40                  45

Leu Met Arg Ile Leu Ser Gly Leu Ile Gly Lys Asp Ser Gly Gln Ile
    50                  55                  60

Lys Gln Leu Gln Pro Tyr Arg Met Gly Ser Ile Ile Glu Ser Pro Thr
65                  70                  75                  80

Leu Tyr Pro Asn Met Thr Ala His Asp Asn Leu Tyr Tyr Ala Ala Leu
                85                  90                  95

Gln Leu Arg Leu Ala Asp Ala Lys Glu Arg Ile His Glu Val Leu Glu
            100                 105                 110

Leu Ile Gly Leu Glu Lys Val Ser Lys Lys Lys Lys Val Lys Asp Tyr
        115                 120                 125

Ser Leu Gly Met Arg Gln Arg Leu Ala Ile Gly Leu Ser Ile Leu Asp
    130                 135                 140
```

-continued

```
Phe Pro Glu Phe Leu Ile Leu Asp Glu Pro Ile Asn Gly Leu Asp Pro
145                 150                 155                 160

Ala Gly Ile Lys Glu Met Arg Gln Ile Ile Leu Asn Leu Arg Asp Cys
                165                 170                 175

Tyr Gly Ile Thr Ile Leu Ile Ser Ser His Ile Leu Ser Glu Leu Asp
            180                 185                 190

Leu Val Val Asp Arg Tyr Val Ile Met His Lys Gly Lys Val Ile Lys
        195                 200                 205

Ser Met Asp Lys Ala Glu Leu Lys Ala Gln Val Lys Val Gln Ile Ala
    210                 215                 220

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

Gly Leu Arg Val Glu Thr Asp Gly Gln Met Leu Leu Ile Lys Pro Thr
                245                 250                 255

Leu Ser Val Met Glu Leu Ile Lys Ile Val Leu Asp Leu Pro Val Glu
            260                 265                 270

Ile Phe Asp Ile Tyr His His Gln Val Ser Phe Glu His Tyr Tyr Leu
        275                 280                 285

Asp Leu Leu Gly Lys Asp Ala Ala Ser Pro Leu Ile
    290                 295                 300
```

<210> SEQ ID NO 56
<211> LENGTH: 903
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 56

```
atgacacagc aatcaatgtt actaagtatt gagcaagtaa ataaatccta tggtaaaaat      60

caggttttaa gtgatatctc ttttgatatt tacaaaggag aaatttgcgg ccttgtgggt     120

caaaatggtg ctggaaagac aacgttaatg cgtattttat ctggcctaat tggaaaagat     180

tcagggcaaa tcaaacagtt acaaccctat cgaatgggat caattattga gtcaccgaca     240

ctttatccca atatgacagc tcatgataat ctttactatg cagcgttgca attgagatta     300

gctgatgcaa aagagcgcat acatgaggtt ttggaactta ttgggttaga aaaagtgagc     360

aaaaagaaaa aggtgaaaga ttattcttta gggatgcgcc aacgtttggc tattggtctt     420

tcgatactgg attttccaga atttttaatc ttggatgaac ccattaatgg tcttgatcca     480

gcaggaatca aagaaatgcg tcagattatt ttgaacctaa gagattgcta tggtattacg     540

attttgattt ccagtcatat tttatcagaa ttagacttag ttgttgatcg ttacgtgatt     600

atgcataaag gcaaagttat taagagtatg gacaaagcag agcttaaagc tcaagtaaaa     660

gtacaaattg cccttcatac aagcgatgat cagctggtaa aaaatagact tttagaattg     720

gggcttagag ttgagactga tggtcagatg ctactaataa aaccaacttt atcagtaatg     780

gagcttatca aaattgttct agatctgcct gttgagattt ttgacattta tcatcatcaa     840

gtgagctttg aacattatta cctcgatttg ttaggtaaag atgcagcatc accattaatt     900

tag                                                                   903
```

<210> SEQ ID NO 57
<211> LENGTH: 294
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

-continued

```
<400> SEQUENCE: 57

Met Ile Lys Arg Cys Lys Gly Ile Gly Leu Ala Leu Met Ala Phe Phe
1               5                   10                  15

Leu Val Ala Cys Val Asn Gln His Pro Lys Thr Ala Lys Glu Thr Glu
            20                  25                  30

Gln Gln Arg Ile Val Ala Thr Ser Val Ala Val Val Asp Ile Cys Asp
        35                  40                  45

Arg Leu Asn Leu Asp Leu Val Gly Val Cys Asp Ser Lys Leu Tyr Thr
    50                  55                  60

Leu Pro Lys Arg Tyr Asp Ala Val Lys Arg Val Gly Leu Pro Met Asn
65                  70                  75                  80

Pro Asp Ile Glu Leu Ile Ala Ser Leu Lys Pro Thr Trp Ile Leu Ser
                85                  90                  95

Pro Asn Ser Leu Gln Glu Asp Leu Glu Pro Lys Tyr Gln Lys Leu Asp
            100                 105                 110

Thr Glu Tyr Gly Phe Leu Asn Leu Arg Ser Val Glu Gly Met Tyr Gln
        115                 120                 125

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

Glu Leu Arg Gln Gln Tyr Gln Asp Tyr Tyr Arg Ala Phe Gln Ala Lys
145                 150                 155                 160

Arg Lys Gly Lys Lys Lys Pro Lys Val Leu Ile Leu Met Gly Leu Pro
                165                 170                 175

Gly Ser Tyr Leu Val Ala Thr Asn Gln Ser Tyr Val Gly Asn Leu Leu
            180                 185                 190

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

Leu Ser Ala Asn Pro Glu Asp Met Leu Ala Lys Glu Pro Asp Leu Ile
    210                 215                 220

Leu Arg Thr Ala His Ala Ile Pro Asp Lys Val Lys Val Met Phe Asp
225                 230                 235                 240

Lys Glu Phe Ala Glu Asn Asp Ile Trp Lys His Phe Thr Ala Val Lys
                245                 250                 255

Glu Gly Lys Val Tyr Asp Leu Asp Asn Thr Leu Phe Gly Met Ser Ala
            260                 265                 270

Lys Leu Asn Tyr Pro Glu Ala Leu Asp Thr Leu Thr Gln Leu Phe Asp
        275                 280                 285

His Val Gly Asp His Pro
    290


<210> SEQ ID NO 58
<211> LENGTH: 885
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 58

atgataaaac gatgtaaagg aattggtcta gccttaatgg ccttcttttt ggtagcttgt     60

gtgaatcagc accctaaaac ggctaaagag actgaacagc agagaattgt agccacttcg    120

gttgctgtgg ttgatatctg tgaccgttta aatttagacc tcgttggggt ttgtgatagt    180

aaattatata cccttcctaa acgctatgat gctgttaagc gtgtgggttt acccatgaat    240
```

-continued

```
cctgatatag agttgattgc ttctttgaaa ccaacttgga ttttgagtcc caattcttta    300

caagaagatt tggaacccaa gtatcaaaaa ttggatactg agtatggttt tttgaactta    360

cgaagtgttg agggcatgta ccagtccatt gatgatttag ggaacctttt ccaacgtcaa    420

caagaagcaa aagaattgcg ccagcaatac caggactatt atcgtgcttt ccaagctaaa    480

cgtaagggga agaaaaagcc taaagtgctt attcttatgg gcttgccagg tagttatttg    540

gtggcgacga accaatctta tgtagggaat cttttggact tggcaggtgg tgagaatgtt    600

tatcagtcag atgagaaaga atttctatca gctaatcctg aagacatgct ggctaaggag    660

cctgacttga ttttacgaac agctcatgcc attccagaca aggtaaaagt gatgtttgac    720

aaagaatttg ctgaaaatga tatttggaaa cattttacgg cagtcaagga agggaaagtc    780

tatgatttgg acaataccct gtttggcatg agtgctaaat tgaactaccc agaagccttg    840

gacaccttaa cacagctttt tgaccacgtg ggagatcatc cgtaa                    885
```

<210> SEQ ID NO 59
<211> LENGTH: 208
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 59

```
Met Thr Lys Ala Leu Ser Gly Ser Phe Leu Glu Glu Asn Met Lys His
1               5                   10                  15

Leu Asp Thr Tyr Ile Ala Phe Asp Leu Glu Phe Asn Thr Val Asn Asp
            20                  25                  30

Val Ser His Ile Ile Gln Val Ser Ala Val Lys Tyr Asp His His Lys
        35                  40                  45

Glu Val Asp Ser Phe Asp Thr Tyr Val Tyr Thr Asp Val Pro Leu Gln
    50                  55                  60

Ser Phe Ile Asn Gly Leu Thr Gly Ile Thr Ser Asp Lys Ile Ala Ala
65                  70                  75                  80

Glu Pro Lys Val Glu Glu Val Met Ala Ala Phe Lys Asn Phe Val Gly
                85                  90                  95

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

Leu Ala Glu Asn Gly Leu Asp Leu Arg Asp Gln Tyr Gln Ile Asp Leu
        115                 120                 125

Phe Asp Glu Ala Tyr Asp Arg Arg Ser Ala Asp Leu Asn Gly Ile Ala
    130                 135                 140

Asn Leu Arg Leu Gln Thr Val Ala Thr Phe Leu Gly Ile Lys Gly Arg
145                 150                 155                 160

Gly His Asn Ser Leu Glu Asp Ala Arg Met Thr Ala Val Ile Tyr Lys
                165                 170                 175

Ser Phe Leu Glu Thr Asp Thr Asn Lys Ala Tyr Leu Ser Gln Gln Glu
            180                 185                 190

Glu Val Thr Thr Asp Asn Pro Phe Ala Ala Leu Gly Asp Phe Phe Asp
        195                 200                 205
```

<210> SEQ ID NO 60
<211> LENGTH: 627
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 60

-continued

```
atgacgaagg ccctatcagg gtctttttg gaggaaaaca tgaaacactt agatacttat     60

attgcctttg atttagaatt taacactgtc aatgacgtta gtcatatcat tcaagtatca    120

gcagtcaaat atgaccacca taaagaagtt gacagctttg acacctatgt ttacacagat    180

gttcccttac agagctttat caatggccta acaggaatca catctgacaa gattgctgcg    240

gaaccaaaag tagaggaggt tatggctgcg tttaaaaatt ttgtgggaga gttaccactg    300

attggttata atgctcaaaa atctgacctg cctattctag ctgaaaatgg cttggattta    360

agggaccaat accagattga cctctttgat gaagcttacg atagacgtag cgcagactta    420

aatgggattg ctaaccttcg tctgcaaaca gtggcaacct ttttaggcat taagggtcga    480

ggtcataata gcttagaaga tgccagaatg acagcagtaa tctataagtc tttttagaa    540

acagatacaa acaaagcata tctcagccag caagaagagg taaccacaga taacccttc    600

gcagctttgg gagacttttt cgactaa                                       627


<210> SEQ ID NO 61
<211> LENGTH: 193
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 61

Met Val Leu Phe Leu Ile Arg Ile Phe Ser Asp Ser Asp Lys Glu Glu
1               5                   10                  15

Asn Met Gly Ile Glu Lys Thr Val Ser Glu Leu Ala Asp Ile Leu Gly
            20                  25                  30

Val Ser Arg Gln Ala Val Asn Asn Arg Val Lys Ser Leu Pro Glu Glu
        35                  40                  45

Asp Leu Asp Lys Asn Glu Lys Gly Val Thr Val Val Lys Arg Ser Gly
    50                  55                  60

Leu Val Lys Leu Glu Glu Ile Tyr Lys Lys Thr Ile Phe Asp Asp Glu
65                  70                  75                  80

Pro Ile Ser Glu Glu Thr Lys Gln Arg Glu Leu Leu Glu Ile Leu Val
                85                  90                  95

Asp Glu Lys Asn Thr Glu Ile Thr Arg Leu Tyr Glu Gln Leu Lys Ala
            100                 105                 110

Lys Asp Ala Gln Leu Ala Ser Lys Asp Glu Gln Met Arg Val Lys Asp
        115                 120                 125

Val Gln Ile Ala Glu Lys Asp Lys Gln Leu Asp Gln Gln Gln Gln Leu
    130                 135                 140

Thr Ala Lys Ala Met Ala Asp Lys Glu Thr Leu Lys Leu Glu Leu Glu
145                 150                 155                 160

Glu Ala Lys Ala Glu Ala Asn Gln Ala Arg Leu Gln Val Glu Glu Val
                165                 170                 175

Gln Ala Glu Val Gly Pro Lys Lys Gly Phe Phe Thr Arg Leu Phe Ala
            180                 185                 190

Lys


<210> SEQ ID NO 62
<211> LENGTH: 582
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 62
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-continued

atggtactat ttttaataag aatattcagt gatagtgata aagaggaaaa tatgggaatt 60

gaaaagacag ttagtgaact agctgatatt ttgggagtga gtcgtcaggc cgtcaataat 120

cgtgttaagt ctttacccga agaagatctt gacaaaaatg aaaaaggcgt tactgtggtt 180

aagcgcagtg gtcttgttaa gctggaagag atctataaaa aaacaatttt tgacgatgag 240

cctatcagtg aagaaacgaa acaacgtgag cttttagaga ttctcgtgga tgagaagaac 300

actgaaatca cgcgccttta tgagcaactc aaagccaaag atgctcaact tgcctcaaaa 360

gatgagcaaa tgcgtgttaa agacgtgcag atcgctgaaa aagataaaca attggatcag 420

cagcaacaat taactgctaa agccatggct gataaagaaa ccctaaaatt agaattggaa 480

gaagctaaag cagaagccaa ccaagctcgc ttacaagtcg aagaagttca ggctgaagtt 540

ggccctaaaa aaggcttttt cacccgcttg tttgcgaaat aa 582

<210> SEQ ID NO 63
<211> LENGTH: 191
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 63

Met Lys Leu Asp Val Phe Ala Gly Gln Glu Lys Ser Glu Leu Ser Met
1 5 10 15

Ile Glu Val Ala Arg Ala Ile Leu Glu Glu Arg Gly Arg Asp Asn Glu
20 25 30

Met Tyr Phe Ser Asp Leu Val Asn Glu Ile Gln Asn Tyr Leu Gly Lys
35 40 45

Ser Asp Ala Gly Ile Arg His Ala Leu Pro Phe Phe Tyr Thr Asp Leu
50 55 60

Asn Thr Asp Gly Ser Phe Ile Pro Leu Gly Glu Asn Lys Trp Gly Leu
65 70 75 80

Arg Ser Trp Tyr Ala Ile Asp Glu Ile Asp Glu Glu Ile Ile Thr Leu
85 90 95

Glu Glu Asp Glu Asp Gly Ala Gln Lys Arg Lys Lys Lys Arg Val Asn
100 105 110

Ala Phe Met Asp Gly Asp Glu Asp Ala Ile Asp Tyr Arg Asp Asp Asp
115 120 125

Pro Glu Asp Glu Asp Phe Thr Glu Glu Ser Ala Glu Val Glu Tyr Asp
130 135 140

Glu Glu Asp Pro Asp Asp Glu Lys Ser Glu Val Glu Ser Tyr Asp Ser
145 150 155 160

Glu Leu Asn Glu Ile Ile Pro Glu Asp Asp Phe Glu Glu Val Asp Ile
165 170 175

Asn Glu Glu Asp Glu Glu Asp Glu Glu Asp Glu Glu Pro Val Leu
180 185 190

<210> SEQ ID NO 64
<211> LENGTH: 576
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 64

ttgaaattag acgtatttgc aggacaagaa aaaagcgagc tttccatgat tgaagtggcg 60

cgtgccattt tggaagaacg cggtcgcgac aatgagatgt actttagcga tttagtcaat 120

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gagattcaaa attacttagg aaaatctgat gcaggtattc gtcatgcatt accatttttc    180

tatactgact taaatacgga tggctcattt attcctctag gtgaaaacaa atggggactt    240

cgttcgtggt atgctattga tgaaattgat gaagaaatta ttactctaga agaagatgaa    300

gatggcgcac aaaaacgtaa gaaaaaaacgc gttaatgctt tcatggatgg agatgaagac    360

gctattgatt atagagatga tgatccagaa gatgaagatt tcacagaaga atcagctgag    420

gttgaatatg atgaagaaga tccagatgat gaaaaaatcag aagtggagtc atatgattca    480

gaattgaatg aaattatccc tgaagatgat tttgaagaag ttgatatcaa tgaagaagac    540

gaagaagatg aagaagatga agaaccagtt ctctaa                              576


<210> SEQ ID NO 65
<211> LENGTH: 309
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 65

Met Ile Leu Thr Val Thr Leu Asn Pro Ala Ile Asp Val Ser Tyr Pro
1               5                   10                  15

Leu Asp Glu Leu Lys Cys Asp Thr Val Asn Arg Val Val Asp Val Thr
            20                  25                  30

Lys Thr Pro Gly Gly Lys Gly Leu Asn Val Ser Arg Val Leu Asn Glu
        35                  40                  45

Phe Gly Glu Thr Val Lys Ala Thr Gly Cys Val Gly Gly Glu Ser Gly
    50                  55                  60

Asp Phe Ile Ile Asn His Leu Pro Asp Ser Ile Leu Ser Arg Phe Tyr
65                  70                  75                  80

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

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

Ile Asp Gly Phe Thr His His Phe Lys Tyr Leu Leu Asn Asp Val Asp
        115                 120                 125

Val Val Thr Leu Ser Gly Ser Leu Pro Ala Gly Met Pro Asp Asp Tyr
    130                 135                 140

Tyr Gln Lys Leu Ile Lys Ile Ala Asn Leu Asn Gly Lys Lys Thr Val
145                 150                 155                 160

Leu Asp Cys Ser Gly Asn Ala Leu Glu Ala Val Leu Lys Gly Asp Ser
                165                 170                 175

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

Gly Lys Glu Met Thr Lys Asp Phe Asp Ala Leu Lys Glu Val Leu Gln
        195                 200                 205

Asp Glu Leu Phe Asp Gly Ile Glu Trp Ile Ile Val Ser Leu Gly Ala
    210                 215                 220

Asp Gly Val Phe Ala Lys His Lys Asp Thr Phe Tyr Asn Val Asp Ile
225                 230                 235                 240

Pro Lys Ile Lys Ile Val Ser Ala Val Gly Ser Gly Asp Ser Thr Val
                245                 250                 255

Ala Gly Ile Ala Ser Gly Leu Ala Asn Asp Glu Asp Asp Arg Ala Leu
            260                 265                 270
```

-continued

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

Thr Gly His Val Asn Met Ala Asn Tyr Asp Lys Leu Tyr Gln Ser Ile
290 295 300

Lys Val Lys Glu Val
305

<210> SEQ ID NO 66
<211> LENGTH: 930
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 66

gtgattttaa cagttacttt aaatccagct attgatgtct cctacccttt ggatgagcta 60

aaatgcgata ctgtcaatcg agttgtagac gttacaaaga cacccggtgg taaaggcttg 120

aatgtttccc gagttcttaa tgaattcggt gagacagtca aagctacagg ttgtgtaggt 180

ggagaaagcg gtgattttat cattaatcat cttcctgatt cgattttaag tcgcttctat 240

aaaatttcag gtgatactag aacttgtata gccattttac acgaaggtaa tcaaacggag 300

attttagaaa aaggaccgat gttaagtgta gatgaaattg atggatttac tcatcatttt 360

aagtatttac tgaatgatgt tgacgtagtg acgctctcag gcagtttgcc tgctggtatg 420

ccagatgatt actatcagaa gttaatcaag attgccaatc ttaatggtaa gaaaacggtt 480

ctggattgtt ctggaaatgc tctagaagca gtactaaaag gtgatagtaa accaacagtt 540

atcaaaccta atcttgaaga actttctcaa cttctaggta aagaaatgac aaaagatttt 600

gatgccttaa aagaagtctt acaagatgaa ctatttgatg gaattgaatg gataatcgtt 660

tctcttggtg ctgatggtgt atttgcaaag cacaaggata cgttttataa cgttgacatt 720

cctaaaatca aaattgtaag cgctgtaggt tcaggggatt ctacagtggc aggtattgct 780

tcaggtttag cgaatgatga agatgatcga gctttattaa caaaagcaaa tgtcttaggg 840

atgttaaatg cgcaagaaaa aacaactggg catgttaaca tggcaaatta cgataagtta 900

tatcaatcta ttaaagtcaa agaggtataa 930

<210> SEQ ID NO 67
<211> LENGTH: 224
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 67

Met Leu Asn Leu Lys Asp Ile Arg Lys Ser Tyr His Leu Gly Thr Glu
1 5 10 15

Glu Phe Ala Ile Leu Lys Gly Ile Asp Leu Glu Val Asn Glu Gly Asp
20 25 30

Phe Leu Ala Ile Met Gly Pro Ser Gly Ser Gly Lys Ser Thr Leu Met
35 40 45

Asn Ile Ile Gly Cys Leu Asp Lys Pro Gly Ser Gly Ser Tyr Ala Ile
50 55 60

Glu Gly Arg Asp Val Ser Ser Leu Ser Asp Asn Glu Leu Ala Asp Leu
65 70 75 80

Arg Asn Gln Lys Ile Gly Phe Val Phe Gln Asn Phe Asn Leu Met Pro
85 90 95

Lys Leu Thr Ala Cys Gln Asn Val Glu Leu Pro Leu Thr Tyr Met Asn

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            100                 105                 110

Val Pro Lys Lys Glu Arg Arg Lys Arg Ala Leu Glu Met Leu Lys Leu
        115                 120                 125

Val Gly Leu Glu Glu Arg Ser Glu Phe Lys Pro Met Glu Leu Ser Gly
    130                 135                 140

Gly Gln Lys Gln Arg Val Ala Ile Ala Arg Ala Leu Val Thr Asn Pro
145                 150                 155                 160

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

Ser Val Gln Ile Met Asp Leu Phe Lys Gln Phe Asn Asp Asn Gly Lys
            180                 185                 190

Thr Ile Ile Ile Ile Thr His Glu Pro Glu Val Ala Ala Leu Cys Lys
        195                 200                 205

Lys Thr Val Ile Leu Arg Asp Gly Asn Ile Glu His Ser Asp Ile Glu
    210                 215                 220


<210> SEQ ID NO 68
<211> LENGTH: 675
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 68

ttgttaaacc ttaaagatat tcgaaaaagc tatcatcttg gaactgaaga atttgcgatt      60

ttaaaaggaa tcgatttaga agttaacgag ggtgactttt tagccatcat gggaccatca     120

ggttcgggaa agtcaacatt gatgaatatc attgggtgtt tagataagcc tggctctggc     180

tcatatgcca ttgaaggcag agacgtgtca tccttatctg ataatgaact tgctgatttg     240

cgtaatcaaa aaatcggctt tgtttttcaa aattttaacc tgatgcccaa gctaacagct     300

tgtcaaaatg tcgaattacc cttgacttat atgaatgttc ctaaaaaaga gcgtcgcaaa     360

cgagccctag agatgttaaa gctagtagga ctagaagaac gtagtgaatt taaaccgatg     420

gagctatctg gtgggcaaaa acagcgtgta gcgattgcaa gagctttagt cactaacccg     480

agttttatcc ttggtgatga gccaacaggt gcactagaca caaaaaccag cgtccaaatc     540

atggacctat ttaaacaatt caatgataac ggcaaaacga ttattatcat cacacacgag     600

cctgaagtag ctgccctatg caaaaagacg gtgatcctaa gagatggtaa tatagaacat     660

tccgatatag agtaa                                                      675


<210> SEQ ID NO 69
<211> LENGTH: 422
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 69

Met Phe Gln Leu Arg Lys Lys Met Thr Arg Lys Gln Leu Ala Leu Leu
1               5                   10                  15

Ser Ala Gly Val Leu Thr Cys Val Val Gly Gly Ser Tyr Leu Ile Met
            20                  25                  30

Asn His Gln Gln Gln Glu Ile Val Ser Ser Val Asn Lys Val Lys Ala
        35                  40                  45

Leu Thr Ile Lys Glu Ala Met Glu Gln Gly Lys Asp Ile Ser Leu Thr
    50                  55                  60

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

Ser Ser Lys Gly Glu Val Lys Glu Val Phe Val Lys Lys Gly Asp Val
                85                  90                  95

Val Lys Val Gly Gln Pro Leu Phe Ser Tyr Glu Thr Ser Gln Arg Leu
            100                 105                 110

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

Gln Val Ala Lys Thr Asn Ala Ala Leu Lys Trp Glu Thr Tyr Asn Arg
    130                 135                 140

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

Asp Glu Ser Leu Leu Glu Gln Ile Arg Ser Ala Glu Asp Ser Val Ser
                165                 170                 175

Gln Ala Leu Ser Asp Ala Lys Thr Ala Asp Ser Asp Val Lys Thr Ala
            180                 185                 190

Gln Ile Glu Leu Asp Lys Ala Asn Ala Thr Ala Thr Thr Glu Lys Gly
        195                 200                 205

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

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

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

Asn Ile Ser Glu Phe Asp Arg Asp Lys Leu Lys Ile Gly Gln Lys Val
            260                 265                 270

Glu Val Ile Asp Arg Lys Asp Asn Ser Lys Lys Trp Thr Gly Lys Val
        275                 280                 285

Thr Gln Val Gly Asn Leu Lys Ala Glu Glu Lys Gly Gln Gly Gln Gly
    290                 295                 300

Gln Gly Gly Asn Asp Gln Gln Asp Asn Pro Asn Gln Ala Lys Phe Pro
305                 310                 315                 320

Tyr Val Ile Glu Leu Asp Gln Ser Asp Lys Gln Pro Leu Ile Gly Ser
                325                 330                 335

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

Val Leu Lys Glu Thr Phe Thr Met Ala Glu Asn Gly Lys Thr Tyr Val
        355                 360                 365

Trp Lys Val Asp Lys Asn Lys Val Lys Lys Gln Glu Ile Lys Thr Lys
    370                 375                 380

Pro Phe Ser Lys Gly Tyr Val Glu Val Thr Ser Gly Leu Thr Met Gln
385                 390                 395                 400

Asp Lys Ile Ala Gln Pro Leu Pro Gly Met Lys Asp Gly Met Glu Val
                405                 410                 415

Gly Ser Ile Val Lys Pro
            420


<210> SEQ ID NO 70
<211> LENGTH: 1269
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 70
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```
atgtttcagt taagaaaaaa aatgacgcgc aaacaattag ccttgttgag tgctggagtg     60

ttgacctgtg tggttggtgg tagctacttg ataatgaacc atcaacaaca agaaattgtc    120

tctagtgtca acaaagtaaa agccttaacc ataaaagaag ccatggaaca aggaaaagat    180

atcagcttga ccttagctgg cgaagtaaca gctaacaaca gcagcaaagt caaaatcgac    240

tcaagtaaag gagaagtcaa agaggtcttt gttaaaaaag gcgatgttgt caaagtagga    300

caacccttgt ttagctatga aacgtcacag cggttaacgg ctcaaagttc agaatttgat    360

gttcaaacca aagccaatca gctccaagtt gctaaaacca atgcagcatt gaagtgggaa    420

acctacaatc gcaaggtcaa tgaaatcaac accctaaaat ctcgctacaa cactgcacca    480

gatgagagct tactagagca aattcgcagc gcagaagaca gtgtatccca agcactaagc    540

gatgccaaaa cagcagatag cgatgtcaaa accgctcaaa tcgaactcga taaagctaat    600

gctactgcca caacggaaaa aggtaaacta gagtatgaca ccgttaagtc agacaccgca    660

ggaaccattg ttagtctaaa tactgatttg ccaaatcaat caaaatccaa aaaagaaaat    720

gaaactttta tggaaattat cgacaaatca aaaatgttag tcaaaggtaa cattagtgaa    780

tttgaccgtg acaagttaaa aatcggtcaa aaagtcgaag tgattgaccg caaagacaac    840

tctaaaaaat ggactggaaa agtaacccaa gttggcaacc tcaaagcaga ggaaaaaggc    900

caaggtcaag gccaaggtgg caatgaccaa caagataatc caaaccaagc aaaattccct    960

tatgttattg aacttgacca atcagacaag cagccactca ttggctcaca cacctatgtt   1020

aatgtgctca acaatgttcc agaagctggc aagatcgtat tgaaagaaac ctttacaatg   1080

gcagaaaatg gaaaaaccta tgtgtggaaa gttgataaaa acaaggtcaa aaaacaagaa   1140

atcaagacta agcccttctc aaaaggttat gttgaggtaa caagtggctt gactatgcaa   1200

gataagattg ctcagccgct tcctggcatg aaagacggta tggaggtagg aagtattgtt   1260

aaaccttaa                                                           1269


<210> SEQ ID NO 71
<211> LENGTH: 126
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 71

Met Lys Thr Ile Arg Arg Tyr Asp Val Asn Glu Asp Arg Gly His Thr
1               5                   10                  15

Gly Leu Val Glu Ala Gly Asp Phe Tyr Tyr Leu Asn Tyr Cys Val Gly
            20                  25                  30

Asn Val Gly Gln Asp Ile Glu Ser Gln Ile Asn Gly Ala Phe Asp Glu
        35                  40                  45

Met Glu Arg Arg Leu Ala Leu Val Gly Leu Thr Leu Asp Ala Val Val
    50                  55                  60

Gln Met Asp Cys Leu Phe Arg Asp Val Trp Asn Ile Pro Val Met Glu
65                  70                  75                  80

Lys Met Ile Lys Glu Arg Phe Asn Gly Arg Tyr Pro Ala Arg Lys Ser
                85                  90                  95

Ile Gln Thr Glu Phe Ala His His Gly Gly Pro Gln Gly Leu Leu Phe
            100                 105                 110

Gln Val Asp Gly Val Ala Tyr Ser Lys His Ile Ser Met Thr
        115                 120                 125
```

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<210> SEQ ID NO 72
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 72

atgaaaacaa ttagacgtta tgatgttaac gaagatagag ggcatacagg ccttgtagaa    60

gcaggagatt tctattattt aaactattgt gtcggcaatg ttggacaaga cattgaaagt   120

cagattaatg gagcctttga cgagatggag cgccgattag cattggtggg gctcacatta   180

gatgcagttg ttcaaatgga ttgtctattt cgagacgttt ggaacatacc tgtgatggaa   240

aaaatgatta aagagcgctt taatggcaga taccctgctc gaaaatcgat tcaaacggaa   300

tttgcacatc acggtggacc acaaggacta ctctttcaag tggatggtgt ggcttattca   360

aagcatattt cgatgaccta a                                             381


<210> SEQ ID NO 73
<211> LENGTH: 272
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 73

Met Leu Ile Pro Arg Lys Ile Arg His Phe Leu Arg Thr Lys Lys His
1               5                   10                  15

Val Leu Ile Asn Gly His Ser Val Asn Trp Gln Ser Cys Val Lys Tyr
            20                  25                  30

Gly Asp Gln Val Lys Leu Phe Phe Asp His Glu Asp Tyr Pro Glu Lys
        35                  40                  45

Ile Ile Val Met Gly Gln Ala Glu Lys Val Thr Cys Leu Tyr Glu Asp
    50                  55                  60

Glu His Ile Ile Ile Val Asn Lys Pro Glu Gly Met Lys Thr His Gly
65                  70                  75                  80

Asn Asp Pro Thr Glu Leu Ala Leu Leu Asn His Val Ser Ala Tyr Thr
                85                  90                  95

Gly Gln Thr Cys Tyr Val Val His Arg Leu Asp Lys Glu Thr Ser Gly
            100                 105                 110

Ala Ile Leu Phe Ala Lys Thr Pro Phe Ile Leu Pro Ile Leu Asn Arg
        115                 120                 125

Leu Leu Glu Lys Arg Asp Ile His Arg Glu Tyr Leu Ala Leu Val His
    130                 135                 140

Gly Ser Leu Asp Ser Pro Arg Val Thr Tyr His His Pro Ile Gly Arg
145                 150                 155                 160

His Arg His Asp Arg Arg Lys Arg Val Val Asp Pro Ile Asn Gly Lys
                165                 170                 175

Lys Ala Ile Thr Glu Val Thr Leu Val Lys Asn Phe His Lys Thr Ala
            180                 185                 190

Ser Leu Leu Thr Cys Gln Leu Gln Thr Gly Arg Thr His Gln Ile Arg
        195                 200                 205

Val His Leu Ala His Gln Gly His Val Leu Phe Gly Asp Pro Leu Tyr
    210                 215                 220

Ser Asn Gly Lys Lys Asp Cys Ala Arg Leu Met Leu His Ala Tyr Gln
225                 230                 235                 240

Leu Arg Leu Lys His Pro Leu Thr Gln Glu Asp Ile Cys Val Gln Ala
```

-continued

245 250 255

Lys Ser Ala Thr Phe Asp Ala Val Leu Asn Ala Gln Lys Ala Arg Lys
260 265 270

<210> SEQ ID NO 74
<211> LENGTH: 819
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 74

ttgttaattc cccgtaaaat taggcatttt ctgagaacta aaaaacatgt tcttattaat 60

ggtcattctg ttaactggca aagttgtgtt aaatacggtg atcaggtcaa acttttttt 120

gatcacgaag attatcctga aaagattatc gtgatggggc aggccgaaaa agtaacctgc 180

ctttatgaag atgagcacat cattattgtt aacaaacctg aagggatgaa aacacacggc 240

aatgatccaa cagagttggc gctgctcaac cacgtgtctg cttacacggg acagacctgc 300

tatgtggttc atcgtctgga taaggaaaca agtggggcca ttttatttgc taaaacacct 360

tttatcttac caatccttaa tcgtctttta gaaaaacgag atatccatcg agaatatttg 420

gcactagttc acggatcctt agacagtcct agggtaactt accatcatcc aattggtcgt 480

catcgacatg accgcagaaa acgtgttgtc gatccgataa atggcaagaa agctattact 540

gaggtaactc tagtcaaaaa cttccacaaa acggcaagct tactcacttg tcaattacaa 600

actggacgga ctcatcaaat tcgagtccat ttagcccatc aaggtcatgt tttatttggt 660

gatcctttgt attccaatgg aaaaaaagat tgtgctcgac tgatgctcca tgcttatcaa 720

ttacgtttga aacaccctct aacccaagaa gacatttgcg tgcaagctaa atcagctaca 780

tttgacgcag tcttaaacgc tcaaaaggct aggaaataa 819

<210> SEQ ID NO 75
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 75

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

Tyr Leu Leu Arg Leu Tyr His Glu Arg Gly Asp Lys Ser Met Gln Ser
20 25 30

Gln Leu Thr Tyr Asp Leu Leu Lys Lys Gln Ile Ala Glu Glu Leu Phe
35 40 45

Asp Glu Phe Lys Lys Leu Ile Gln Glu Lys Asp Leu Ala Asn Gln Trp
50 55 60

Val Asn Gln Thr Thr Leu Val Asn Glu Tyr Gly Tyr Ser Trp Gln Thr
65 70 75 80

Ile Lys Arg Met Glu Ser Tyr Gly Leu Lys Ser Phe Lys Asn Gly Lys
85 90 95

Asp Lys Met Tyr Cys Leu Ala Asp Val Asn Glu Ile Lys His Leu Met
100 105 110

Lys Gln

<210> SEQ ID NO 76
<211> LENGTH: 345
<212> TYPE: DNA

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<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 76

atgattatat caaaaaaagt ccgacggcaa tcggactcta aagaatacta tttacttaga      60

ttataccacg aaaggggtga taaatctatg caatcacaac ttacttacga tttactaaaa     120

aagcagatag cagaagagct ttttgatgag tttaagaaac tcatacagga aaaagattta     180

gcgaatcagt gggtcaatca aacaacgctc gtcaatgaat acggctactc atggcaaact     240

ataaaacgca tggagagcta tggccttaaa tcttttaaaa acggtaaaga caaaatgtat     300

tgtcttgctg atgtcaacga aatcaaacac ttaatgaaac aataa                     345


<210> SEQ ID NO 77
<211> LENGTH: 429
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 77

Met Thr Lys Asp Leu Leu Ser Glu Leu Ile Gln Lys His Arg Ser Phe
1               5                   10                  15

Asn Leu Ser Tyr Ser Ala Tyr Lys Gln Leu Tyr Glu Gly Asp His Ala
            20                  25                  30

Ile Leu Gln Gln Lys Gln Lys Glu Gln Tyr Lys Pro Asp Asn Arg Leu
        35                  40                  45

Val Val Asn Phe Ala Lys Tyr Ile Val Asp Thr Phe Asn Gly Tyr Phe
    50                  55                  60

Ile Gly Val Pro Val Gln Thr Ser His Glu Asn Lys Gln Val Ser Asn
65                  70                  75                  80

Tyr Leu Glu Leu Leu Asp Gly Tyr Asn Asp Gln Asp Asp Asn Asn Ala
                85                  90                  95

Glu Leu Ser Lys Ile Cys Ser Ile Tyr Gly His Gly Tyr Glu Leu Val
            100                 105                 110

Phe Asn Asp Glu Asn Ala Glu Ala Gly Ile Thr Tyr Leu Thr Pro Leu
        115                 120                 125

Glu Ala Phe Ile Val Tyr Asp Asp Ser Ile Arg Gln Lys Pro Leu Phe
    130                 135                 140

Ala Val Arg Tyr Phe Tyr Asn Lys Gly Gly Val Leu Glu Gly Ser Tyr
145                 150                 155                 160

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

Glu Ile Gly Glu Ser Glu Pro His Pro Phe Asp Gly Val Pro Met Ile
            180                 185                 190

Glu Tyr Val Glu Asn Glu Glu Arg Gln Ser Leu Leu Ala Ser Val Val
        195                 200                 205

Thr Leu Ile Asn Ala Phe Asn Lys Ala Ile Ser Glu Lys Ala Asn Asp
    210                 215                 220

Val Glu Tyr Phe Ala Asp Ala Tyr Leu Lys Ile Leu Gly Ala Glu Leu
225                 230                 235                 240

Asp Asp Glu Thr Leu Lys Ser Leu Arg Asp Thr Arg Ile Ile Asn Leu
                245                 250                 255

Lys Asp Thr Asp Ala Gln Gln Leu Thr Val Glu Phe Leu Gln Lys Pro
            260                 265                 270

Asp Ala Asp Ala Thr Gln Glu His Leu Leu Asp Arg Leu Glu Asn Leu
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        275                 280                 285

Ile Phe Arg Thr Ala Met Val Ala Asn Ile Ser Asp Glu Ser Phe Gly
    290                 295                 300

Thr Ala Ser Gly Ile Ala Leu Arg Tyr Arg Leu Gln Ala Met Asp Asn
305                 310                 315                 320

Leu Ala Lys Thr Lys Glu Arg Lys Phe Met Ser Gly Met Asn Arg Arg
                325                 330                 335

Tyr Lys Leu Ile Ala Ser Tyr Pro Thr Ser Lys Ile Gly Pro Lys Asp
            340                 345                 350

Trp Ile Gly Ile Lys Tyr Lys Phe Thr Arg Asn Leu Pro Ala Asn Leu
        355                 360                 365

Leu Glu Glu Ser Gln Ile Ala Gly Asn Leu Ala Gly Ile Val Ser Glu
    370                 375                 380

Glu Thr Gln Val Gly Val Leu Ser Ile Val Glu Asn Pro Gln Lys Glu
385                 390                 395                 400

Ile Glu Arg Lys Asn Ser Asp Lys Ser Thr Leu Ile Ser Arg Gln Ala
                405                 410                 415

Gly Gly Leu Asn Gly Gln Asn Thr Thr Thr Ile Leu Glu
            420                 425


<210> SEQ ID NO 78
<211> LENGTH: 1290
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 78

atgacaaaag atttgttaag cgagttaatc caaaaacaca ggtcgtttaa ccttagttat      60

tcagcgtata agcagctata tgagggtgat catgctattt tgcaacaaaa acaaaaagag     120

caatacaagc ctgataatcg cttggttgtt aattttgcaa aatacatcgt tgatacattt     180

aacggctatt ttatcggtgt gccagtccaa acgagccacg agaataaaca agtcagcaat     240

tatttagagt tattagacgg atacaatgat caagacgata acaacgcaga actatcaaag     300

atttgcagta tttacggaca tggctatgaa ttagttttta atgacgagaa tgcagaggct     360

ggaattactt atctgacacc gcttgaagct tttattgtct atgatgattc cattaggcaa     420

aagccgttat ttgctgtgcg ctatttttat aataagggcg gcgttttgga ggggtcttat     480

tcagatgcta gcaacatcac ttatttcaaa gacggcgaaa aaggcattga aattggagag     540

agtgagccac atccgtttga tggcgtgccg atgattgagt acgttgaaaa cgaagagcga     600

caaagcttgc tagctagtgt tgtgacattg attaatgcgt ttaataaagc tatctccgaa     660

aaagccaatg acgttgagta tttcgcagac gcttatctta aattttggg tgctgagtta      720

gacgacgaga cattaaagtc tcttagagac acccgcatta tcaatctaaa agacaccgat     780

gcacagcaat taactgttga gtttttacaa aagccagatg ccgatgcaac gcaagaacat     840

ttgctcgacc gattagagaa cttaattttt aggactgcta tggttgctaa tatcagtgat     900

gaatcgttcg gtacagctag cggcatcgct ttacgttatc gtttgcaagc tatggataac     960

ttagctaaga caaaagagcg taagtttatg agcgggatga accgcagata taagcttatt    1020

gcaagctatc ctacgtctaa gataggacct aaagattgga ttggcattaa gtataaattt    1080

actcgcaatc taccagcaaa tctcttagag gagtctcaaa tcgcaggtaa cttagcgggg    1140

attgtctcag aagaaacaca ggtcggtgtg ctatctattg tggagaaccc acaaaaagaa    1200
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attgaaagga aaaatagtga caagtcaact ttgattagcc gacaagcagg aggtctgaat   1260

ggacaaaaca ccacaacaat attggaatga                                    1290
```

<210> SEQ ID NO 79
<211> LENGTH: 98
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 79

```
Met Ala Ile Glu Ile Phe Gly Pro Glu Phe Arg Lys Lys Leu Leu Glu
1               5                   10                  15

Asp Leu Ile Ala Leu Asn Met Glu Ala Ile Lys Ile Ala Gln Thr Lys
            20                  25                  30

Asn Ala Lys Ser Ile Glu Trp Ile Thr Met Lys Arg Leu Glu Lys Glu
        35                  40                  45

Thr Gly Trp Gly Arg Thr Lys Leu Thr Gln Trp Arg Glu Gln Gly Lys
    50                  55                  60

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

Ala Asp Val Asn Arg Phe Leu Arg Thr Ser Gly Tyr Glu Lys Gly Glu
                85                  90                  95

Thr Thr
```

<210> SEQ ID NO 80
<211> LENGTH: 297
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 80

```
atggccattg aaatatttgg acctgagttt agaaaaaaac tgcttgaaga tttaatcgct     60

ctaaatatgg aagcgataaa aatagcgcag accaaaaacg ccaagtctat tgaatggata    120

accatgaagc ggctagaaaa agaaactgga tgggggcgaa ctaaattgac ccagtggaga    180

gaacaaggga aatttaactt taaaaggtca tcagaaaacg ggaaagtact atatgaccta    240

gcagatgtta atagattttt acggaccagt ggatatgaaa aaggagaaac aacatga      297
```

<210> SEQ ID NO 81
<211> LENGTH: 58
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 81

```
Met Lys Lys Lys Leu Asp Lys Ile Leu Ile Asp Lys Gly Met Ser Lys
1               5                   10                  15

Lys Glu Leu Ser Glu Lys Thr Gly Ile Ser Tyr Asn Thr Ile Met Asn
            20                  25                  30

Ile Gly Lys Lys Asp Ile Ser Phe Asn Lys Val Lys Lys Ile Ala Asp
        35                  40                  45

Val Leu Gly Val Ser Leu Asp Glu Phe Arg
    50                  55
```

<210> SEQ ID NO 82
<211> LENGTH: 177
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes

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<400> SEQUENCE: 82

atgaagaaaa aactagacaa aattctcatt gataaaggaa tgagtaaaaa agagttatcg      60

gagaaaacag gaattagtta caacaccatt atgaatatcg gtaaaaaaga tatttcgttt     120

aacaaagtga aaaaaattgc cgatgtcttg ggcgtcagct tagacgaatt tagatag       177


<210> SEQ ID NO 83
<211> LENGTH: 1465
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 83

Met Ser Asp Leu Phe Ala Lys Leu Met Asp Gln Ile Glu Met Pro Leu
1               5                   10                  15

Asp Met Arg Arg Ser Ser Ala Phe Ser Ser Ala Asp Ile Ile Glu Val
            20                  25                  30

Lys Val His Ser Val Ser Arg Leu Trp Glu Phe His Phe Ala Phe Ala
        35                  40                  45

Ala Val Leu Pro Ile Ala Thr Tyr Arg Glu Leu His Asp Arg Leu Ile
    50                  55                  60

Arg Thr Phe Glu Ala Ala Asp Ile Lys Val Thr Phe Asp Ile Gln Ala
65                  70                  75                  80

Ala Gln Val Asp Tyr Ser Asp Asp Leu Leu Gln Ala Tyr Tyr Gln Glu
                85                  90                  95

Ala Phe Glu His Ala Pro Cys Asn Ser Ala Ser Phe Lys Ser Ser Phe
            100                 105                 110

Ser Lys Leu Lys Val Thr Tyr Glu Asp Asp Lys Leu Ile Ile Ala Ala
        115                 120                 125

Pro Gly Phe Val Asn Asn Asp His Phe Arg Asn Asn His Leu Pro Asn
    130                 135                 140

Leu Val Lys Gln Leu Glu Ala Phe Gly Phe Gly Ile Leu Thr Ile Asp
145                 150                 155                 160

Met Val Ser Asp Gln Glu Met Thr Glu His Leu Thr Lys Asn Phe Val
                165                 170                 175

Ser Ser Arg Gln Ala Leu Val Lys Lys Ala Val Gln Asp Asn Leu Glu
            180                 185                 190

Ala Gln Lys Ser Leu Glu Ala Met Met Pro Pro Val Glu Glu Ala Thr
        195                 200                 205

Pro Ala Pro Lys Phe Asp Tyr Lys Glu Arg Ala Ala Lys Arg Gln Ala
    210                 215                 220

Gly Phe Glu Lys Ala Thr Ile Thr Pro Met Ile Glu Ile Glu Thr Glu
225                 230                 235                 240

Glu Asn Arg Ile Val Phe Glu Gly Met Val Phe Asp Val Glu Arg Lys
                245                 250                 255

Thr Thr Arg Thr Gly Arg His Ile Ile Asn Phe Lys Met Thr Asp Tyr
            260                 265                 270

Thr Ser Ser Phe Ala Leu Gln Lys Trp Ala Lys Asp Asp Glu Glu Leu
        275                 280                 285

Arg Lys Phe Asp Met Ile Ala Lys Gly Ala Trp Leu Arg Val Gln Gly
    290                 295                 300

Asn Ile Glu Thr Asn Pro Phe Thr Lys Ser Leu Thr Met Asn Val Gln
305                 310                 315                 320
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```
Gln Val Lys Glu Ile Val Arg His Glu Arg Lys Asp Leu Met Pro Glu
                325                 330                 335

Gly Gln Lys Arg Val Glu Leu His Ala His Thr Asn Met Ser Thr Met
            340                 345                 350

Asp Ala Leu Pro Thr Val Glu Ser Leu Ile Asp Thr Ala Ala Lys Trp
        355                 360                 365

Gly His Lys Ala Ile Ala Ile Thr Asp His Ala Asn Val Gln Ser Phe
    370                 375                 380

Pro His Gly Tyr His Arg Ala Arg Lys Ala Gly Ile Lys Ala Ile Phe
385                 390                 395                 400

Gly Leu Glu Ala Asn Ile Val Glu Asp Lys Val Pro Ile Ser Tyr Glu
                405                 410                 415

Pro Val Asp Met Asp Leu His Glu Ala Thr Tyr Val Val Phe Asp Val
            420                 425                 430

Glu Thr Thr Gly Leu Ser Ala Met Asn Asn Asp Leu Ile Gln Ile Ala
        435                 440                 445

Ala Ser Lys Met Phe Lys Gly Asn Ile Val Glu Gln Phe Asp Glu Phe
    450                 455                 460

Ile Asp Pro Gly His Pro Leu Ser Ala Phe Thr Thr Glu Leu Thr Gly
465                 470                 475                 480

Ile Thr Asp Lys His Leu Gln Gly Ala Lys Pro Leu Val Thr Val Leu
                485                 490                 495

Lys Ala Phe Gln Asp Phe Cys Lys Asp Ser Ile Leu Val Ala His Asn
            500                 505                 510

Ala Ser Phe Asp Val Gly Phe Met Asn Ala Asn Tyr Glu Arg His Asp
        515                 520                 525

Leu Pro Lys Ile Thr Gln Pro Val Ile Asp Thr Leu Glu Phe Ala Arg
    530                 535                 540

Asn Leu Tyr Pro Glu Tyr Lys Arg His Gly Leu Gly Pro Leu Thr Lys
545                 550                 555                 560

Arg Phe Gln Val Ser Leu Asp His His His Met Ala Asn Tyr Asp Ala
                565                 570                 575

Glu Ala Thr Gly Arg Leu Leu Phe Ile Phe Leu Lys Asp Ala Arg Glu
            580                 585                 590

Lys His Gly Ile Lys Asn Leu Leu Gln Leu Asn Thr Asp Leu Val Ala
        595                 600                 605

Glu Asp Ser Tyr Lys Lys Ala Arg Ile Lys His Ala Thr Ile Tyr Val
    610                 615                 620

Gln Asn Gln Val Gly Leu Lys Asn Met Phe Lys Leu Val Ser Leu Ser
625                 630                 635                 640

Asn Ile Lys Tyr Phe Glu Gly Val Pro Arg Ile Pro Arg Thr Val Leu
                645                 650                 655

Asp Ala His Arg Glu Gly Leu Leu Leu Gly Thr Ala Cys Ser Asp Gly
            660                 665                 670

Glu Val Phe Asp Ala Val Leu Thr Lys Gly Ile Asp Ala Ala Val Asp
        675                 680                 685

Leu Ala Arg Tyr Tyr Asp Phe Ile Glu Ile Met Pro Pro Ala Ile Tyr
    690                 695                 700

Gln Pro Leu Val Val Arg Glu Leu Ile Lys Asp Gln Ala Gly Ile Glu
705                 710                 715                 720
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```
Gln Val Ile Arg Asp Leu Ile Glu Val Gly Lys Arg Ala Lys Lys Pro
                725                 730                 735

Val Leu Ala Thr Gly Asn Val His Tyr Leu Glu Pro Glu Glu Glu Ile
            740                 745                 750

Tyr Arg Glu Ile Ile Val Arg Ser Leu Gly Gln Gly Ala Met Ile Asn
        755                 760                 765

Arg Thr Ile Gly Arg Gly Glu Gly Ala Gln Pro Ala Pro Leu Pro Lys
    770                 775                 780

Ala His Phe Arg Thr Thr Asn Glu Met Leu Asp Glu Phe Ala Phe Leu
785                 790                 795                 800

Gly Lys Asp Leu Ala Tyr Gln Val Val Val Gln Asn Thr Gln Asp Phe
                805                 810                 815

Ala Asp Arg Ile Glu Glu Val Glu Val Val Lys Gly Asp Leu Tyr Thr
            820                 825                 830

Pro Tyr Ile Asp Lys Ala Glu Glu Thr Val Ala Glu Leu Thr Tyr Gln
        835                 840                 845

Lys Ala Phe Glu Ile Tyr Gly Asn Pro Leu Pro Asp Ile Ile Asp Leu
    850                 855                 860

Arg Ile Glu Lys Glu Leu Thr Ser Ile Leu Gly Asn Gly Phe Ala Val
865                 870                 875                 880

Ile Tyr Leu Ala Ser Gln Met Leu Val Asn Arg Ser Asn Glu Arg Gly
                885                 890                 895

Tyr Leu Val Gly Ser Arg Gly Ser Val Gly Ser Ser Phe Val Ala Thr
            900                 905                 910

Met Ile Gly Ile Thr Glu Val Asn Pro Met Pro Pro His Tyr Val Cys
        915                 920                 925

Pro Ser Cys Gln His Ser Glu Phe Ile Thr Asp Gly Ser Val Gly Ser
    930                 935                 940

Gly Tyr Asp Leu Pro Asn Lys Pro Cys Pro Lys Cys Gly Thr Pro Tyr
945                 950                 955                 960

Gln Lys Asp Gly Gln Asp Ile Pro Phe Glu Thr Phe Leu Gly Phe Asp
                965                 970                 975

Gly Asp Lys Val Pro Asp Ile Asp Leu Asn Phe Ser Gly Asp Asp Gln
            980                 985                 990

Pro Ser Ala His Leu Asp Val Arg  Asp Ile Phe Gly Asp  Glu Tyr Ala
        995                 1000                 1005

Phe Arg  Ala Gly Thr Val Gly  Thr Val Ala Glu Lys  Thr Ala Tyr
    1010                 1015                 1020

Gly Phe  Val Lys Gly Tyr Glu  Arg Asp Tyr Gly Lys  Phe Tyr Arg
    1025                 1030                 1035

Asp Ala  Glu Val Asp Arg Leu  Ala Ala Gly Ala Ala  Gly Val Lys
    1040                 1045                 1050

Arg Thr  Thr Gly Gln His Pro  Gly Gly Ile Val Val  Ile Pro Asn
    1055                 1060                 1065

Tyr Met  Asp Val Tyr Asp Phe  Thr Pro Val Gln Tyr  Pro Ala Asp
    1070                 1075                 1080

Asp Val  Thr Ala Ser Trp Gln  Thr Thr His Phe Asn  Phe His Asp
    1085                 1090                 1095

Ile Asp  Glu Asn Val Leu Lys  Leu Asp Ile Leu Gly  His Asp Asp
    1100                 1105                 1110

Pro Thr  Met Ile Arg Lys Leu  Gln Asp Leu Ser Gly  Ile Asp Pro
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    1115                 1120                 1125

Ile Thr  Ile Pro Ala Asp Asp  Pro Gly Val Met Ala  Leu Phe Ser
    1130                 1135                 1140

Gly Thr  Glu Val Leu Gly Val  Thr Pro Glu Gln Ile  Gly Thr Pro
    1145                 1150                 1155

Thr Gly  Met Leu Gly Ile Pro  Glu Phe Gly Thr Asn  Phe Val Arg
    1160                 1165                 1170

Gly Met  Val Asn Glu Thr His  Pro Thr Thr Phe Ala  Glu Leu Leu
    1175                 1180                 1185

Gln Leu  Ser Gly Leu Ser His  Gly Thr Asp Val Trp  Leu Gly Asn
    1190                 1195                 1200

Ala Gln  Asp Leu Ile Lys Glu  Gly Ile Ala Thr Leu  Lys Thr Val
    1205                 1210                 1215

Ile Gly  Cys Arg Asp Asp Ile  Met Val Tyr Leu Met  His Ala Gly
    1220                 1225                 1230

Leu Glu  Pro Lys Met Ala Phe  Thr Ile Met Glu Arg  Val Arg Lys
    1235                 1240                 1245

Gly Leu  Trp Leu Lys Ile Ser  Glu Glu Glu Arg Asn  Gly Tyr Ile
    1250                 1255                 1260

Asp Ala  Met Arg Glu Asn Asn  Val Pro Asp Trp Tyr  Ile Glu Ser
    1265                 1270                 1275

Cys Gly  Lys Ile Lys Tyr Met  Phe Pro Lys Ala His  Ala Ala Ala
    1280                 1285                 1290

Tyr Val  Leu Met Ala Leu Arg  Val Ala Tyr Phe Lys  Val His His
    1295                 1300                 1305

Pro Ile  Met Tyr Tyr Cys Ala  Tyr Phe Ser Ile Arg  Ala Lys Ala
    1310                 1315                 1320

Phe Glu  Leu Lys Thr Met Ser  Gly Gly Leu Asp Ala  Val Lys Ala
    1325                 1330                 1335

Arg Met  Glu Asp Ile Thr Ile  Lys Arg Lys Asn Asn  Glu Ala Thr
    1340                 1345                 1350

Asn Val  Glu Asn Asp Leu Phe  Thr Thr Leu Glu Ile  Val Asn Glu
    1355                 1360                 1365

Met Leu  Glu Arg Gly Phe Lys  Phe Gly Lys Leu Asp  Leu Tyr Lys
    1370                 1375                 1380

Ser Asp  Ala Ile Glu Phe Gln  Ile Lys Gly Asp Thr  Leu Ile Pro
    1385                 1390                 1395

Pro Phe  Ile Ala Leu Glu Gly  Leu Gly Glu Asn Val  Ala Lys Gln
    1400                 1405                 1410

Ile Val  Lys Ala Arg Gln Glu  Gly Glu Phe Leu Ser  Lys Met Glu
    1415                 1420                 1425

Leu Arg  Lys Arg Gly Gly Ala  Ser Ser Thr Leu Val  Glu Lys Met
    1430                 1435                 1440

Asp Glu  Met Gly Ile Leu Gly  Asn Met Pro Glu Asp  Asn Gln Leu
    1445                 1450                 1455

Ser Leu  Phe Asp Asp Phe Phe
    1460                 1465

<210> SEQ ID NO 84
<211> LENGTH: 4398
<212> TYPE: DNA
<213> ORGANISM: Streptococcus pyogenes
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<400> SEQUENCE: 84

atgtcagatt tattcgctaa attgatggac cagatagaaa tgccacttga catgagacgt 60

tcaagtgcct tttcatctgc tgatattatc gaggtaaagg tacattcggt gtcacgcttg 120

tgggaatttc attttgcctt tgcagcggtt ttaccgattg caacttatcg tgaattgcat 180

gatcgtttga taagaacttt tgaggcggct gacattaagg taacctttga catccaagct 240

gctcaggtgg attattcaga tgatctgctt caagcttatt accaagaagc ttttgagcat 300

gcaccgtgta atagtgctag ttttaaatct tctttctcaa agctcaaagt gacttatgag 360

gatgacaaac tcattattgc agcgccaggt tttgtgaata acgatcattt tagaaacaat 420

catctgccta atctggtcaa gcaattagaa gcctttggct ttggcatctt gaccatagat 480

atggtgtcag atcaggaaat gactgagcat ttgaccaaga attttgtttc cagtcgtcag 540

gctcttgtga aaaaggctgt gcaggataat ttggaagccc aaaaatctct tgaagccatg 600

atgccaccag ttgaggaagc cacacctgct cctaagtttg actacaagga acgagcagct 660

aagcgtcagg cagggtttga aaaagcaacc atcacaccaa tgattgagat tgagaccgaa 720

gaaaaccgga ttgtctttga gggtatggtt tttgacgtgg agcgtaaaac gactaggaca 780

ggtcgccata tcatcaactt taaaatgaca gactatacct cctcgtttgc tctccaaaaa 840

tgggctaaag acgatgagga gctccgtaaa tttgatatga ttgctaaggg agcttggtta 900

cgggtacaag ggaatattga gaccaatcct tttacgaaga gtctcaccat gaatgtccag 960

caggtcaaag aaattgtccg tcatgagcgc aaagacctga tgccagaagg gcaaaagcgg 1020

gtcgaacttc atgcccacac caatatgtct accatggatg ccttaccgac agtagaaagc 1080

ttgattgata cggcagccaa gtggggacac aaggcgattg ctatcaccga ccatgctaat 1140

gtgcaaagtt ttcctcatgg ctaccatagg gctcgcaaag ctgggattaa ggctattttt 1200

ggcctagaag ccaatattgt tgaggacaag gtgcctattt cttatgaacc tgttgatatg 1260

gatttgcacg aagctaccta tgtggtcttt gacgtggaaa ccacaggtct atctgctatg 1320

aataatgacc tgattcagat tgcggcttcc aaaatgttta aaggaaatat tgtagagcag 1380

tttgatgaat tcattgatcc tgggcatcct ctttcagcct ttaccaccga attgacagga 1440

attaccgata agcatttgca gggcgccaag ccattggtta ctgtcctaaa agcttttcag 1500

gacttttgca aagatagtat cttggttgcc cacaacgcca gttttgacgt gggctttatg 1560

aacgccaatt atgaacgcca cgacttgccc aaaatcacac agcctgtgat tgataccttta 1620

gaatttgcta gaaacttgta tcctgagtac aagcgtcacg gtttgggacc gctcaccaag 1680

cgtttccaag tgagtctaga ccaccatcat atggccaatt acgacgcgga agccacagga 1740

cgtcttttgt ttatttttct aaaagatgcc agagaaaagc atggcatcaa aaatcttttg 1800

caactcaata cagatttggt ggctgaggat tcttacaaaa aagcgcggat taagcatgcg 1860

actatctatg tgcaaaatca ggttggtctt aaaaatatgt ttaagttggt cagcctttcc 1920

aatatcaaat attttgaagg ggtgccgcgt attccaagaa ccgtcttaga tgctcacaga 1980

gagggtttgt tacttggtac agcttgttct gacggcgagg tttttgatgc cgttctgact 2040

aaaggaattg atgcagcggt tgatttggct aggtattatg attttatcga aatcatgcca 2100

ccagccattt accagccatt ggttgtccgt gaattaatca aagatcaagc aggtattgag 2160

caggtgattc gtgacctcat tgaagtaggg aaacgagcta agaaacctgt gcttgccact 2220

-continued

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1. An immunogenic composition for protecting mammals against infection by Group A *Streptococcus* (GAS) comprising an effective amount of a molecule selected from the group consisting of:

(a) a region of at least one Group A *Streptococcus* marker listed in Tables 3, 4 or 5 that defines an epitope which induces the formation of bactericidal antibodies against GAS;

(b) a polypeptide listed in Table 3, 4 or 5;

(c) a peptide derived from (a) or (b);

(d) a chemically produced, synthetic peptide derived from (a), (b) or (c); and

(e) a combination of the molecules of (a) through (d).

2. A composition as claimed in claim **1**, wherein the region is immunoreactive and found in the most prevalent GAS serotypes associated with a GAS disease.

3. A composition as claimed in claim **1** comprising a synthetic peptides about 5 to 200 amino acids in length which is a portion of a polypeptide listed in Tables 3, 4 or 5.

4-5. (canceled)

6. A composition as claimed in claim **1**, further comprising a pharmaceutically acceptable carriers, an excipient, a diluent, a vehicles, or another immune-stimulatory molecules.

7. A method of inhibiting or reducing the growth of Group A *Streptococcus* in blood or of reducing phagocytic resistance in a subject or of immunizing a human against infection by Group A *Streptococcus* comprising administering an effective amount of an immunogenic composition as claimed in claims **1**.

8. (canceled)

9. A method for treating or preventing a GAS disease in a subject comprising administering to a subject in need thereof antibodies specific for one or more polypeptide listed in Tables 3, 4 or 5 or a composition as claimed in claim **1**.

10. A method for stimulating or enhancing in a subject production of antibodies directed against one or more polypeptide listed in Tables 3, 4 or 5, comprising administering to the subject an immunogenic composition as claimed in claim **1** in a dose effective for stimulating or enhancing production of the antibodies.

11. (canceled)

12. A method as claimed in claim **14**, wherein the method comprises:

(a) obtaining a sample from a subject;

(b) detecting in proteins extracted from the sample one or more GAS markers that are associated with the disease; and

(c) comparing the detected amount with an amount detected for a standard, wherein the GAS markers comprise at least one polypeptide listed in Tables 3, 4 or 5.

13. A method as claimed in claim **12** comprising:

(a) contacting a biological sample obtained from a subject with one or more antibody that specifically binds to the GAS markers or parts thereof; and

(b) detecting in the sample amounts of GAS markers that bind to the antibody relative to a predetermined standard or cut-off value, and therefrom determining the presence or absence of the GAS disease in the subject.

14. A method for determining the presence or absence of Group A *Streptococcus* (GAS) markers associated with a GAS disease in a subject comprising detecting one or more GAS markers or polynucleotides encoding GAS markers in a sample from the subject and relating the detected amount to the presence of a GAS disease, wherein the GAS markers comprise at least one polypeptide listed in Tables 3, 4 or 5.

15. A method as claimed in claim **14** wherein the GAS marker is a polynucleotide in Table 3, 4 or 5 or a fragment or modified form thereof.

16. A method as claimed in claim **14** wherein the polynucleotides detected are mRNA.

17. A method as claimed in claim **14** wherein the polynucleotide is detected by

(a) contacting the sample with oligonucleotides that hybridize to the polynucleotides; and

(b) detecting in the sample levels of nucleic acids that hybridize to the polynucleotides relative to a predetermined standard or cut-off value, and therefrom determining the presence or absence of a GAS disease in the subject.

18. A method as claimed in claim **16** wherein the mRNA is detected using an amplification reaction.

19. A method as claimed in claim **14** comprising reacting one or more GAS marker polypeptide in Tables 3, 4 or 5 with a test sample from a subject suspected of comprising antibodies specific for the GAS marker polypeptide under conditions that allow polypeptide/antibody complexes to form and detecting polypeptide/antibody complexes, wherein the detection of polypeptide/antibody complexes is an indication of GAS disease or infection.

20. A method as claimed in claim **19** wherein the GAS marker polypeptide comprises or consists essentially of one or more epitope of a GAS marker polypeptide of Table 4 or 5.

21. A diagnostic composition comprising

(a) an agent that binds to one or more GAS markers or hybridizes to a polynucleotide encoding such marker, wherein the GAS markers comprise at least one polypeptide listed in Tables 3, 4 or 5; or

(b) a set of markers comprising a plurality of polypeptides comprising or consisting of one or more polypeptide or polynucleotide listed in Table 3, 4 or 5.

22. A diagnostic composition as claimed in claim **21** wherein the agent is an antibody.

23-24. (canceled)

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专利名称(译)	一组链球菌的治疗和诊断		
公开(公告)号	US20100285047A1	公开(公告)日	2010-11-11
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[标]申请(专利权)人(译)	萨利姆KOWTHAR DE AZAVEDO JOYCE cvitkovitch丹尼斯		
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摘要(译)

描述了包含GAS标记的免疫原性组合物和疫苗。还描述了用于检测受试者中的GAS疾病的方法，包括测量来自受试者的样品中的GAS标志物。本发明进一步提供了用于实施本发明方法的试剂盒和使用GAS标记的GAS疾病的治疗应用，编码标记的多核苷酸和/或标记物的结合剂。