Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2413576 C 2012/11/13

(11)(21) 2 413 576

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2001/07/06
(87) Date publication PCT/PCT Publication Date: 2002/01/17
(45) Date de délivrance/Issue Date: 2012/11/13
(85) Entrée phase nationale/National Entry: 2002/12/20
(86) N° demande PCT/PCT Application No.: CA 2001/001001
(87) N° publication PCT/PCT Publication No.: 2002/004495
(30) Priorité/Priority: 2000/07/06 (US60/216,465)

(51) Cl.Int./Int.Cl. *C12N 15/31* (2006.01), *A61K 39/09* (2006.01), *C07K 14/315* (2006.01), *C12N 15/63* (2006.01), *A61K 39/00* (2006.01)

(72) Inventeurs/Inventors:
MARTIN, DENIS, CA;
HAMEL, JOSEE, CA;
BRODEUR, BERNARD, CA;
RIOUX, STEPHANE, CA;
BOYER, MARTINE, CA

(73) Propriétaire/Owner:
ID BIOMEDICAL CORPORATION OF QUEBEC, CA

(74) Agent: NORTON ROSE CANADA S.E.N.C.R.L.,S.R.L./LLP

(54) Titre : ANTIGENES DE STREPTOCOCCUS PYOGENES
(54) Title: STREPTOCOCCUS PYOGENES ANTIGENS

(57) Abrégé/Abstract:
The present invention relates to an antigen of Streptococcus pygenes (also called group A Streptococcus (GAS)), which is useful as vaccine component for therapy and/or prophylaxis.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 January 2002 (17.01.2002)

PCT

(10) International Publication Number
WO 02/04495 A3

(51) International Patent Classification[7]: C12N 15/31, 15/63, C07K 14/315, A61K 39/09

(21) International Application Number: PCT/CA01/01001

(22) International Filing Date: 6 July 2001 (06.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/216,465 6 July 2000 (06.07.2000) US

(71) Applicant *(for all designated States except US)*: **SHIRE BIOCHEM INC.** [CA/CA]; Intellectual Property Department, 275 Armand Frappier Boulevard, Laval, Québec H7V 4A7 (CA).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **MARTIN, Denis** [CA/CA]; 4728-G Gaboury, St-Augustin, Québec G3A 1E9 (CA). **HAMEL, Josée** [CA/CA]; 2401 Mauritain, Sillery, Québec G1T 1N6 (CA). **BRODEUR, Bernard** [CA/CA]; 2401 Mauritain, Sillery, Québec G1T 1N6 (CA).

(74) Agents: **CAWTHORN, Christian** et al.; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College Avenue, Montreal, Québec H3A 2Y3 (CA).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
13 June 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/04495 A3

(54) Title: STREPTOCOCCUS PYOGENES ANTIGEN

(57) Abstract: The present invention relates to an antigen of Streptococcus pygenes (also called group A Streptococcus (GAS)), which is useful as vaccine component for therapy and/or prophylaxis.

STREPTOCOCCUS PYOGENES ANTIGENS

FIELD OF THE INVENTION

The present invention is related to antigens, more particularly a polypeptide antigen of Streptococcus pyogenes (also called group A Streptococcus (GAS)) bacterial pathogen which may be useful for prophylaxis, diagnostic and/or therapy of streptococcal infection.

BACKGROUND OF THE INVENTION

Streptococci are gram (+) bacteria which are differentiated by group specific carbohydrate antigens A through O which are found at the cell surface. Streptococcus pyogenes isolates are further distinguished by type-specific M protein antigens. M proteins are important virulence factors which are highly variable both in molecular weights and in sequences. Indeed, more than 80-M protein types have been identified on the basis of antigenic differences.

Streptococcus pyogenes is responsible for many diverse infection types, including pharyngitis, erysipelas and impetigo, scarlet fever, and invasive diseases such as bacteremia and necrotizing fasciitis and also toxic shock. A resurgence of invasive disease in recent years has been documented in many countries, including those in North America and Europe. Although the organism is sensitive to antibiotics, the high attack rate and rapid onset of sepsis results in high morbidity and mortality.

To develop a vaccine that will protect individuals from Streptococcus pyogenes infection, efforts have concentrated on virulence factors such as the type-specific M proteins. However, the amino-terminal portion of M proteins was found to induce cross-reactive antibodies which reacted with human myocardium, tropomyosin, myosin, and vimentin, which might be implicated in

autoimmune diseases. Others have used recombinant techniques to produce complex hybrid proteins containing amino-terminal peptides of M proteins from different serotypes. However, a safe vaccine containing all Streptococcus pyogenes serotypes will be highly complex to produce and standardize.

In addition to the serotype-specific antigens, other Streptococcus pyogenes proteins have generated interest as potential vaccine candidates. The C5a peptidase, which is expressed by at least Streptococcus pyogenes 40 serotypes, was shown to be immunogenic in mice, but its capacity to reduce the level of nasopharyngeal colonization was limited. Other investigators have also focused on the streptococcal pyrogenic exotoxins which appear to play an important role in pathogenesis of infection. Immunization with these proteins prevented the deadly symptoms of toxic shock, but did not prevent colonization.

Therefore there remains an unmet need for *Streptococcus pyogenes* antigens that may be used vaccine components for prophylaxis, diagnostic and/or therapy of Streptococcus infection.

SUMMARY OF THE INVENTION

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from **SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20** or fragments, analogues or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 95% identity to a second polypeptide comprising a sequence chosen from **SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20** or fragments, analogues or derivatives thereof.

In other aspects, there are provided novel polypeptides encoded

by polynucleotides of the invention, vectors comprising polynucleotides of the invention operably linked to an expression control region, as well as host cells transfected with said vectors, pharmaceutical or vaccine compositions and methods of producing polypeptides comprising culturing said host cells under conditions suitable for expression.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is the DNA sequence of BVH-P1 gene from serotype 3 S. pyogenes strain ATCC12384 with a secretion signal at position 1 to 75; **SEQ ID NO:1.**

Figure 2 is the amino acid sequence BVH-P1 protein from serotype 3 S. pyogenes strain ATCC12384 with a secretion signal at position 1 to 25; **SEQ ID NO:2.**

Figure 3 is the DNA sequence of BVH-P1 gene from S. pyogenes strain LSPQ2699(ATCC19615) with a secretion signal at position 1 to 75; **SEQ ID NO:3.**

Figure 4 is the amino acid sequence BVH-P1 protein from S. pyogenes strain LSPQ2699(ATCC19615) with a secretion signal at position 1 to 25; **SEQ ID NO:4.**

Figure 5 is the DNA sequence of BVH-P1 gene from S. pyogenes strain SPY57 with a secretion signal at position 1 to 75; **SEQ ID NO:5.**

Figure 6 is the amino acid sequence BVH-P1 protein from S. pyogenes strain SPY57 with a secretion signal at position 1 to 25; **SEQ ID NO:6.**

Figure 7 is the DNA sequence of BVH-P1 gene from S. pyogenes strain B514 with a secretion signal at position 1 to 75; **SEQ ID NO:7.**

Figure 8 is the amino acid sequence BVH-P1 protein from S. pyogenes strain B514 with a secretion signal at position 1 to 25; **SEQ ID NO:8.**

Figure 9 is the DNA sequence BVH-P1 gene without a secretion signal from serotype 3 S.pyogenes strain ATCC12384 ; **SEQ ID NO:9.**

Figure 10 is the amino acid sequence BVH-P1 protein without a secretion signal from serotype 3 S.pyogenes strain ATCC12384 ; **SEQ ID NO:10.**

Figure 11 is the DNA sequence BVH-P1 gene without a secretion signal from serotype 3 S.pyogenes strain LSPQ2699 (ATCC19615) ; **SEQ ID NO:11.**

Figure 12 is the amino acid sequence BVH-P1 protein without a secretion signal from serotype 3 S.pyogenes strain LSPQ2699 (ATCC19615) ; **SEQ ID NO:12.**

Figure 13 is the DNA sequence BVH-P1 gene without a secretion signal from serotype 3 S.pyogenes strain SPY57 ; **SEQ ID NO:13.**

Figure 14 is the amino acid sequence BVH-P1 protein without a secretion signal from serotype 3 S.pyogenes strain SPY57 ; **SEQ ID NO:14.**

Figure 15 is the DNA sequence BVH-P1 gene without a secretion signal from serotype 3 S.pyogenes strain B514 ; **SEQ ID NO:15.**

Figure 16 is the amino acid sequence BVH-P1 protein without a secretion signal from serotype 3 S.pyogenes strain B514 ; **SEQ ID NO:16.**

Figure 17 depicts the comparison of the nucleotide sequences of the BVH-P1 genes from ATCC12384, LSPQ2699(ATCC19615), SPY57, B514, ATCC 70029 (Oklahoma) and T28/51/4 (UO9352) S. pyogenes strains by using the program Clustal W from MacVector sequence analysis software (version 6.5). Underneath the alignment, there is a consensus line. Shaded nucleotides are identical between every sequences and gaps in the sequence introduced by alignment are indicated by hyphens.

Figure 18 depicts the comparison of the predicted amino acid sequences of the BVH-P1 open reading frames from ATCC12384, LSPQ2699(ATCC19615), SPY57, B514, ATCC 70029 (Oklahoma) and T28/51/4 (UO9352) S. pyogenes strains by using the program Clustal W from MacVector sequence analysis software (version 6.5). Underneath the alignment, there is a consensus line. Shaded amino acid residues are identical between every sequences and gaps in the sequence introduced by alignment are indicated by hyphens.

Figure 19 is the DNA sequence of a gene from S. pneumonia; **SEQ ID NO:17.**

Figure 20 is the amino acid sequence of a protein from S. pneumonia; **SEQ ID NO:18.**

DETAILED DESCRIPTION OF THE INVENTION

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from **SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20** or fragments, analogues or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 95% identity to a second polypeptide comprising a sequence chosen from **SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20** or fragments, analogues or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising **SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20** or fragments, analogues or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide capable of generating antibodies having binding specificity for a polypeptide comprising a sequence chosen from **SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20** or fragments, analogues or derivatives thereof.

In accordance with the present invention, there is provided a consensus nucleotide sequence depicted in Figure 17. As can be seen by the alignement, the polynucleotide encoding the polypeptide of the invention is well conserved. Without restricting the scope of the invention, the following table 1 shows the possible modifications. SEQ ID NO:19 covers the consensus nucleotide sequence depicted in Figure 17 with the modifications illustrated in Table 1:

Position on alignement in Figure 17	Possible nucleotide
21	C or T
53	C or T
69	G or A
103	G or C
149	C or T

150	A or T
195	G or A
244	T or C
273	A or C
282	T or C
302	C or A
318	A or G
334	G or T
394	C or T
400	G or A
415	C or T
428-448	[CTGATGTCCCAACGACACCAT] or none
450	C or A
473	C or T
501	G or A
527	T or C
572	T or A
573	T or A
595	A or C
596	C or G
597	G or C
630	A or G
632	A or C
633	C or T
634	C or T
665	A or G
666	G or A
683	T or C
708	C or T
733	[CAGATGTTAACT] or none
798	T or C
883	G or none
927	T or A

930	T or C
943	T or none
952	T or A
955	G or A
964	T or C
973	G or A
976	T or G
978	A or T
979	A or T
981	A or G
982	T or C
986	G or A
988	T or G
1033	G or C
1034	C or G
1102	C or T
1143	A or T
1144	A or T
1145	A or T
1146	A or T

In accordance with the present invention, there is provided a consensus amino acid sequence depicted in Figure 18. As can be seen by the alignement, the polypeptide of the invention is well conserved. Without restricting the scope of the invention, the following table 2 shows the possible modifications. SEQ ID NO:20 covers the consensus nucleotide sequence depicted in Figure 18 with the modifications illustrated in Table 2:

Position on alignement in Figure 18	Possible amino acid
18	A or V
35	E or Q
50	T or I
101	T or N
112	A or S
132	P or S
134	V or I
139	S or P
143 to 149	SDVPTTP or none
150	F or L
158	S or F
176	L or s
191	V or E
199	T or P or S
211	D or A
212	P or S
222	E or G
228	V or A
242 to 245	ETSQ or none
246	E or M
247	T or L
248	S or T
295	A or L
296	S or L
297	A or P
298	F or L
299	G or V
300	I or L
301	T or R
302	S or H
303	F or L

304	S or V
305	G or V
306	Y or T
307	R or V
308	P or Q
309	G or E
310	D or I
311	P or Q
312	G or E
313	D or I
314	H or I
326	E or V
327	N or S
329	A or T
344	E or D
345	R or G
380	E or V
381	N or F

In accordance with the present invention, all polynucleotides encoding polypeptides are within the scope of the present invention.

In a further embodiment, the polypeptides in accordance with the present invention are antigenic.

In a further embodiment, the polypeptides in accordance with the present invention are immunogenic.

In a further embodiment, the polypeptides in accordance with the present invention can elicit an immune response in an individual.

In a further embodiment, the present invention also relates to

polypeptides which are able to raise antibodies having binding specificity to the polypeptides of the present invention as defined above.

An antibody that "has binding specificity" is an antibody that recognizes and binds the selected polypeptide but which does not substantially recognize and bind other molecules in a sample, e.g., a biological sample. Specific binding can be measured using an ELISA assay in which the selected polypeptide is used as an antigen.

In accordance with the present invention, "protection" in the biological studies is defined by a significant increase in the survival curve, rate or period. Statistical analysis using the Log rank test to compare survival curves, and Fisher exact test to compare survival rates and numbers of days to death, respectively, might be useful to calculate P values and determine whether the difference between the two groups is statistically significant. P values of 0.05 are regarded as not significant.

As used herein, "fragments", "analogues" or "derivatives" of the polypeptides of the invention include those polypeptides in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably conserved) and which may be natural or unnatural. In one embodiment, derivatives and analogues of polypeptides of the invention will have about 70% identity with those sequences illustrated in the figures or fragments thereof. That is, 70% of the residues are the same. In a further embodiment, polypeptides will have greater than 75% homology. In a further embodiment, polypeptides will have greater than 80% homology. In a further embodiment, polypeptides will have greater than 85% homology. In a further embodiment, polypeptides will have greater than 90% homology. In a further embodiment, polypeptides will have greater than 95% homology. In a further embodiment,

polypeptides will have greater than 99% homology. In a further embodiment, derivatives and analogues of polypeptides of the invention will have less than about 20 amino acid residue substitutions, modifications or deletions and more preferably less than 10. Preferred substitutions are those known in the art as conserved i.e. the substituted residues share physical or chemical properties such as hydrophobicity, size, charge or functional groups.

The skilled person will appreciate that fragments, analogues or derivatives of the proteins or polypeptides of the invention will also find use in the context of the present invention, i.e. as antigenic/immunogenic material. Thus, for instance proteins or polypeptides which include one or more additions, deletions, substitutions or the like are encompassed by the present invention. In addition, it may be possible to replace one amino acid with another of similar "type". For instance replacing one hydrophobic amino acid with another hydropholic amino acid.

One can use a program such as the CLUSTAL program to compare amino acid sequences. This program compares amino acid sequences and finds the optimal alignment by inserting spaces in either sequence as appropriate. It is possible to calculate amino acid identity or similarity (identity plus conservation of amino acid type) for an optimal alignment. A program like BLASTx will align the longest stretch of similar sequences and assign a value to the fit. It is thus possible to obtain a comparison where several regions of similarity are found, each having a different score. Both types of identity analysis are contemplated in the present invention.

In an alternative approach, the analogues or derivatives could be fusion proteins, incorporating moieties which render purification easier, for example by effectively tagging the desired protein or polypeptide, it may be necessary to remove

the "tag" or it may be the case that the fusion protein itself retains sufficient antigenicity to be useful.

In an additional aspect of the invention there are provided antigenic/immunogenic fragments of the proteins or polypeptides of the invention, or of analogues or derivatives thereof.

The fragments of the present invention should include one or more epitopic regions or be sufficiently similar to such regions to retain their antigenic/immunogenic properties. Thus, for fragments according to the present invention the degree of identity is perhaps irrelevant, since they may be 100% identical to a particular part of a protein or polypeptide, homologue or derivative as described herein. The key issue, once again, is that the fragment retains the antigenic/immunogenic properties.

Thus, what is important for analogues, derivatives and fragments is that they possess at least a degree of the antigenicity/immunogenic of the protein or polypeptide from which they are derived.

Also included are polypeptides which have fused thereto other compounds which alter the polypeptides biological or pharmacological properties i.e. polyethylene glycol (PEG) to increase half-life; leader or secretory amino acid sequences for ease of purification; prepro- and pro- sequences; and (poly)saccharides.

Furthermore, in those situations where amino acid regions are found to be polymorphic, it may be desirable to vary one or more particular amino acids to more effectively mimic the different epitopes of the different streptococcus strains.

Moreover, the polypeptides of the present invention can be modified by terminal $-NH_2$ acylation (eg. by acetylation, or

thioglycolic acid amidation, terminal carbosy amidation, e.g. with ammonia or methylamine) to provide stability, increased hydrophobicity for linking or binding to a support or other molecule.

Also contemplated are hetero and homo polypeptide multimers of the polypeptide fragments, analogues and derivatives. These polymeric forms include, for example, one or more polypeptides that have been cross-linked with cross-linkers such as avidin/biotin, gluteraldehyde or dimethylsuperimidate. Such polymeric forms also include polypeptides containing two or more tandem or inverted contiguous sequences, produced from multicistronic mRNAs generated by recombinant DNA technology.

Preferably, a fragment, analog or derivative of a polypeptide of the invention will comprise at least one antigenic region i.e. at least one epitope.

In order to achieve the formation of antigenic polymers (i.e. synthetic multimers), polypeptides may be utilized having bishaloacetyl groups, nitroarylhalides, or the like, where the reagents being specific for thio groups. Therefore, the link between two mercapto groups of the different peptides may be a single bond or may be composed of a linking group of at least two, typically at least four, and not more than 16, but usually not more than about 14 carbon atoms.

In a particular embodiment, polypeptide fragments, analogues and derivatives of the invention do not contain a methionine (Met) starting residue. Preferably, polypeptides will not incorporate a leader or secretory sequence (signal sequence). The signal portion of a polypeptide of the invention may be determined according to established molecular biological techniques. In general, the polypeptide of interest may be isolated from a streptococcal culture and subsequently sequenced to determine the initial residue of the mature protein and therefore the

sequence of the mature polypeptide.

According to another aspect, there are provided vaccine compositions comprising one or more streptococcal polypeptides of the invention in admixture with a pharmaceutically acceptable carrier diluent or adjuvant. Suitable adjuvants include oils i.e. Freund's complete or incomplete adjuvant; salts i.e. $AlK(SO_4)_2$, $AlNa(SO_4)_2$, $AlNH_4(SO_4)_2$, silica, kaolin, carbon polynucleotides i.e. poly IC and poly AU. Preferred adjuvants include QuilA and Alhydrogel. Vaccines of the invention may be administered parenterally by injection, rapid infusion, nasopharyngeal absorption, dermoabsorption, or bucal or oral. Pharmaceutically acceptable carriers also include tetanus toxoid.

The term vaccine is also meant to include antibodies. In accordance with the present invention, there is also provided the use of one or more antibodies having binding specificity for the polypeptides of the present invention for the treatment or prophylaxis of streptococcus infection and/or diseases and symptoms mediated by streptococcus infection.

Vaccine compositions of the invention are used for the treatment or prophylaxis of streptococcal infection and/or diseases and symptoms mediated by streptococcal infection As described in P.R. Murray (Ed, in chief),E.J. Baron, M.A. Pfaller, F.C. Tenover and R.H. Yolken. Manual of Clinical Microbiology, ASM Press, Washington, D.C. sixth edition, 1995, 1482p which are herein incorporated by reference. In one embodiment, vaccine compositions of the present invention are used for the prophylaxis or treatment of pharyngitis, erysipelas and impetigo, scarlet fever, and invasive diseases such as bacteremia and necrotizing fasciitis and also toxic shock. In one embodiment, vaccine compositions of the invention are used for the prophylaxis or treatment of *streptococcus* infection and/or diseases and symptoms mediated by *streptococcus*

infection, in particular group A *streptococcus* (*pyogenes*), group B *streptococcus* (GBS or *agalactiae*), S.pneumoniae, *dysgalactiae*, *uberis*, *nocardia* as well as *Staphylococcus aureus*. In a further embodiment, the streptococcus infection is Streptococcus pyogenes.

In a particular embodiment, vaccines are administered to those individuals at risk of streptococcus infection such as infants, elderly and immunocompromised individuals.

As used in the present application, the term " individuals" include mammals. In a further embodiment, the mammal is human.

Vaccine compositions are preferably in unit dosage form of about 0.001 to 100 µg/kg (antigen/body weight) and more preferably 0.01 to 10 µg/kg and most preferably 0.1 to 1 µg/kg 1 to 3 times with an interval of about 1 to 6 week intervals between immunizations.

Vaccine compositions are preferably in unit dosage form of about 0.1 µg to 10 mg and more preferably 1µg to 1 mg and most preferably 10 to 100 µg 1 to 3 times with an interval of about 1 to 6 week intervals between immunizations.

According to another aspect, there are provided polynucleotides encoding polypeptides characterized by the amino acid sequence chosen from **SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20** or fragments, analogues or derivatives thereof.

In one embodiment, polynucleotides are those illustrated in **SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 19** which may include the open reading frames (ORF), encoding polypeptides of the invention.

It will be appreciated that the polynucleotide sequences illustrated in the figures may be altered with degenerate codons

yet still encode the polypeptides of the invention. Accordingly the present invention further provides polynucleotides which hybridize to the polynucleotide sequences herein above described (or the complement sequences thereof) having 50% identity between sequences. In one embodiment, at least 70% identity between sequences. In one embodiment, at least 75% identity between sequences. In one embodiment, at least 80% identity between sequences. In one embodiment, at least 85% identity between sequences. In one embodiment, at least 90% identity between sequences. In a further embodiment, polynucleotides are hybridizable under stringent conditions i.e. having at least 95% identity. In a further embodiment, more than 97% identity.

Suitable stringent conditions for hybridation can be readily determined by one of skilled in the art (see for example Sambrook et al., (1989) Molecular cloning : A Laboratory Manual, 2nd ed, Cold Spring Harbor, N.Y.; Current Protocols in Molecular Biology, (1999) Edited by Ausubel F.M. et al., John Wiley & Sons, Inc., N.Y.).

In a further embodiment, the present invention provides polynucleotides that hybridise under stringent conditions to either

(a) a DNA sequence encoding a polypeptide or

(b) the complement of a DNA sequence encoding a polypeptide;

wherein said polypeptide comprising a sequence chosen from **SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20** or fragments or analogues thereof.

In a further embodiment, the present invention provides polynucleotides that hybridise under stringent conditions to either

(a) a DNA sequence encoding a polypeptide or

(b) the complement of a DNA sequence encoding a polypeptide;

wherein said polypeptide comprises at least 10 contiguous amino acid residues from a polypeptide comprising a sequence chosen from

SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20 or fragments or analogues thereof.

In a further embodiment, polynucleotides are those encoding polypeptides of the invention illustrated in **SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20.**

In a further embodiment, polynucleotides are those illustrated in **SEQ ID NOs : 1, 3, 5, 7, 9, 11, 13, 15, 19** encoding polypeptides of the invention.

As will be readily appreciated by one skilled in the art, polynucleotides include both DNA and RNA.

The present invention also includes polynucleotides complementary to the polynucleotides described in the present application.

In a further aspect, polynucleotides encoding polypeptides of the invention, or fragments, analogues or derivatives thereof, may be used in a DNA immunization method. That is, they can be incorporated into a vector which is replicable and expressible upon injection thereby producing the antigenic polypeptide in vivo. For example polynucleotides may be incorporated into a plasmid vector under the control of the CMV promoter which is functional in eukaryotic cells. Preferably the vector is injected intramuscularly.

According to another aspect, there is provided a process for producing polypeptides of the invention by recombinant techniques by expressing a polynucleotide encoding said polypeptide in a host cell and recovering the expressed polypeptide product. Alternatively, the polypeptides can be produced according to established synthetic chemical techniques i.e. solution phase or solid phase synthesis of oligopeptides which are ligated to produce the full polypeptide (block

ligation).

General methods for obtention and evaluation of polynucleotides and polypeptides are described in the following references: Sambrook et al, Molecular Cloning: A Laboratory Manual, 2nd ed, Cold Spring Harbor, N.Y., 1989; Current Protocols in Molecular Biology, Edited by Ausubel F.M. et al., John Wiley and Sons, Inc. New York; PCR Cloning Protocols, from Molecular Cloning to Genetic Engineering, Edited by White B.A., Humana Press, Totowa, New Jersey, 1997, 490 pages; Protein Purification, Principles and Practices, Scopes R.K., Springer-Verlag, New York, 3rd Edition, 1993, 380 pages; Current Protocols in Immunology, Edited by Coligan J.E. et al., John Wiley & Sons Inc., New York.

For recombinant production, host cells are transfected with vectors which encode the polypeptide, and then cultured in a nutrient media modified as appropriate for activating promoters, selecting transformants or amplifying the genes. Suitable vectors are those that are viable and replicable in the chosen host and include chromosomal, non-chromosomal and synthetic DNA sequences e.g. bacterial plasmids, phage DNA, baculovirus, yeast plasmids, vectors derived from combinations of plasmids and phage DNA. The polypeptide sequence may be incorporated in the vector at the appropriate site using restriction enzymes such that it is operably linked to an expression control region comprising a promoter, ribosome binding site (consensus region or Shine-Dalgarno sequence), and optionally an operator (control element). One can select individual components of the expression control region that are appropriate for a given host and vector according to established molecular biology principles (Sambrook et al, Molecular Cloning: A Laboratory Manual, 2nd ed, Cold Spring Harbor, N.Y., 1989; Current Protocols in Molecular Biology, Edited by Ausubel F.M. et al., John Wiley and Sons, Inc. New York. Suitable promoters include but are not limited to LTR or SV40 promoter,

E.coli lac, tac or trp promoters and the phage lambda P_L promoter. Vectors will preferably incorporate an origin of replication as well as selection markers i.e. ampicilin resistance gene. Suitable bacterial vectors include pET, pQE70, pQE60, pQE-9, pbs, pD10 phagescript, psiX174, pbluescript SK, pbsks, pNH8A, pNH16a, pNH18A, pNH46A, ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 and eukaryotic vectors pBlueBacIII, pWLNEO, pSV2CAT, pOG44, pXT1, pSG, pSVK3, pBPV, pMSG and pSVL. Host cells may be bacterial i.e. E.coli, Bacillus subtilis, Streptomyces; fungal i.e. Aspergillus niger, Aspergillus nidulins; yeast i.e. Saccharomyces or eukaryotic i.e. CHO, COS.

Upon expression of the polypeptide in culture, cells are typically harvested by centrifugation then disrupted by physical or chemical means (if the expressed polypeptide is not secreted into the media) and the resulting crude extract retained to isolate the polypeptide of interest. Purification of the polypeptide from culture media or lysate may be achieved by established techniques depending on the properties of the polypeptide i.e. using ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, hydroxylapatite chromatography and lectin chromatography. Final purification may be achieved using HPLC.

The polypeptide may be expressed with or without a leader or secretion sequence. In the former case the leader may be removed using post-translational processing (see US 4,431,739; US 4,425,437; and US 4,338,397
or be chemically removed subsequent to purifying the expressed polypeptide.

According to a further aspect, the streptococcal polypeptides of the invention may be used in a diagnostic test for streptococcus infection, in particular Streptococcus pyogenes infection.

Several diagnostic methods are possible, for example detecting streptococcus organism in a biological sample, the following procedure may be followed:

a) obtaining a biological sample from an individual;

b) incubating an antibody or fragment thereof reactive with a streptococcus polypeptide of the invention with the biological sample to form a mixture; and

c) detecting specifically bound antibody or bound fragment in the mixture which indicates the presence of streptococcus.

Alternatively, a method for the detection of antibody specific to a streptococcus antigen in a biological sample containing or suspected of containing said antibody may be performed as follows:

a) obtaining a biological sample from an individual;

b) incubating one or more streptococcus polypeptides of the invention or fragments thereof with the biological sample to form a mixture; and

c) detecting specifically bound antigen or bound fragment in the mixture which indicates the presence of antibody specific to streptococcus.

One of skill in the art will recognize that this diagnostic test may take several forms, including an immunological test such as an enzyme-linked immunosorbent assay (ELISA), a radioimmunoassay or a latex agglutination assay, essentially to determine whether antibodies specific for the protein are present in an individual.

The DNA sequences encoding polypeptides of the invention may also be used to design DNA probes for use in detecting the presence of streptococcus in a biological sample suspected of containing such bacteria. The detection method of this invention comprises:

a) obtaining the biological sample from an individual;

b) incubating one or more DNA probes having a DNA sequence

encoding a polypeptide of the invention or fragments thereof with the biological sample to form a mixture; and

c) detecting specifically bound DNA probe in the mixture which indicates the presence of streptococcus bacteria.

The DNA probes of this invention may also be used for detecting circulating streptococcus i.e. Streptococcus pyogenes nucleic acids in a sample, for example using a polymerase chain reaction, as a method of diagnosing streptococcus infections. The probe may be synthesized using conventional techniques and may be immobilized on a solid phase, or may be labelled with a detectable label. A preferred DNA probe for this application is an oligomer having a sequence complementary to at least about 6 contiguous nucleotides of the Streptococcus pyogenes polypeptides of the invention.

Another diagnostic method for the detection of streptococcus in an individual comprises:

a) labelling an antibody reactive with a polypeptide of the invention or fragment thereof with a detectable label;

b) administering the labelled antibody or labelled fragment to the patient; and

c) detecting specifically bound labelled antibody or labelled fragment in the patient which indicates the presence of streptococcus.

A further aspect of the invention is the use of the streptococcus polypeptides of the invention as immunogens for the production of specific antibodies for the diagnosis and in particular the treatment of streptococcus infection. Suitable antibodies may be determined using appropriate screening methods, for example by measuring the ability of a particular antibody to passively protect against streptococcus infection in a test model. One example of an animal model is the mouse model described in the examples herein. The antibody may be a whole antibody or an antigen-binding fragment thereof and may belong

to any immunoglobulin class. The antibody or fragment may be of animal origin, specifically of mammalian origin and more specifically of murine, rat or human origin. It may be a natural antibody or a fragment thereof, or if desired, a recombinant antibody or antibody fragment. The term recombinant antibody or antibody fragment means antibody or antibody fragment which was produced using molecular biology techniques. The antibody or antibody fragments may be polyclonal, or preferably monoclonal. It may be specific for a number of epitopes associated with the Streptococcus pyogenes polypeptides but is preferably specific for one.

A further aspect of the invention is the use of the antibodies directed to the streptococcus polypeptides of the invention for passive immunization. One could use the antibodies described in the present application. Suitable antibodies may be determined using appropriate screening methods, for example by measuring the ability of a particular antibody to passively protect against streptococcus infection in a test model. One example of an animal model is the mouse model described in the examples herein. The antibody may be a whole antibody or an antigen-binding fragment thereof and may belong to any immunoglobulin class. The antibody or fragment may be of animal origin, specifically of mammalian origin and more specifically of murine, rat or human origin. It may be a natural antibody or a fragment thereof, or if desired, a recombinant antibody or antibody fragment. The term recombinant antibody or antibody fragment means antibody or antibody fragment which was produced using molecular biology techniques. The antibody or antibody fragments may be polyclonal, or preferably monoclonal. It may be specific for a number of epitopes associated with the streptococcus pneumoniae polypeptides but is preferably specific for one.

Unless otherwise defined, 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. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

EXAMPLE 1

This example illustrates the cloning of S. pyogenes gene.

The coding region of S. pyogenes gene BVH-P1 (SEQ ID NO:1) was amplified by PCR (DNA Thermal Cycler GeneAmp PCR system 2400 Perkin Elmer, San Jose, CA) from genomic DNA of serotype 3 S. pyogenes strain ATCC12384 using the following oligos that contained base extensions for the addition of restriction sites *Nco*I (CCATGG) and *Xho*I (CTCGAG): DMAR16 (5'-CAGGCCATGGAGTGGACACCACGATCGGTTAC-3'); DMAR17 (5'-GCCGCTCGAGAGCATTAAAGGAGACATGAACATGATC-3'). PCR products were purified from agarose gel using a QIAquick gel extraction kit from QIAgen following the manufacturer's instructions (Chatsworth, CA), and digested with *Nco*I and *Xho*I (Pharmacia Canada Inc, Baie d'Urfé, Canada). The pET-21d(+) vector (Novagen, Madison, WI) was digested with *Nco*I and *Xho*I and purified from agarose gel using a QIAquick gel extraction kit from QIAgen (Chatsworth, CA). The *Nco*I-*Xho*I PCR products were ligated to the *Nco*I-*Xho*I pET-21d(+)expression vector. The ligated products were transformed into E. coli strain E. coli strain DH5α [ϕ80d*lac*ZΔM15 Δ(*lac*ZYA-*arg*F)U169 *end*A1 *rec*A1 *hsd*R17(r_K-m_K+) *deo*R *thi*-1 *sup*E44 λ$^-$ *gyr*A96 *rel*A1] (Gibco BRL, Gaithersburg, MD) according to the method of Simanis (Hanahan, D. DNA Cloning, 1985, D.M. Glover (ed), pp. 109-135). Recombinant pET-21d(+)plasmid (rpET21d(+)) containing BVH-P1

gene was purified using a QIAgen plasmid kit (Chatsworth, CA) and DNA insert was sequenced (Taq Dye Deoxy Terminator Cycle Sequencing kit, ABI, Foster City, CA).

It was determined that the open reading frame (ORF) which codes for BVH-P1 contains 1170-bp and encodes a 389 amino acid residues polypeptide with a predicted pI of 4.37 and a predicted molecular mass of 41054 Da.

Analysis of the predicted amino acid residues sequence (SEQ ID NO:2)using the Spscan sofware (Wisconsin Sequence Analysis Package; Genetics Computer Group) suggested the existence of a 25 amino acid residues signal peptide (MIITKKSLFVTSVALSLAPLATAQA), which ends with a cleavage site situated between an alanine and a glutamine residues. Analysis of this ORF did not revealed the presence of repetitive structures, cell wall anchoring motif (LPXTG), or IgA binding motif (MLKKIE).

An ORF which shares 62% with the S. pyogenes BVH-P1 gene was initially presented in the patent application PCT/CA99/00114 which described Group B streptococcus antigens. BVH-P1 gene was also found to share homology (62% identity) with an ORF present in the genome of S. pneumoniae (The Institute for Genomic Research).

EXAMPLE 2

This example describes the PCR amplification and sequencing of BVH-P1 gene from other S. pyogenes strains and the evaluation of the level of molecular conservation of this gene.

Lancefield's serogroup A S. pyogenes LSPQ2296 (ATCC 19615) was provided by the laboratoire de la santé publique du Québec, Sainte-Anne-de-Bellevue; serotype 1 S. pyogenes SPY57 clinical isolate was provided by the centre de recherche en infectiologie du centre hospitalier de l'université Laval, Sainte-Foy; and S. pyogenes strain B514 which was initially isolated from a mouse

was provided by Susan Hollingshead, from University of Alabama, Birmingham. The respective coding region of S. pyogenes gene BVH-P1 from strains ATCC 12384 (SEQ ID NO:1), LSPQ2699(ATCC19615)(SEQ ID NO:3), SPY57 (SEQ ID NO:5), and B514 (SEQ ID NO:7) were amplified by PCR (DNA Thermal Cycler GeneAmp PCR system 2400 Perkin Elmer, San Jose, CA) from bacterial cell lysates using the following oligos DMAR69 (5'-CTGGGAAGATTATCTAGCACATTAATAC-3'); DMAR72 (5'-CATAACGTTAAAACTGTCTAAAGGG-3'). PCR products were purified from agarose gel using a QIAquick gel extraction kit from QIAgen following the manufacturer's instructions (Chatsworth, CA) and the DNA insert were sequenced (Taq Dye Deoxy Terminator Cycle Sequencing kit, ABI, Foster City, CA). The predicted amino acid sequences from strains ATCC12384 (SEQ ID NO:2), LSPQ2699(ATCC19615) (SEQ ID NO:4), SPY57 (SEQ ID NO:6), and B514 (SEQ ID NO:8) were respectively presented in the following figures 2, 4, 6, and 8.

The figures 17 and 18 respectively depict the consensus nucleotide and predicted amino acid sequences established for S. pyogenes BVH-P1. In addition to the sequences presented herewith, the BVH-P1 gene sequences from the genome sequencing project at the University of Oklahoma (serotype M1 S. pyogenes strain ATCC 70029) and from (Kil et al. 1994. Infect. Immun. 62 :2440-2449 : GenBank accession number U09352) were also included. No function or role in the pathogenesis of the bacteria or protection against infection was described by Kil et al. for the sequence with GenBank accession number U09352. This latter sequence presented by Kil et al. was shown to be located upstream of a S.pyogenes 67kDa myosin-cross-reactive antigen.

Pairwise comparison of the BVH-P1 predicted protein sequences revealed between 95 to 100% identity with the exception of the BVH-P1 sequence obtained from GenBank under the accesssion number U09352. Pairwise comparison of that particular sequence

with the other five BVH-P1 sequences indicated identity between 87 to 91%. This lower homology can be explained by the presence of two regions (119-124 and 262-281) which are more divergent comparatively to the other BVH-P1 gene sequences. Beside these two regions in the BVH-P1 sequence obtained from GenBank under the accesssion number U09352, the BVH-P1 genes showed great similarity in overall organization.

EXAMPLE 3

This example illustrates the cloning of S. pyogenes protein gene in CMV plasmid pCMV-GH.

The DNA coding region of a S. pyogenes protein was inserted in phase downstream of a human growth hormone (hGH) gene which was under the transcriptional control of the cytomegalovirus (CMV) promotor in the plasmid vector pCMV-GH (Tang et al., Nature, 1992, 356 :152). The CMV promotor is a non functional plasmid in E. coli cells but is active upon administration of the plasmid in eukaryotic cells. The vector also incorporated the ampicillin resistance gene.

The coding region of BVH-P1 gene (SEQ ID NO:9) without its leader peptide region was amplified by PCR (DNA Thermal Cycler GeneAmp PCR system 2400 Perkin Elmer, San Jose, CA) from genomic DNA of serotype 3 S. pyogenes strain ATCC12384 using the following oligos that contained base extensions for the addition of restriction sites *BamHI* (GGATCC) and *SalI* (GTCGAC): DMAR24 (5'-TACCCGGATCCCCAAGAGTGGACACCACGATCGG-3'); DMAR25 (5'-GCGCTCGTCGACGCGTATCTCAGCCTCTTATAGGGC-3'). The PCR product was purified from agarose gel using a QIAquick gel extraction kit from QIAgen (Chatsworth, CA), digested with restriction enzymes (Pharmacia Canada Inc, Baie d'Urfe, Canada). The pCMV-GH vector (Laboratory of Dr. Stephen A. Johnston, Department of Biochemistry, The University of Texas, Dallas, Texas) was digested with *BamHI* and *SalI* and purified from agarose gel using

the QIAquick gel extraction kit from QIAgen (Chatsworth, CA). The *BamH*I-*Sal*I DNA fragments were ligated to the *BamH*I-*Sal*I pCMV-GH vector to create the hGH-BVH-P1 fusion protein under the control of the CMV promoter. The ligated products were transformed into E. coli strain DH5α [ϕ80d*lac*ZΔM15 Δ(*lac*ZYA-*arg*F)U169 *end*A1 *rec*A1 *hsd*R17(r_K-m_K+) *deo*R *thi*-1 *sup*E44 λ⁻ *gyr*A96 *rel*A1] (Gibco BRL, Gaithersburg, MD) according to the method of Simanis (Hanahan, D. DNA Cloning, 1985, D.M. Glover (ed), pp. 109-135). The recombinant pCMV plasmid was purified using a QIAgen plasmid kit (Chatsworth, CA) and the nucleotide sequence of the DNA insert was verified by DNA sequencing.

EXAMPLE 4

This example illustrates the use of DNA to elicit an immune response to S. pyogenes antigens.

A group of 8 female BALB/c mice (Charles River, St-Constant, Québec, Canada) were immunized by intramuscular injection of 100 μl three times at two- or three-week intervals with 50 μg of recombinant pCMV-GH encoding BVH-P1 gene in presence of 50 μg of granulocyte-macrophage colony-stimulating factor (GM-CSF)-expressing plasmid pCMV-GH-GM-CSF (Laboratory of Dr. Stephen A. Johnston, Department of Biochemistry, The University of Texas, Dallas, Texas). As control, a group of mice were injected with 50 μg of pCMV-GH in presence of 50 μg of pCMV-GH-GM-CSF. Blood samples were collected from the orbital sinus prior to each immunization and seven days following the third injection and serum antibody responses were determined by ELISA using purified BVH-P1-His•Tag from SEQ ID NO:11 S. pyogenes recombinant protein as coating antigen.

EXAMPLE 5

This example illustrates the production and purification of recombinant S. pyogenes BVH-P1 protein.

The recombinant pET-21d(+)plasmid with BVH-P1 gene corresponding to the SEQ ID NO:9 was used to transform by electroporation (Gene Pulser II apparatus, BIO-RAD Labs, Mississauga, Canada) E. coli strain BL21(DE3) (F^-ompT $hsdS_B$ ($r^-_Bm^-_B$) gal dcm (DE3)) (Novagen, Madison, WI). In this strain of E. coli, the T7 promotor controlling expression of the recombinant protein is specifically recognized by the T7 RNA polymerase (present on the λDE3 prophage) whose gene is under the control of the lac promotor which is inducible by isopropyl-ß-d-thio-galactopyranoside (IPTG). The transformant BL21(DE3)/rpET was grown at 37°C with agitation at 250 rpm in LB broth (peptone 10g/L, yeast extract 5g/L, NaCl 10g/L) containing 100 μg of carbenicillin (Sigma-Aldrich Canada Ltd., Oakville, Canada) per ml until the A_{600} reached a value of 0.6. In order to induce the production of S. pyogenes BVH-P1-His•Tag recombinant protein (from SEQ ID NO:10), the cells were incubated for 3 additional hours in the presence of IPTG at a final concentration of 1 mM. Induced cells from a 500 ml culture were pelleted by centrifugation and frozen at -70°C.

The purification of the recombinant proteins from the soluble cytoplasmic fraction of IPTG-induced BL21(DE3)/rpET21b(+) was done by affinity chromatography based on the properties of the His•Tag sequence (6 consecutive histidine residues) to bind to divalent cations (Ni^{2+}) immobilized on the His•Bind metal chelation resin. Briefly, the pelleted cells obtained from a 500 mL culture induced with IPTG was resuspended in lysis buffer (20 mM Tris, 500 mM NaCl, 10 mM imidazole, pH 7.9) containing 1mM PMSF, sonicated and centrifuged at 12,000 X g for 20 min to remove debris. The supernatant was deposited on a Ni-NTA agarose column (Qiagen, Mississauga, Ontario, Canada). The S.

pyogenes BVH-P1-His•Tag recombinant protein (from SEQ ID NO:10) was eluted with 250 mM imidazole-500mM NaCl-20 mM Tris pH 7.9. The removal of the salt and imidazole from the sample was done by dialysis against PBS at 4°C. The quantities of recombinant protein obtained from the soluble fraction of E. coli was estimated by MicroBCA (Pierce, Rockford, Illinois).

EXAMPLE 6

This example illustrates the accessibility to antibodies of the BVH-P1 protein at the surface of S. pyogenes strain.

Bacteria were grown in Tood Hewitt (TH) broth (Difco Laboratories, Detroit MI) with 0.5% Yeast extract (Difco Laboratories) and 0.5% peptone extract (Merck, Darmstadt, Germany) at 37°C in a 8% CO_2 atmosphere to give an OD_{490nm} of 0.600 (~10^8 CFU/ml). Dilutions of anti-BVH-P1 or control sera were then added and allowed to bind to the cells, which were incubated for 2 h at 4°C. Samples were washed 4 times in blocking buffer [phosphate-buffered saline (PBS) containing 2% bovine serum albumin (BSA)], and then 1 ml of goat fluorescein (FITC)-conjugated anti-mouse IgG + IgM diluted in blocking buffer was added. After an additional incubation of 60 min at room temperature, samples were washed 4 times in blocking buffer and fixed with 0.25 % formaldehyde in PBS buffer for 18-24 h at 4°C. Cells were washed 2 times in PBS buffer and resuspended in 500 µl of PBS buffer. Cells were kept in the dark at 4°C until analyzed by flow cytometry (Epics® XL; Beckman Coulter, Inc.).

Flow cytometric analysis revealed that BVH-P1-specific antibodies efficiently recognized their corresponding surface exposed epitopes on both the homologous (ATCC12384; serotype3) and the heterologous (SPY57; seotype 1) S. pyogenes strains tested. It was determined that more than 90 % of the 10,000 S. pyogenes cells analyzed were labeled with the antobodies present in the BVH-MC1 specific anti-sera. These observations clearly

demonstrate that the BVH-P1 protein is accessible at the surface where it can be easily recognized by antibodies. Anti- S. pyogenes antibodies were shown to play an important role in the protection against S. pyogenes infection.

EXAMPLE 7

This example illustrates the protection against fatal S. pyogenes infection induced by passive immunization of mice with rabbit hyper-immune sera.

New Zealand rabbits (Charles River laboratories, Montreal, Canada) were injected subcutaneously at multiple sites with approximately 50 μg and 100 μg of BVH-P1-His•Tag protein (from SEQ ID NO:10) that was produced and purified as described in Example 5 and adsorbed to Alhydrogel adjuvant (Superfos Biosector a/s). Rabbits were immunized three times at three-week intervals with the BVH-P1-His•Tag protein (from SEQ ID NO:10). Blood samples were collected three weeks after the third injection. The antibodies present in the serum were purified by precipitation using 40% saturated ammonium sulfate. Groups of 10 female CD-1 mice (Charles River) were injected intravenously with 500 μl of purified serum collected either from BVH-P1-His•Tag (from SEQ ID NO:10) immunized rabbits or rabbits immunized with an unrelated control recombinant protein. Eighteen hours later the mice were challenged with approximately $2x10^7$ CFU of the type 3 S. pyogenes strain ATCC12384. Samples of the S. pyogenes challenge inoculum were plated on blood agar plates to determine the CFU and to verify the challenge dose. Deaths were recorded for a period of 5 days.

EXAMPLE 8

This example illustrates the protection of mice against fatal S. pyogenes infection induced by immunization with BVH-P1 protein.

Groups of 8 female CD-1 mice (Charles River) were immunized subcutaneously three times at three-week intervals with 20 μg of affinity purified S. pyogenes BVH-P1-His•Tag recombinant protein (from SEQ ID NO:10) in presence of 10 μg of QuilA adjuvant (Cedarlane Laboratories Ltd, Hornby, Canada). or, as control, with QuilA adjuvant alone in PBS. Blood samples were collected from the orbital sinus on day 1, 22 and 43 prior to each immunization and seven days (day 50) following the third injection. Analysis by ELISA using purified recombinant BVH-P1 protein (from SEQ ID NO:10) clearly indicated that this protein is highly immunogenic in animals. Indeed reciprocal ELISA titers higher than 10^6 were determined for the mice immunized with this recombinant protein. Two weeks later the mice were challenged with approximately $2x10^7$ CFU of the type 3 S. pyogenes strain ATCC12384. Samples of the S. pyogenes challenge inoculum were plated on blood agar plates to determine the CFU and to verify the challenge dose. Deaths were recorded for a period of 5 days. Five out of the 8 (62%) mice immunized with three injections of 20 μg of purified recombinant BVH-P1 (from SEQ ID NO:10) and QuilA adjuvant survived the bacterial challenge to only 2/7 (28%)in the control group.

Table 3. Immunization of CD-1 mice with purified recombinant BVH-P1 protein confers protection against subsequent challenge with S. pyogenes strain ATCC 12384

Groups	Survival of the mice challenged with S. pyogenes strain ATCC 12384 (Day after challenge: number of survivors/total number of mice challenged))				
	1	2	3	4	5
20 μg of BVH-P1-His•Tag	8/8	8/8	7/8	6/8	5/8
Control	7/7	6/7	3/7	2/7	2/7

SEQUENCE LISTING

<110> SHIRE BIOCHEM INC.

<120> STREPTOCOCCUS PYOGENES ANTIGENS

<130> 12806-20CA

<150> PCT/CA01/01001

<151> 2001-07-06

<150> US 60/216,465

<151> 2000-07-06

<160> 29

<170> FastSEQ for Windows Version 4.0

<210> 1

<211> 1170

<212> DNA

<213> S. pyogenes

<400> 1

atgattatta ctaaaaagag cttatttgtg acaagtgtcg ctttgtcgtt agcacctttg 60

gcgacagcac aggcacaaga gtggacacca cgatcggtta cagaaatcaa gtctgaactc 120

gtcctagttg ataatgtttt tacttatact gtaaaatacg gtgacacttt aagcacaatt 180

gctgaagcaa tgggaattga tgtgcatgtc ttaggagata ttaatcatat tgctaatatt 240

gacttaattt ttccagacac gatcctaaca gccaactaca accaacacgg tcaggcaacg 300

actttgacgg ttcaagcgcc tgcttctagt ccagctagcg ttagtcatgt acctagcagt 360

gagccattac cccaagcatc tgccacctct caatcgactg ttcctatggc accatctgcg 420

acaccatctg atgtcccaac gacaccattc gcatctgcaa agccagatag ttctgtgaca 480

gcgtcatctg agctcacatc gtcaacgaat gatgtttcga ctgagttgtc tagcgaatca 540

caaaagcagc cagaagtacc acaagaagca gttccaactc ctaaagcagc tgaaacgact 600

gaagtcgaac ctaagacaga catctcagag gattcaactt cagctaatag gcctgtacct 660

aacgagagtg cttcagaaga agtttcttct gcggccccag cacaagcccc agcagaaaaa 720

gaagaaacct ctgcgccagc agcacaaaaa gctgtagctg acaccacaag tgttgcaacc 780

tcaaatggcc tttcttacgc tccaaaccat gcctacaatc caatgaatgc agggcttcaa 840

ccacaaacag cagccttcaa agaagaagtg gcttctgcct ttggtattac gtcatttagt 900

ggttaccgtc caggtgatcc aggagatcat ggtaaaggtt tggccattga ttttatggtg 960

cctgaaaatt ctgctcttgg tgatcaagtt gctcaatatg ccattgacca tatggcagag 1020

cgtggtattt catacgttat ttggaaacag cgattctatg cgccatttgc aagtatttac 1080

ggaccagcct acacatggaa ccccatgcca gatcgcggca gtattacaga aaaccattat 1140

gatcatgttc atgtctcctt taatgcttaa 1170

<210> 2

<211> 389

<212> PRT

<213> S. pyogenes

<400> 2

Met Ile Ile Thr Lys Lys Ser Leu Phe Val Thr Ser Val Ala Leu Ser

1 5 10 15

Leu Ala Pro Leu Ala Thr Ala Gln Ala Gln Glu Trp Thr Pro Arg Ser

20 25 30

Val Thr Glu Ile Lys Ser Glu Leu Val Leu Val Asp Asn Val Phe Thr

```
        35                  40                  45

Tyr Thr Val Lys Tyr Gly Asp Thr Leu Ser Thr Ile Ala Glu Ala Met

    50                  55                  60

Gly Ile Asp Val His Val Leu Gly Asp Ile Asn His Ile Ala Asn Ile

65                  70                  75                  80

Asp Leu Ile Phe Pro Asp Thr Ile Leu Thr Ala Asn Tyr Asn Gln His

                85                  90                  95

Gly Gln Ala Thr Thr Leu Thr Val Gln Ala Pro Ala Ser Ser Pro Ala

            100                 105                 110

Ser Val Ser His Val Pro Ser Ser Glu Pro Leu Pro Gln Ala Ser Ala

        115                 120                 125

Thr Ser Gln Ser Thr Val Pro Met Ala Pro Ser Ala Thr Pro Ser Asp

    130                 135                 140

Val Pro Thr Thr Pro Phe Ala Ser Ala Lys Pro Asp Ser Ser Val Thr

145                 150                 155                 160

Ala Ser Ser Glu Leu Thr Ser Ser Thr Asn Asp Val Ser Thr Glu Leu

                165                 170                 175

Ser Ser Glu Ser Gln Lys Gln Pro Glu Val Pro Gln Glu Ala Val Pro

            180                 185                 190

Thr Pro Lys Ala Ala Glu Thr Thr Glu Val Glu Pro Lys Thr Asp Ile

        195                 200                 205

Ser Glu Asp Ser Thr Ser Ala Asn Arg Pro Val Pro Asn Glu Ser Ala

    210                 215                 220

Ser Glu Glu Val Ser Ser Ala Ala Pro Ala Gln Ala Pro Ala Glu Lys

225                 230                 235                 240

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

                245                 250                 255

Ser Val Ala Thr Ser Asn Gly Leu Ser Tyr Ala Pro Asn His Ala Tyr

            260                 265                 270
```

Asn Pro Met Asn Ala Gly Leu Gln Pro Gln Thr Ala Ala Phe Lys Glu
275 280 285

Glu Val Ala Ser Ala Phe Gly Ile Thr Ser Phe Ser Gly Tyr Arg Pro
290 295 300

Gly Asp Pro Gly Asp His Gly Lys Gly Leu Ala Ile Asp Phe Met Val
305 310 315 320

Pro Glu Asn Ser Ala Leu Gly Asp Gln Val Ala Gln Tyr Ala Ile Asp
325 330 335

His Met Ala Glu Arg Gly Ile Ser Tyr Val Ile Trp Lys Gln Arg Phe
340 345 350

Tyr Ala Pro Phe Ala Ser Ile Tyr Gly Pro Ala Tyr Thr Trp Asn Pro
355 360 365

Met Pro Asp Arg Gly Ser Ile Thr Glu Asn His Tyr Asp His Val His
370 375 380

Val Ser Phe Asn Ala
385

<210> 3

<211> 1182

<212> DNA

<213> S. pyogenes

<400> 3

atgattatta ctaaaaagag cttatttgtg acaagtgtcg ctttgtcgtt agcacctttg 60

gcgacagcgc aggcacaaga gtggacacca cgatcggtta cagaaatcaa gtctgaactc 120

gtcctagttg ataatgtttt tacttatata gtaaaatacg gtgacacttt aagcacaatt 180

gctgaagcaa tggggattga tgtgcatgtc ttaggagata ttaatcatat tgctaatatt 240

gacttaattt ttccagacac gatcctaaca gcaaactaca accaacacgg tcaggcaacg 300

actttgacgg ttcaagcacc tgcttctagt ccatctagcg ttagtcatgt acctagcagt 360

gagccattac cccaagcatc tgccacctct caaccgactg ttcctatggc accatctgcg 420

acaccatctg atgtcccaac gacaccattc gcatctgcaa agccagatag ttctgtgaca 480

gcgtcatctg agctcacatc gtcaacgaat gatgtttcga ctgagttgtc tagcgaatca 540

caaaagcagc cagaagtacc acaagaagca gttccaactc ctaaagcagc tgaaccgact 600

gaagtcgaac ctaagacaga catctcagaa gacccaactt cagctaatag gcctgtacct 660

aacgagagtg cttcagaaga agcttcttct gcggccccag cacaagctcc agcagaaaaa 720

gaagaaacct ctcagatgtt aactgcgcca gcagcacaaa aagctgtagc tgacaccaca 780

agtgttgcaa cctcaaacgg cctttcttac gctccaaacc atgcctacaa tccaatgaat 840

gcagggcttc aaccacaaac agcagccttc aaagaagaag tggcttctgc ctttggtatt 900

acgtcattta gtggttaccg tccaggagat ccaggagatc atggtaaagg attagccatt 960

gactttatgg taccggttag ctctacgctt ggtgatcaag ttgctcaata tgccattgac 1020

catatggcag agcgtggtat ttcatacgtt atttggaaac agcgattcta tgcgccattt 1080

gcaagtattt acggaccagc ctacacatgg aaccccatgc cagatcgcgg cagtattaca 1140

gaaaaccatt atgatcatgt tcatgtctcc tttaatgctt aa 1182

<210> 4

<211> 393

<212> PRT

<213> S. pyogenes

<400> 4

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

Leu Ala Pro Leu Ala Thr Ala Gln Ala Gln Glu Trp Thr Pro Arg Ser
20 25 30

Val Thr Glu Ile Lys Ser Glu Leu Val Leu Val Asp Asn Val Phe Thr
35 40 45

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

Gly Ile Asp Val His Val Leu Gly Asp Ile Asn His Ile Ala Asn Ile

65 70 75 80

Asp Leu Ile Phe Pro Asp Thr Ile Leu Thr Ala Asn Tyr Asn Gln His

85 90 95

Gly Gln Ala Thr Thr Leu Thr Val Gln Ala Pro Ala Ser Ser Pro Ser

100 105 110

Ser Val Ser His Val Pro Ser Ser Glu Pro Leu Pro Gln Ala Ser Ala

115 120 125

Thr Ser Gln Pro Thr Val Pro Met Ala Pro Ser Ala Thr Pro Ser Asp

130 135 140

Val Pro Thr Thr Pro Phe Ala Ser Ala Lys Pro Asp Ser Ser Val Thr

145 150 155 160

Ala Ser Ser Glu Leu Thr Ser Ser Thr Asn Asp Val Ser Thr Glu Leu

165 170 175

Ser Ser Glu Ser Gln Lys Gln Pro Glu Val Pro Gln Glu Ala Val Pro

180 185 190

Thr Pro Lys Ala Ala Glu Pro Thr Glu Val Glu Pro Lys Thr Asp Ile

195 200 205

Ser Glu Asp Pro Thr Ser Ala Asn Arg Pro Val Pro Asn Glu Ser Ala

210 215 220

Ser Glu Glu Ala Ser Ser Ala Ala Pro Ala Gln Ala Pro Ala Glu Lys

225 230 235 240

Glu Glu Thr Ser Gln Met Leu Thr Ala Pro Ala Ala Gln Lys Ala Val

245 250 255

Ala Asp Thr Thr Ser Val Ala Thr Ser Asn Gly Leu Ser Tyr Ala Pro

260 265 270

Asn His Ala Tyr Asn Pro Met Asn Ala Gly Leu Gln Pro Gln Thr Ala

275 280 285

Ala Phe Lys Glu Glu Val Ala Ser Ala Phe Gly Ile Thr Ser Phe Ser

290 295 300

Gly Tyr Arg Pro Gly Asp Pro Gly Asp His Gly Lys Gly Leu Ala Ile

305 310 315 320

Asp Phe Met Val Pro Val Ser Ser Thr Leu Gly Asp Gln Val Ala Gln

325 330 335

Tyr Ala Ile Asp His Met Ala Glu Arg Gly Ile Ser Tyr Val Ile Trp

340 345 350

Lys Gln Arg Phe Tyr Ala Pro Phe Ala Ser Ile Tyr Gly Pro Ala Tyr

355 360 365

Thr Trp Asn Pro Met Pro Asp Arg Gly Ser Ile Thr Glu Asn His Tyr

370 375 380

Asp His Val His Val Ser Phe Asn Ala

385 390

<210> 5

<211> 1170

<212> DNA

<213> S. pyogenes

<400> 5

atgattatta ctaaaaagag cttatttgtg acaagtgtcg ctttgtcgtt agtacctttg 60

gcgacagcgc aggcacaaga gtggacacca cgatcggtta cagaaatcaa gtctgaactc 120

gtcctagttg ataatgtttt tacttatact gtaaaatacg gtgacacttt aagcacaatt 180

gctgaagcaa tggggattga tgtgcatgtc ttaggagata ttaatcatat tgctaatatt 240

gacctaattt ttccagacac gatcctaaca gcaaactaca atcaacacgg tcaggcaacg 300

aatttgacgg ttcaagcacc tgcttctagt ccagctagcg ttagtcatgt acctagcagt 360

gagccattac cccaagcatc tgccacctct caaccgactg ttcctatggc accacctgcg 420

acaccatctg atgtcccaac gacaccattc gcatctgcaa agccagatag ttctgtgaca 480

gcgtcatctg agctcacatc gtcaacgaat gatgtttcga ctgagttgtc tagcgaatca 540

caaaagcagc cagaagtacc acaagaagca gttccaactc ctaaagcagc tgaaacgact 600

gaagtcgaac ctaagacaga catctcagaa gccccaactt cagctaatag gcctgtacct 660

aacgagagtg cttcagaaga agtttcttct gcggccccag cacaagcccc agcagaaaaa 720

gaagaaacct ctgcgccagc agcacaaaaa gctgtagctg acaccacaag tgttgcaacc 780

tcaaatggcc tttcttacgc tccaaaccat gcctacaatc caatgaatgc agggcttcaa 840

ccacaaacag cagccttcaa agaagaagtg gcttctgcct ttggtattac gtcatttagt 900

ggttaccgtc caggtgatcc aggagatcat ggtaaaggtt tggccattga ttttatggtg 960

cctgaaaatt ctgctcttgg tgatcaagtt gctcaatatg ccattgacca tatggcagag 1020

cgtggtattt catacgttat ttggaaacag cgattctatg cgccatttgc aagtatttac 1080

ggaccagcct acacatggaa ccccatgcca gatcgcggca gtattacaga aaaccattat 1140

gatcatgttc atgtctcctt taatgcttaa 1170

<210> 6

<211> 389

<212> PRT

<213> S. pyogenes

<400> 6

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

Leu Val Pro Leu Ala Thr Ala Gln Ala Gln Glu Trp Thr Pro Arg Ser
20 25 30

Val Thr Glu Ile Lys Ser Glu Leu Val Leu Val Asp Asn Val Phe Thr
35 40 45

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

Gly Ile Asp Val His Val Leu Gly Asp Ile Asn His Ile Ala Asn Ile
65 70 75 80

Asp Leu Ile Phe Pro Asp Thr Ile Leu Thr Ala Asn Tyr Asn Gln His

85 90 95

Gly Gln Ala Thr Asn Leu Thr Val Gln Ala Pro Ala Ser Ser Pro Ala

100 105 110

Ser Val Ser His Val Pro Ser Ser Glu Pro Leu Pro Gln Ala Ser Ala

115 120 125

Thr Ser Gln Pro Thr Val Pro Met Ala Pro Pro Ala Thr Pro Ser Asp

130 135 140

Val Pro Thr Thr Pro Phe Ala Ser Ala Lys Pro Asp Ser Ser Val Thr

145 150 155 160

Ala Ser Ser Glu Leu Thr Ser Ser Thr Asn Asp Val Ser Thr Glu Leu

165 170 175

Ser Ser Glu Ser Gln Lys Gln Pro Glu Val Pro Gln Glu Ala Val Pro

180 185 190

Thr Pro Lys Ala Ala Glu Thr Thr Glu Val Glu Pro Lys Thr Asp Ile

195 200 205

Ser Glu Ala Pro Thr Ser Ala Asn Arg Pro Val Pro Asn Glu Ser Ala

210 215 220

Ser Glu Glu Val Ser Ser Ala Ala Pro Ala Gln Ala Pro Ala Glu Lys

225 230 235 240

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

245 250 255

Ser Val Ala Thr Ser Asn Gly Leu Ser Tyr Ala Pro Asn His Ala Tyr

260 265 270

Asn Pro Met Asn Ala Gly Leu Gln Pro Gln Thr Ala Ala Phe Lys Glu

275 280 285

Glu Val Ala Ser Ala Phe Gly Ile Thr Ser Phe Ser Gly Tyr Arg Pro

290 295 300

Gly Asp Pro Gly Asp His Gly Lys Gly Leu Ala Ile Asp Phe Met Val

305 310 315 320

Pro Glu Asn Ser Ala Leu Gly Asp Gln Val Ala Gln Tyr Ala Ile Asp
325 330 335
His Met Ala Glu Arg Gly Ile Ser Tyr Val Ile Trp Lys Gln Arg Phe
340 345 350
Tyr Ala Pro Phe Ala Ser Ile Tyr Gly Pro Ala Tyr Thr Trp Asn Pro
355 360 365
Met Pro Asp Arg Gly Ser Ile Thr Glu Asn His Tyr Asp His Val His
370 375 380
Val Ser Phe Asn Ala
385

<210> 7

<211> 1149

<212> DNA

<213> S. pyogenes

<400> 7

atgattatta ctaaaaagag cttatttgtg acaagtgtcg ctttgtcgtt agcacctttg 60

gcgacagcgc aggcacaaga gtggacacca cgatcggtta cagaaatcaa gtctgaactc 120

gtcctagttg ataatgtttt tacttataca gtaaaatacg gtgacacttt aagcacaatt 180

gctgaagcaa tggggattga tgtgcatgtc ttaggagata ttaatcatat tgctaatatt 240

gacttaattt ttccagacac gatcctaaca gcaaactaca atcaacacgg tcaggcaacg 300

actttgacgg ttcaagcacc tgcttctagt ccagctagcg ttagtcatgt acctagcagt 360

gagccattac cccaagcatc tgccacctct caaccgactg ttcctatggc accatctgcg 420

acaccattag catctgcaaa gccagatagt tctgtgacag cgtcatctga gctcacatcg 480

tcaacgaatg atgtttcgac tgagtcgtct agcgaatcac aaaagcagcc agaagtacca 540

caagaagcag ttccaactcc taaagcagct gaaacgactg aagtcgaacc taagacagac 600

atctcagaag acccaacttc agctaatagg cctgtaccta acgagagtgc ttcagaagaa 660

gtttcttctg cggccccagc acaagcccca gcagaaaaag aagaaacctc tgcgccagca 720

gcacaaaaag ctgtagctga caccacaagt gttgcaacct caaacggcct ttcttacgct 780

ccaaaccatg cctacaatcc aatgaatgca gggcttcaac cacaaacagc agccttcaaa 840

gaagaagtgg cttctgcctt tggtattacg tcatttagtg gttaccgtcc aggtgaccca 900

ggagatcatg gtaaaggttt ggccattgat tttatggtgc ctgaaaattc tgctcttggt 960

gatcaagttg ctcaatatgc cattgaccat atggcagagc gtggtatttc atacgttatt 1020

tggaaacagc gattctatgc gccatttgca agtatttacg gaccagctta cacatggaac 1080

cccatgccag atcgcggcag tattacagaa aaccattatg atcatgttca tgtctccttt 1140

aatgcttaa 1149

<210> 8

<211> 382

<212> PRT

<213> S. pyogenes

<400> 8

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

Leu Ala Pro Leu Ala Thr Ala Gln Ala Gln Glu Trp Thr Pro Arg Ser
20 25 30

Val Thr Glu Ile Lys Ser Glu Leu Val Leu Val Asp Asn Val Phe Thr
35 40 45

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

Gly Ile Asp Val His Val Leu Gly Asp Ile Asn His Ile Ala Asn Ile
65 70 75 80

Asp Leu Ile Phe Pro Asp Thr Ile Leu Thr Ala Asn Tyr Asn Gln His
85 90 95

Gly Gln Ala Thr Thr Leu Thr Val Gln Ala Pro Ala Ser Ser Pro Ala
100 105 110

Ser Val Ser His Val Pro Ser Ser Glu Pro Leu Pro Gln Ala Ser Ala
115 120 125
Thr Ser Gln Pro Thr Val Pro Met Ala Pro Ser Ala Thr Pro Leu Ala
130 135 140
Ser Ala Lys Pro Asp Ser Ser Val Thr Ala Ser Ser Glu Leu Thr Ser
145 150 155 160
Ser Thr Asn Asp Val Ser Thr Glu Ser Ser Ser Glu Ser Gln Lys Gln
165 170 175
Pro Glu Val Pro Gln Glu Ala Val Pro Thr Pro Lys Ala Ala Glu Thr
180 185 190
Thr Glu Val Glu Pro Lys Thr Asp Ile Ser Glu Asp Pro Thr Ser Ala
195 200 205
Asn Arg Pro Val Pro Asn Glu Ser Ala Ser Glu Glu Val Ser Ser Ala
210 215 220
Ala Pro Ala Gln Ala Pro Ala Glu Lys Glu Glu Thr Ser Ala Pro Ala
225 230 235 240
Ala Gln Lys Ala Val Ala Asp Thr Thr Ser Val Ala Thr Ser Asn Gly
245 250 255
Leu Ser Tyr Ala Pro Asn His Ala Tyr Asn Pro Met Asn Ala Gly Leu
260 265 270
Gln Pro Gln Thr Ala Ala Phe Lys Glu Glu Val Ala Ser Ala Phe Gly
275 280 285
Ile Thr Ser Phe Ser Gly Tyr Arg Pro Gly Asp Pro Gly Asp His Gly
290 295 300
Lys Gly Leu Ala Ile Asp Phe Met Val Pro Glu Asn Ser Ala Leu Gly
305 310 315 320
Asp Gln Val Ala Gln Tyr Ala Ile Asp His Met Ala Glu Arg Gly Ile
325 330 335
Ser Tyr Val Ile Trp Lys Gln Arg Phe Tyr Ala Pro Phe Ala Ser Ile

340 345 350

Tyr Gly Pro Ala Tyr Thr Trp Asn Pro Met Pro Asp Arg Gly Ser Ile

355 360 365

Thr Glu Asn His Tyr Asp His Val His Val Ser Phe Asn Ala

370 375 380

<210> 9

<211> 1095

<212> DNA

<213> S. pyogenes

<400> 9

caagagtgga caccacgatc ggttacagaa atcaagtctg aactcgtcct agttgataat 60

gtttttactt atactgtaaa atacggtgac actttaagca caattgctga agcaatggga 120

attgatgtgc atgtcttagg agatattaat catattgcta atattgactt aatttttcca 180

gacacgatcc taacagccaa ctacaaccaa cacggtcagg caacgacttt gacggttcaa 240

gcgcctgctt ctagtccagc tagcgttagt catgtaccta gcagtgagcc attaccccaa 300

gcatctgcca cctctcaatc gactgttcct atggcaccat ctgcgacacc atctgatgtc 360

ccaacgacac cattcgcatc tgcaaagcca gatagttctg tgacagcgtc atctgagctc 420

acatcgtcaa cgaatgatgt ttcgactgag ttgtctagcg aatcacaaaa gcagccagaa 480

gtaccacaag aagcagttcc aactcctaaa gcagctgaaa cgactgaagt cgaacctaag 540

acagacatct cagaggattc aacttcagct aataggcctg tacctaacga gagtgcttca 600

gaagaagttt cttctgcggc cccagcacaa gccccagcag aaaaagaaga aacctctgcg 660

ccagcagcac aaaaagctgt agctgacacc acaagtgttg caacctcaaa tggcctttct 720

tacgctccaa accatgccta caatccaatg aatgcagggc ttcaaccaca aacagcagcc 780

ttcaaagaag aagtggcttc tgcctttggt attacgtcat ttagtggtta ccgtccaggt 840

gatccaggag atcatggtaa aggtttggcc attgatttta tggtgcctga aaattctgct 900

cttggtgatc aagttgctca atatgccatt gaccatatgg cagagcgtgg tatttcatac 960

gttatttgga aacagcgatt ctatgcgcca tttgcaagta tttacggacc agcctacaca 1020

tggaacccca tgccagatcg cggcagtatt acagaaaacc attatgatca tgttcatgtc 1080

tcctttaatg cttaa 1095

<210> 10

<211> 364

<212> PRT

<213> S. pyogenes

<400> 10

Gln Glu Trp Thr Pro Arg Ser Val Thr Glu Ile Lys Ser Glu Leu Val
1 5 10 15

Leu Val Asp Asn Val Phe Thr Tyr Thr Val Lys Tyr Gly Asp Thr Leu
20 25 30

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

Ile Asn His Ile Ala Asn Ile Asp Leu Ile Phe Pro Asp Thr Ile Leu
50 55 60

Thr Ala Asn Tyr Asn Gln His Gly Gln Ala Thr Thr Leu Thr Val Gln
65 70 75 80

Ala Pro Ala Ser Ser Pro Ala Ser Val Ser His Val Pro Ser Ser Glu
85 90 95

Pro Leu Pro Gln Ala Ser Ala Thr Ser Gln Ser Thr Val Pro Met Ala
100 105 110

Pro Ser Ala Thr Pro Ser Asp Val Pro Thr Thr Pro Phe Ala Ser Ala
115 120 125

Lys Pro Asp Ser Ser Val Thr Ala Ser Ser Glu Leu Thr Ser Ser Thr
130 135 140

Asn Asp Val Ser Thr Glu Leu Ser Ser Glu Ser Gln Lys Gln Pro Glu
145 150 155 160

Val Pro Gln Glu Ala Val Pro Thr Pro Lys Ala Ala Glu Thr Thr Glu
165 170 175
Val Glu Pro Lys Thr Asp Ile Ser Glu Asp Ser Thr Ser Ala Asn Arg
180 185 190
Pro Val Pro Asn Glu Ser Ala Ser Glu Glu Val Ser Ser Ala Ala Pro
195 200 205
Ala Gln Ala Pro Ala Glu Lys Glu Glu Thr Ser Ala Pro Ala Ala Gln
210 215 220
Lys Ala Val Ala Asp Thr Thr Ser Val Ala Thr Ser Asn Gly Leu Ser
225 230 235 240
Tyr Ala Pro Asn His Ala Tyr Asn Pro Met Asn Ala Gly Leu Gln Pro
245 250 255
Gln Thr Ala Ala Phe Lys Glu Glu Val Ala Ser Ala Phe Gly Ile Thr
260 265 270
Ser Phe Ser Gly Tyr Arg Pro Gly Asp Pro Gly Asp His Gly Lys Gly
275 280 285
Leu Ala Ile Asp Phe Met Val Pro Glu Asn Ser Ala Leu Gly Asp Gln
290 295 300
Val Ala Gln Tyr Ala Ile Asp His Met Ala Glu Arg Gly Ile Ser Tyr
305 310 315 320
Val Ile Trp Lys Gln Arg Phe Tyr Ala Pro Phe Ala Ser Ile Tyr Gly
325 330 335
Pro Ala Tyr Thr Trp Asn Pro Met Pro Asp Arg Gly Ser Ile Thr Glu
340 345 350
Asn His Tyr Asp His Val His Val Ser Phe Asn Ala
355 360

<210> 11

<211> 1106

<212> DNA

<213> S. pyogenes

<400> 11

caagagtgga caccacgatc ggttacagaa atcaagtctg aactcgtcct agttgataat 60

gtttttactt atatagtaaa atacggtgac actttaagca caattgctga agcaatgggg 120

attgatgtgc atgtcttagg agatattaat catattgcta atattgactt aatttttcca 180

gacacgatcc taacagcaaa ctacaaccaa cacggtcagg caacgacttt gacggttcaa 240

gcacctgctt ctagtccatc tagcgttagt catgtaccta gcagtgagcc attaccccaa 300

gcatctgcca cctctcaacc gactgttcct atggcaccat ctgcgacacc atctgatgtc 360

ccaacgacac cattcgcatc tgcaaagcca gatagttctg tgacagcgtc atctgagctc 420

acatcgtcaa cgaatgatgt ttcgactgag ttgtctagcg aatcacaaaa gcagccagaa 480

gtaccacaag aagcagttcc aactcctaaa gcagctgaac cgactgaagt cgaacctaag 540

acagacatct cagaagaccc aacttcagct aataggcctg acctaacgag agtgcttcag 600

aagaagcttc ttctgcggcc ccagcacaag ctccagcaga aaaagaagaa acctctcaga 660

tgttaactgc gccagcagca caaaaagctg tagctgacac cacaagtgtt gcaacctcaa 720

acggcctttc ttacgctcca aaccatgcct acaatccaat gaatgcaggg cttcaaccac 780

aaacagcagc cttcaaagaa gaagtggctt ctgcctttgg tattacgtca tttagtggtt 840

accgtccagg agatccagga gatcatggta aaggattagc cattgacttt atggtaccgg 900

ttagctctac gcttggtgat caagttgctc aatatgccat tgaccatatg gcagagcgtg 960

gtatttcata cgttatttgg aaacagcgat tctatgcgcc atttgcaagt atttacggac 1020

cagcctacac atggaacccc atgccagatc gcggcagtat tacagaaaac cattatgatc 1080

atgttcatgt ctcctttaat gcttaa 1106

<210> 12

<211> 368

<212> PRT

<213> S. pyogenes

<400> 12

Gln Glu Trp Thr Pro Arg Ser Val Thr Glu Ile Lys Ser Glu Leu Val
1 5 10 15

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

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

Ile Asn His Ile Ala Asn Ile Asp Leu Ile Phe Pro Asp Thr Ile Leu
50 55 60

Thr Ala Asn Tyr Asn Gln His Gly Gln Ala Thr Thr Leu Thr Val Gln
65 70 75 80

Ala Pro Ala Ser Ser Pro Ser Ser Val Ser His Val Pro Ser Ser Glu
85 90 95

Pro Leu Pro Gln Ala Ser Ala Thr Ser Gln Pro Thr Val Pro Met Ala
100 105 110

Pro Ser Ala Thr Pro Ser Asp Val Pro Thr Thr Pro Phe Ala Ser Ala
115 120 125

Lys Pro Asp Ser Ser Val Thr Ala Ser Ser Glu Leu Thr Ser Ser Thr
130 135 140

Asn Asp Val Ser Thr Glu Leu Ser Ser Glu Ser Gln Lys Gln Pro Glu
145 150 155 160

Val Pro Gln Glu Ala Val Pro Thr Pro Lys Ala Ala Glu Pro Thr Glu
165 170 175

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

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

Ala Gln Ala Pro Ala Glu Lys Glu Glu Thr Ser Gln Met Leu Thr Ala
210 215 220

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

<210> 13

<211> 1095

<212> DNA

<213> S. pyogenes

<400> 13

caagagtgga caccacgatc ggttacagaa atcaagtctg aactcgtcct agttgataat 60

gtttttactt atactgtaaa atacggtgac actttaagca caattgctga agcaatgggg 120

attgatgtgc atgtcttagg agatattaat catattgcta atattgacct aatttttcca 180

gacacgatcc taacagcaaa ctacaatcaa cacggtcagg caacgaattt gacggttcaa 240

gcacctgctt ctagtccagc tagcgttagt catgtaccta gcagtgagcc attaccccaa 300

gcatctgcca cctctcaacc gactgttcct atggcaccac ctgcgacacc atctgatgtc 360

ccaacgacac cattcgcatc tgcaaagcca gatagttctg tgacagcgtc atctgagctc 420

acatcgtcaa cgaatgatgt ttcgactgag ttgtctagcg aatcacaaaa gcagccagaa 480

gtaccacaag aagcagttcc aactcctaaa gcagctgaaa cgactgaagt cgaacctaag 540

acagacatct cagaagcccc aacttcagct aataggcctg tacctaacga gagtgcttca 600

gaagaagttt cttctgcggc cccagcacaa gccccagcag aaaaagaaga aacctctgcg 660

ccagcagcac aaaaagctgt agctgacacc acaagtgttg caacctcaaa tggcctttct 720

tacgctccaa accatgccta caatccaatg aatgcagggc ttcaaccaca aacagcagcc 780

ttcaaagaag aagtggcttc tgcctttggt attacgtcat ttagtggtta ccgtccaggt 840

gatccaggag atcatggtaa aggtttggcc attgatttta tggtgcctga aaattctgct 900

cttggtgatc aagttgctca atatgccatt gaccatatgg cagagcgtgg tatttcatac 960

gttatttgga aacagcgatt ctatgcgcca tttgcaagta tttacggacc agcctacaca 1020

tggaacccca tgccagatcg cggcagtatt acagaaaacc attatgatca tgttcatgtc 1080

tcctttaatg cttaa 1095

<210> 14

<211> 364

<212> PRT

<213> S. pyogenes

<400> 14

Gln Glu Trp Thr Pro Arg Ser Val Thr Glu Ile Lys Ser Glu Leu Val

1 5 10 15

Leu Val Asp Asn Val Phe Thr Tyr Thr Val Lys Tyr Gly Asp Thr Leu

20 25 30

Ser Thr Ile Ala Glu Ala Met Gly Ile Asp Val His Val Leu Gly Asp

35 40 45

Ile Asn His Ile Ala Asn Ile Asp Leu Ile Phe Pro Asp Thr Ile Leu

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

Leu Ala Ile Asp Phe Met Val Pro Glu Asn Ser Ala Leu Gly Asp Gln
290 295 300
Val Ala Gln Tyr Ala Ile Asp His Met Ala Glu Arg Gly Ile Ser Tyr
305 310 315 320
Val Ile Trp Lys Gln Arg Phe Tyr Ala Pro Phe Ala Ser Ile Tyr Gly
325 330 335
Pro Ala Tyr Thr Trp Asn Pro Met Pro Asp Arg Gly Ser Ile Thr Glu
340 345 350
Asn His Tyr Asp His Val His Val Ser Phe Asn Ala
355 360

<210> 15

<211> 1074

<212> DNA

<213> S. pyogenes

<400> 15

caagagtgga caccacgatc ggttacagaa atcaagtctg aactcgtcct agttgataat 60

gtttttactt atacagtaaa atacggtgac actttaagca caattgctga agcaatgggg 120

attgatgtgc atgtcttagg agatattaat catattgcta atattgactt aatttttcca 180

gacacgatcc taacagcaaa ctacaatcaa cacggtcagg caacgacttt gacggttcaa 240

gcacctgctt ctagtccagc tagcgttagt catgtaccta gcagtgagcc attaccccaa 300

gcatctgcca cctctcaacc gactgttcct atggcaccat ctgcgacacc attagcatct 360

gcaaagccag atagttctgt gacagcgtca tctgagctca catcgtcaac gaatgatgtt 420

tcgactgagt cgtctagcga atcacaaaag cagccagaag taccacaaga agcagttcca 480

actcctaaag cagctgaaac gactgaagtc gaacctaaga cagacatctc agaagaccca 540

acttcagcta ataggcctgt acctaacgag agtgcttcag aagaagtttc ttctgcggcc 600

ccagcacaag ccccagcaga aaaagaagaa acctctgcgc cagcagcaca aaaagctgta 660

gctgacacca caagtgttgc aacctcaaac ggcctttctt acgctccaaa ccatgcctac 720

aatccaatga atgcagggct tcaaccacaa acagcagcct tcaaagaaga agtggcttct 780

gcctttggta ttacgtcatt tagtggttac cgtccaggtg acccaggaga tcatggtaaa 840

ggtttggcca ttgattttat ggtgcctgaa aattctgctc ttggtgatca agttgctcaa 900

tatgccattg accatatggc agagcgtggt atttcatacg ttatttggaa acagcgattc 960

tatgcgccat ttgcaagtat ttacggacca gcttacacat ggaaccccat gccagatcgc 1020

ggcagtatta cagaaaacca ttatgatcat gttcatgtct ccttttaatgc ttaa 1074

<210> 16

<211> 357

<212> PRT

<213> S. pyogenes

<400> 16

Gln Glu Trp Thr Pro Arg Ser Val Thr Glu Ile Lys Ser Glu Leu Val
1 5 10 15

Leu Val Asp Asn Val Phe Thr Tyr Thr Val Lys Tyr Gly Asp Thr Leu
20 25 30

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

Ile Asn His Ile Ala Asn Ile Asp Leu Ile Phe Pro Asp Thr Ile Leu
50 55 60

Thr Ala Asn Tyr Asn Gln His Gly Gln Ala Thr Thr Leu Thr Val Gln
65 70 75 80

Ala Pro Ala Ser Ser Pro Ala Ser Val Ser His Val Pro Ser Ser Glu
85 90 95

Pro Leu Pro Gln Ala Ser Ala Thr Ser Gln Pro Thr Val Pro Met Ala
100 105 110

Pro Ser Ala Thr Pro Leu Ala Ser Ala Lys Pro Asp Ser Ser Val Thr

115 120 125

Ala Ser Ser Glu Leu Thr Ser Ser Thr Asn Asp Val Ser Thr Glu Ser

130 135 140

Ser Ser Glu Ser Gln Lys Gln Pro Glu Val Pro Gln Glu Ala Val Pro

145 150 155 160

Thr Pro Lys Ala Ala Glu Thr Thr Glu Val Glu Pro Lys Thr Asp Ile

165 170 175

Ser Glu Asp Pro Thr Ser Ala Asn Arg Pro Val Pro Asn Glu Ser Ala

180 185 190

Ser Glu Glu Val Ser Ser Ala Ala Pro Ala Gln Ala Pro Ala Glu Lys

195 200 205

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

210 215 220

Ser Val Ala Thr Ser Asn Gly Leu Ser Tyr Ala Pro Asn His Ala Tyr

225 230 235 240

Asn Pro Met Asn Ala Gly Leu Gln Pro Gln Thr Ala Ala Phe Lys Glu

245 250 255

Glu Val Ala Ser Ala Phe Gly Ile Thr Ser Phe Ser Gly Tyr Arg Pro

260 265 270

Gly Asp Pro Gly Asp His Gly Lys Gly Leu Ala Ile Asp Phe Met Val

275 280 285

Pro Glu Asn Ser Ala Leu Gly Asp Gln Val Ala Gln Tyr Ala Ile Asp

290 295 300

His Met Ala Glu Arg Gly Ile Ser Tyr Val Ile Trp Lys Gln Arg Phe

305 310 315 320

Tyr Ala Pro Phe Ala Ser Ile Tyr Gly Pro Ala Tyr Thr Trp Asn Pro

325 330 335

Met Pro Asp Arg Gly Ser Ile Thr Glu Asn His Tyr Asp His Val His

340 345 350

Val Ser Phe Asn Ala
355

<210> 17

<211> 1113

<212> DNA

<213> S. pneumonia

<400> 17

atgaagaaaa gaatgttatt agcgtcaaca gtagccttgt catttgcccc agtattggca 60

actcaagcag aagaagttct ttggactgca cgtagtgttg agcaaatcca aaacgatttg 120

actaaaacgg acaacaaaac aagttatacc gtacagtatg gtgatacttt gagcaccatt 180

gcagaagcct tgggtgtaga tgtcacagtg cttgcgaatc tgaacaaaat cactaatatg 240

gacttgattt tcccagaaac tgttttgaca acgactgtca atgaagcaga agaagtaaca 300

gaagttgaaa tccaaacacc tcaagcagac tctagtgaag aagtgacaac tgcgacagca 360

gatttgacca ctaatcaagt gaccgttgat gatcaaactg ttcaggttgc agacctttct 420

caaccaattg cagaagttac aaagacagtg attgcttctg aagaagtggc accatctacg 480

ggcacttctg tcccagagga gcaaacgacc gaaacaactc gcccagttga agaagcaact 540

cctcaggaaa cgactccagc tgagaagcag gaaacacaag caagccctca agctgcatca 600

gcagtggaag taactacaac aagttcagaa gcaaaagaag tagcatcatc aaatggagct 660

acagcagcag tttctactta tcaaccagaa gagacgaaaa taatttcaac aacttacgag 720

gctccagctg cgcccgatta tgctggactt gcagtagcaa aatctgaaaa tgcaggtctt 780

caaccacaaa cagctgcctt taaagaagaa attgctaact tgtttggcat tacatccttt 840

agtggttatc gtccaggaga cagtggagat cacggaaaag gtttggctat cgactttatg 900

gtaccagaac gttcagaatt aggggataag attgcggaat atgctattca aaatatggcc 960

agccgtggca ttagttacat catctggaaa caacgtttct atgctccatt cgatagcaaa 1020

tatgggccag ctaacacttg gaacccaatg ccagaccgtg gtagtgtgac agaaaatcac 1080

tatgatcacg ttcacgtttc aatgaatgga taa 1113

<210> 18

<211> 370

<212> PRT

<213> S. pneumonia

<400> 18

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

Pro Val Leu Ala Thr Gln Ala Glu Glu Val Leu Trp Thr Ala Arg Ser
20 25 30

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

Tyr Thr Val Gln Tyr Gly Asp Thr Leu Ser Thr Ile Ala Glu Ala Leu
50 55 60

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

Asp Leu Ile Phe Pro Glu Thr Val Leu Thr Thr Thr Val Asn Glu Ala
85 90 95

Glu Glu Val Thr Glu Val Glu Ile Gln Thr Pro Gln Ala Asp Ser Ser
100 105 110

Glu Glu Val Thr Thr Ala Thr Ala Asp Leu Thr Thr Asn Gln Val Thr
115 120 125

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

Glu Val Thr Lys Thr Val Ile Ala Ser Glu Glu Val Ala Pro Ser Thr
145 150 155 160

Gly Thr Ser Val Pro Glu Glu Gln Thr Thr Glu Thr Thr Arg Pro Val
165 170 175

Glu Glu Ala Thr Pro Gln Glu Thr Thr Pro Ala Glu Lys Gln Glu Thr

180 185 190

Gln Ala Ser Pro Gln Ala Ala Ser Ala Val Glu Val Thr Thr Thr Ser

195 200 205

Ser Glu Ala Lys Glu Val Ala Ser Ser Asn Gly Ala Thr Ala Ala Val

210 215 220

Ser Thr Tyr Gln Pro Glu Glu Thr Lys Ile Ile Ser Thr Thr Tyr Glu

225 230 235 240

Ala Pro Ala Ala Pro Asp Tyr Ala Gly Leu Ala Val Ala Lys Ser Glu

245 250 255

Asn Ala Gly Leu Gln Pro Gln Thr Ala Ala Phe Lys Glu Glu Ile Ala

260 265 270

Asn Leu Phe Gly Ile Thr Ser Phe Ser Gly Tyr Arg Pro Gly Asp Ser

275 280 285

Gly Asp His Gly Lys Gly Leu Ala Ile Asp Phe Met Val Pro Glu Arg

290 295 300

Ser Glu Leu Gly Asp Lys Ile Ala Glu Tyr Ala Ile Gln Asn Met Ala

305 310 315 320

Ser Arg Gly Ile Ser Tyr Ile Ile Trp Lys Gln Arg Phe Tyr Ala Pro

325 330 335

Phe Asp Ser Lys Tyr Gly Pro Ala Asn Thr Trp Asn Pro Met Pro Asp

340 345 350

Arg Gly Ser Val Thr Glu Asn His Tyr Asp His Val His Val Ser Met

355 360 365

Asn Gly

370

<210> 19

<211> 1183

<212> DNA

<213> S. pyogenes

<220>

<221> misc_difference

<222> (428)...(448)

<223> nnnnnnnnnnnnnnnnnnnnn can be ctgatgtccaacgacaccat

or absent

<221> misc_difference

<222> (733)...(744)

<223> nnnnnnnnnnnn can be cagatgttaact or absent

<221> misc_difference

<222> (883)...(883)

<223> n is g or absent

<221> misc_difference

<222> (943)...(943)

<223> n is t or absent

<400> 19

atgattatta ctaaaaagag yttatttgtg acaagtgtcg ctttgtcgtt agyacctttg 60

gcgacagcrc aggcacaaga gtggacacca cgatcggtta casaaatcaa gtctgaactc 120

gtcctagttg ataatgtttt tacttatayw gtaaaatacg gtgacacttt aagcacaatt 180

gctgaagcaa tgggrattga tgtgcatgtc ttaggagata ttaatcatat tgctaatatt 240

gacytaattt ttccagacac gatcctaaca gcmaactaca aycaacacgg tcaggcaacg 300

amtttgacgg ttcaagcrcc tgcttctagt ccakctagcg ttagtcatgt acctagcagt 360

gagccattac cccaagcatc tgccacctct caaycgactr ttcctatggc accayctgcg 420

acaccatnnn nnnnnnnnnn nnnnnnnntm gcatctgcaa agccagatag ttytgtgaca 480

gcgtcatctg agctcacatc rtcaacgaat gatgtttcga ctgagtygtc tagcgaatca 540

caaaagcagc cagaagtacc acaagaagca gwwccaactc ctaaagcagc tgaamssact 600

gaagtcgaac ctaagacaga catctcagar gmyycaactt cagctaatag gcctgtacct 660

aacgrragtg cttcagaaga agyttcttct gcggccccag cacaagcycc agcagaaaaa 720

gaagaaacct ctnnnnnnnn nnnngcgcca gcagcacaaa aagctgtagc tgacaccaca 780

agtgttgcaa cctcaaaygg cctttcttac gctccaaacc atgcctacaa tccaatgaat 840

gcagggcttc aaccacaaac agcagccttc aaagaagaag tgncttctgc ctttggtatt 900

acgtcattta gtggttaccg tccaggwgay ccaggagatc atnggtaaag gwttrgccat 960

tgaytttatg gtrcckgwwa rytctrckct tggtgatcaa gttgctcaat atgccattga 1020

ccatatggca gassgtggta tttcatacgt tatttggaaa cagcgattct atgcgccatt 1080

tgcaagtatt tacggaccag cytacacatg gaaccccatg ccagatcgcg gcagtattac 1140

agwwwwccat tatgatcatg ttcatgtctc ctttaatgct taa 1183

<210> 20

<211> 393

<212> PRT

<213> s. pyogenes

<220>

<221> VARIANT

<222> (18)...(18)

<223> Xaa = Ala or Val

<221> VARIANT

<222> (50)...(50)

<223> Xaa = Thr or Ile

<221> VARIANT

<222> (101)...(101)

<223> Xaa = Thr or Asn

<221> VARIANT

<222> (112)...(112)

<223> Xaa = Ala or Ser

<221> VARIANT

<222> (132)...(132)

<223> Xaa = Pro or Ser

<221> VARIANT

<222> (134)...(134)

<223> Xaa = Val or Ile

<221> VARIANT

<222> (139)...(139)

<223> Xaa = Ser or Pro

<221> VARIANT

<222> (143)...(149)

<223> Xaa Xaa Xaa Xaa Xaa Xaa Xaa = Ser Asp Val Pro Thr

Thr pro or absent

<221> VARIANT

<222> (150)...(150)

<223> Xaa = Phe or Leu

<221> VARIANT

<222> (158)...(158)

<223> Xaa = Ser or Phe

<221> VARIANT

<222> (176)...(176)

<223> Xaa = Leu or Ser

<221> VARIANT

<222> (191)...(191)

<223> Xaa = Val or Glu

<221> VARIANT

<222> (199)...(199)

<223> Xaa = Thr or Pro or Ser

<221> VARIANT

<222> (211)...(211)

<223> Xaa = Asp or Ala

<221> VARIANT

<222> (212)...(212)

<223> Xaa = Pro or Ser

<221> VARIANT

<222> (222)...(222)

<223> Xaa = Glu or Gly

<221> VARIANT

<222> (228)...(228)

<223> Xaa = Val or Ala

<221> VARIANT

<222> (242)...(245)

<223> Xaa Xaa Xaa Xaa = Glu thr Ser Gln or absent

<221> VARIANT

<222> (246)...(246)

<223> Xaa = Glu or Met

<221> VARIANT

<222> (247)...(247)

<223> Xaa = Thr or Leu

<221> VARIANT

<222> (248)...(248)

<223> Xaa = Ser or Thr

<221> VARIANT

<222> (295)...(295)

<223> Xaa = Ala or Leu

<221> VARIANT

<222> (296)...(296)

<223> Xaa = Ser or Leu

<221> VARIANT

<222> (297)...(297)

<223> Xaa = Ala or Pro

<221> VARIANT

<222> (298)...(298)

<223> Xaa = Phe or Leu

<221> VARIANT

<222> (299)...(299)

<223> Xaa = Gly or Val

<221> VARIANT

<222> (300)...(300)

<223> Xaa = Ile or Leu

<221> VARIANT

<222> (301)...(301)

<223> Xaa = Thr or Arg

<221> VARIANT

<222> (302)...(302)

<223> Xaa = Ser or His

<221> VARIANT

<222> (303)...(303)

<223> Xaa = Phe or Leu

<221> VARIANT

<222> (304)...(304)

<223> Xaa = Ser or Val

<221> VARIANT

<222> (305)...(305)

<223> Xaa = Gly or Val

<221> VARIANT

<222> (306)...(306)

<223> Xaa = Tyr or Thr

<221> VARIANT

<222> (307)...(307)

<223> Xaa = Arg or Val

<221> VARIANT

<222> (308)...(308)

<223> Xaa = Pro or Gln

<221> VARIANT

<222> (309)...(309)

<223> Xaa = Gly or Glu

<221> VARIANT

<222> (310)...(310)

<223> Xaa = Asp or Ile

<221> VARIANT

<222> (311)...(311)

<223> Xaa = Pro or Gln

<221> VARIANT

<222> (312)...(312)

<223> Xaa = Gly or Glu

<221> VARIANT

<222> (313)...(313)

<223> Xaa = Asn or Ile

<221> VARIANT

<222> (314)...(314)

<223> Xaa = His or Ile

<221> VARIANT

<222> (326)...(326)

<223> Xaa = Glu or Val

<221> VARIANT

<222> (327)...(327)

<223> Xaa = Asn or Ser

<221> VARIANT

<222> (329)...(329)

<223> Xaa = Ala or Thr

<221> VARIANT

<222> (344)...(344)

<223> Xaa = Glu or Asp

<221> VARIANT

<222> (345)...(345)

<223> Xaa = Arg or Gly

<400> 20

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

Leu Xaa Pro Leu Ala Thr Ala Gln Ala Gln Glu Trp Thr Pro Arg Ser
20 25 30

Val Thr Glx Ile Lys Ser Glu Leu Val Leu Val Asp Asn Val Phe Thr
35 40 45

Tyr Xaa Val Lys Tyr Gly Asp Thr Leu Ser Thr Ile Ala Glu Ala Met
50 55 60

Gly Ile Asp Val His Val Leu Gly Asp Ile Asn His Ile Ala Asn Ile
65 70 75 80

Asp Leu Ile Phe Pro Asp Thr Ile Leu Thr Ala Asn Tyr Asn Gln His
85 90 95

Gly Gln Ala Thr Xaa Leu Thr Val Gln Ala Pro Ala Ser Ser Pro Xaa
100 105 110

Ser Val Ser His Val Pro Ser Ser Glu Pro Leu Pro Gln Ala Ser Ala
115 120 125

Thr Ser Gln Xaa Thr Xaa Pro Met Ala Pro Xaa Ala Thr Pro Xaa Xaa
130 135 140

Xaa Xaa Xaa Xaa Xaa Xaa Ala Ser Ala Lys Pro Asp Ser Xaa Val Thr
145 150 155 160

Ala Ser Ser Glu Leu Thr Ser Ser Thr Asn Asp Val Ser Thr Glu Xaa
165 170 175

Ser Ser Glu Ser Gln Lys Gln Pro Glu Val Pro Gln Glu Ala Xaa Pro
180 185 190

Thr Pro Lys Ala Ala Glu Xaa Thr Glu Val Glu Pro Lys Thr Asp Ile
195 200 205

Ser Glu Xaa Xaa Thr Ser Ala Asn Arg Pro Val Pro Asn Xaa Ser Ala
210 215 220
Ser Glu Glu Xaa Ser Ser Ala Ala Pro Ala Gln Ala Pro Ala Glu Lys
225 230 235 240
Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ala Pro Ala Ala Gln Lys Ala Val
245 250 255
Ala Asp Thr Thr Ser Val Ala Thr Ser Asn Gly Leu Ser Tyr Ala Pro
260 265 270
Asn His Ala Tyr Asn Pro Met Asn Ala Gly Leu Gln Pro Gln Thr Ala
275 280 285
Ala Phe Lys Glu Glu Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
290 295 300
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Lys Gly Leu Ala Ile
305 310 315 320
Asp Phe Met Val Pro Xaa Xaa Ser Xaa Leu Gly Asp Gln Val Ala Gln
325 330 335
Tyr Ala Ile Asp His Met Ala Xaa Xaa Gly Ile Ser Tyr Val Ile Trp
340 345 350
Lys Gln Arg Phe Tyr Ala Pro Phe Ala Ser Ile Tyr Gly Pro Ala Tyr
355 360 365
Thr Trp Asn Pro Met Pro Asp Arg Gly Ser Ile Thr Xaa Xaa His Tyr
370 375 380
Asp His Val His Val Ser Phe Asn Ala
385 390

<210> 21

<211> 32

<212> DNA

<213> Artificial Sequence

<220>

<223> DMAR16 Oligonucleotide

<400> 21

caggccatgg agtggacacc acgatcggtt ac 32

<210> 22

<211> 37

<212> DNA

<213> Artificial Sequence

<220>

<223> DMAR17 Oligonucleotide

<400> 22

gccgctcgag agcattaaag gagacatgaa catgatc 37

<210> 23

<211> 25

<212> PRT

<213> Artificial Sequence

<220>

<223> Signal peptide predicted from analysis of SEQ ID NO:2

<400> 23

Met Ile Ile Thr Lys Lys Ser Leu Phe Val Thr Ser Val Ala Leu Ser

1 5 10 15

Leu Ala Pro Leu Ala Thr Ala Gln Ala

20 25

<210> 24

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<221> VARIANT

<222> (3)...(3)

<223> Xaa = Any Amino Acid

<223> Cell wall anchoring motif

<400> 24

Leu Pro Xaa Thr Gly

1 5

<210> 25

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> IgA binding motif

<400> 25

Met Leu Lys Lys Ile Glu

1 5

<210> 26

<211> 28

<212> DNA

<213> Artificial Sequence

<220>

<223> DMAR69 oligonucleotide

<400> 26

ctgggaagat tatctagcac attaatac 28

<210> 27

<211> 25

<212> DNA

<213> Artificial Sequence

<220>

<223> DMAR72 oligonucleotide

<400> 27

cataacgtta aaactgtcta aaggg 25

<210> 28

<211> 34

<212> DNA

<213> Artificial Sequence

<220>

<223> DMAR24 oligonucleotide

<400> 28

tacccggatc cccaagagtg gacaccacga tcgg 34

<210> 29

<211> 36

<212> DNA

<213> Artificial Sequence

<220>

<223> DMAR25 oligonucleotide

<400> 29

gcgctcgtcg acgcgtatct cagcctctta tagggc 36

WHAT IS CLAIMED IS:

1. An isolated polynucleotide encoding a polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence chosen from SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, and 16, wherein the encoded polypeptide is capable of eliciting an immune response against *Streptococcus pyogenes*, and wherein the encoded polypeptide elicits antibodies that specifically bind to a polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16.

2. The isolated polynucleotide according to claim 1 wherein the polynucleotide encodes a polypeptide that comprises the amino acid sequence chosen from SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, and 16.

3. The polynucleotide according to claim 1, wherein the polynucleotide consists of a nucleotide sequence at least 95% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, and 15.

4. The polynucleotide according to claim 2, wherein the polynucleotide comprises a nucleotide sequence set forth in any one of SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, and 15.

5. An isolated polynucleotide that is complementary to the polynucleotide as defined in any one of claims 1-4.

6. The isolated polynucleotide according to any one of claims 1-4, wherein the isolated polynucleotide is DNA.

7. The isolated polynucleotide according to any one of claims 1-4, wherein the isolated polynucleotide is RNA.

8. A vector comprising the polynucleotide as defined in any one of claims 1-4, wherein the polynucleotide is operably linked to an expression control region.

9. A host cell transfected with the vector as defined by claim 8.

10. A process for producing a polypeptide encoded by the isolated polynucleotide as defined in any one of claims 1-4, said process comprising culturing the host cell as defined in claim 9 under conditions suitable for expression of said polypeptide.

11. The process according to claim 10 further comprising isolating the polypeptide from the host cell culture.

12. An isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence chosen from SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, and 16, wherein the polypeptide is capable of eliciting an immune response against *Streptococcus pyogenes*, and wherein the isolated polypeptide elicits antibodies that specifically bind to a polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16.

13. The isolated polypeptide according to claim 12, wherein the polypeptide comprises the amino acid sequence chosen from SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, and 16.

14. The isolated polypeptide according to claim 12 or claim 13, wherein the N-terminal Met residue of SEQ ID NO: 2, 4, 6, and 8 is deleted.

15. The isolated polypeptide according to claim 12 or claim 13, wherein the secretory amino acid sequence of SEQ ID NO: 2, 4, 6, and 8 is deleted.

16. A vaccine composition comprising the isolated polypeptide as defined in any one of claims 12-15 and a pharmaceutically acceptable carrier, diluent or adjuvant.

17. Use of the polypeptide as defined in any one of claims 12-15 for the manufacture of a medicament for prophylactic or therapeutic treatment of a *Streptococcus pyogenes* infection in an individual susceptible to or infected with *S. pyogenes*.

18. Use of the vaccine composition as defined in claim 16 for the manufacture of a medicament for the prophylactic or therapeutic treatment of a *Streptococcus pyogenes* infection in an individual susceptible to or infected with *S. pyogenes*.

19. Use according to either claim 17 or claim 18 wherein the *S. pyogenes* infection is pharyngitis, erysipelas, impetigo, scarlet fever, bacteremia, necrotizing fasciitis, or toxic shock.

20. Use according to any one of claims 17-19 wherein the individual is a human or non-human mammal.

Figure 1

```
   1 ATGATTATTA CTAAAAAGAG CTTATTTGTG ACAAGTGTCG CTTTGTCGTT AGCACCTTTG
  61 GCGACAGCAC AGGCACAAGA GTGGACACCA CGATCGGTTA CAGAAATCAA GTCTGAACTC
 121 GTCCTAGTTG ATAATGTTTT TACTTATACT GTAAAATACG GTGACACTTT AAGCACAATT
 181 GCTGAAGCAA TGGGAATTGA TGTGCATGTC TTAGGAGATA TTAATCATAT TGCTAATATT
 241 GACTTAATTT TTCCAGACAC GATCCTAACA GCCAACTACA ACCAACACGG TCAGGCAACG
 301 ACTTTGACGG TTCAAGCGCC TGCTTCTAGT CCAGCTAGCG TTAGTCATGT ACCTAGCAGT
 361 GAGCCATTAC CCCAAGCATC TGCCACCTCT CAATCGACTG TTCCTATGGC ACCATCTGCG
 421 ACACCATCTG ATGTCCCAAC GACACCATTC GCATCTGCAA AGCCAGATAG TTCTGTGACA
 481 GCGTCATCTG AGCTCACATC GTCAACGAAT GATGTTTCGA CTGAGTTGTC TAGCGAATCA
 541 CAAAAGCAGC CAGAAGTACC ACAAGAAGCA GTTCCAACTC CTAAAGCAGC TGAAACGACT
 601 GAAGTCGAAC CTAAGACAGA CATCTCAGAG GATTCAACTT CAGCTAATAG GCCTGTACCT
 661 AACGAGAGTG CTTCAGAAGA AGTTTCTTCT GCGGCCCCAG CACAAGCCCC AGCAGAAAAA
 721 GAAGAAACCT CTGCGCCAGC AGCACAAAAA GCTGTAGCTG ACACCACAAG TGTTGCAACC
 781 TCAAATGGCC TTTCTTACGC TCCAAACCAT GCCTACAATC CAATGAATGC AGGGCTTCAA
 841 CCACAAACAG CAGCCTTCAA AGAAGAAGTG GCTTCTGCCT TTGGTATTAC GTCATTTAGT
 901 GGTTACCGTC CAGGTGATCC AGGAGATCAT GGTAAAGGTT TGGCCATTGA TTTTATGGTG
 961 CCTGAAAATT CTGCTCTTGG TGATCAAGTT GCTCAATATG CCATTGACCA TATGGCAGAG
1021 CGTGGTATTT CATACGTTAT TTGGAAACAG CGATTCTATG CGCCATTTGC AAGTATTTAC
1081 GGACCAGCCT ACACATGGAA CCCCATGCCA GATCGCGGCA GTATTACAGA AAACCATTAT
1141 GATCATGTTC ATGTCTCCTT TAATGCTTAA (SEQ ID NO:1)
```

Figure 2

```
   1 MIITKKSLFV TSVALSLAPL ATAQAQEWTP RSVTEIKSEL VLVDNVFTYT VKYGDTLSTI
  61 AEAMGIDVHV LGDINHIANI DLIFPDTILT ANYNQHGQAT TLTVQAPASS PASVSHVPSS
 121 EPLPQASATS QSTVPMAPSA TPSDVPTTPF ASAKPDSSVT ASSELTSSTN DVSTELSSES
 181 QKQPEVPQEA VPTPKAAETT EVEPKTDISE DSTSANRPVP NESASEEVSS AAPAQAPAEK
 241 EETSAPAAQK AVADTTSVAT SNGLSYAPNH AYNPMNAGLQ PQTAAFKEEV ASAFGITSFS
 301 GYRPGDPGDH GKGLAIDFMV PENSALGDQV AQYAIDHMAE RGISYVIWKQ RFYAPFASIY
 361 GPAYTWNPMP DRGSITENHY DHVHVSFNA* (SEQ ID NO:2)
```

Figure 3

```
   1  ATGATTATTA CTAAAAAGAG CTTATTTGTG ACAAGTGTCG CTTTGTCGTT AGCACCTTTG
  61  GCGACAGCGC AGGCACAAGA GTGGACACCA CGATCGGTTA CAGAAATCAA GTCTGAACTC
 121  GTCCTAGTTG ATAATGTTTT TACTTATATA GTAAAATACG GTGACACTTT AAGCACAATT
 181  GCTGAAGCAA TGGGGATTGA TGTGCATGTC TTAGGAGATA TTAATCATAT TGCTAATATT
 241  GACTTAATTT TTCCAGACAC GATCCTAACA GCAAACTACA ACCAACACGG TCAGGCAACG
 301  ACTTTGACGG TTCAAGCACC TGCTTCTAGT CCATCTAGCG TTAGTCATGT ACCTAGCAGT
 361  GAGCCATTAC CCCAAGCATC TGCCACCTCT CAACCGACTG TTCCTATGGC ACCATCTGCG
 421  ACACCATCTG ATGTCCCAAC GACACCATTC GCATCTGCAA AGCCAGATAG TTCTGTGACA
 481  GCGTCATCTG AGCTCACATC GTCAACGAAT GATGTTTCGA CTGAGTTGTC TAGCGAATCA
 541  CAAAAGCAGC CAGAAGTACC ACAAGAAGCA GTTCCAACTC CTAAAGCAGC TGAACCGACT
 601  GAAGTCGAAC CTAAGACAGA CATCTCAGAA GACCCAACTT CAGCTAATAG GCCTGTACCT
 661  AACGAGAGTG CTTCAGAAGA AGCTTCTTCT GCGGCCCCAG CACAAGCTCC AGCAGAAAAA
 721  GAAGAAACCT CTCAGATGTT AACTGCGCCA GCAGCACAAA AAGCTGTAGC TGACACCACA
 781  AGTGTTGCAA CCTCAAACGG CCTTTCTTAC GCTCCAAACC ATGCCTACAA TCCAATGAAT
 841  GCAGGGCTTC AACCACAAAC AGCAGCCTTC AAAGAAGAAG TGGCTTCTGC CTTTGGTATT
 901  ACGTCATTTA GTGGTTACCG TCCAGGAGAT CCAGGAGATC ATGGTAAAGG ATTAGCCATT
 961  GACTTTATGG TACCGGTTAG CTCTACGCTT GGTGATCAAG TTGCTCAATA TGCCATTGAC
1021  CATATGGCAG AGCGTGGTAT TTCATACGTT ATTTGGAAAC AGCGATTCTA TGCGCCATTT
1081  GCAAGTATTT ACGGACCAGC CTACACATGG AACCCCATGC CAGATCGCGG CAGTATTACA
1141  GAAAACCATT ATGATCATGT TCATGTCTCC TTTAATGCTT AA (SEQ ID NO:3)
```

Figure 4

```
   1  MIITKKSLFV TSVALSLAPL ATAQAQEWTP RSVTEIKSEL VLVDNVFTYI VKYGDTLSTI
  61  AEAMGIDVHV LGDINHIANI DLIFPDTILT ANYNQHGQAT TLTVQAPASS PSSVSHVPSS
 121  EPLPQASATS QPTVPMAPSA TPSDVPTTPF ASAKPDSSVT ASSELTSSTN DVSTELSSES
 181  QKQPEVPQEA VPTPKAAEPT EVEPKTDISE DPTSANRPVP NESASEEASS AAPAQAPAEK
 241  EETSQMLTAP AAQKAVADTT SVATSNGLSY APNHAYNPMN AGLQPQTAAF KEEVASAFGI
 301  TSFSGYRPGD PGDHGKGLAI DFMVPVSSTL GDQVAQYAID HMAERGISYV IWKQRFYAPF
 361  ASIYGPAYTW NPMPDRGSIT ENHYDHVHVS FNA* (SEQ ID NO:4)
```

Figure 5

```
   1  ATGATTATTA CTAAAAAGAG CTTATTTGTG ACAAGTGTCG CTTTGTCGTT AGTACCTTTG
  61  GCGACAGCGC AGGCACAAGA GTGGACACCA CGATCGGTTA CAGAAATCAA GTCTGAACTC
 121  GTCCTAGTTG ATAATGTTTT TACTTATACT GTAAAATACG GTGACACTTT AAGCACAATT
 181  GCTGAAGCAA TGGGGATTGA TGTGCATGTC TTAGGAGATA TTAATCATAT TGCTAATATT
 241  GACCTAATTT TTCCAGACAC GATCCTAACA GCAAACTACA ATCAACACGG TCAGGCAACG
 301  AATTTGACGG TTCAAGCACC TGCTTCTAGT CCAGCTAGCG TTAGTCATGT ACCTAGCAGT
 361  GAGCCATTAC CCCAAGCATC TGCCACCTCT CAACCGACTG TTCCTATGGC ACCACCTGCG
 421  ACACCATCTG ATGTCCCAAC GACACCATTC GCATCTGCAA AGCCAGATAG TTCTGTGACA
 481  GCGTCATCTG AGCTCACATC GTCAACGAAT GATGTTTCGA CTGAGTTGTC TAGCGAATCA
 541  CAAAAGCAGC CAGAAGTACC ACAAGAAGCA GTTCCAACTC CTAAAGCAGC TGAAACGACT
 601  GAAGTCGAAC CTAAGACAGA CATCTCAGAA GCCCCAACTT CAGCTAATAG GCCTGTACCT
 661  AACGAGAGTG CTTCAGAAGA AGTTTCTTCT GCGGCCCCAG CACAAGCCCC AGCAGAAAAA
 721  GAAGAAACCT CTGCGCCAGC AGCACAAAAA GCTGTAGCTG ACACCACAAG TGTTGCAACC
 781  TCAAATGGCC TTTCTTACGC TCCAAACCAT GCCTACAATC CAATGAATGC AGGGCTTCAA
 841  CCACAAACAG CAGCCTTCAA AGAAGAAGTG GCTTCTGCCT TTGGTATTAC GTCATTTAGT
 901  GGTTACCGTC CAGGTGATCC AGGAGATCAT GGTAAAGGTT TGGCCATTGA TTTTATGGTG
 961  CCTGAAAATT CTGCTCTTGG TGATCAAGTT GCTCAATATG CCATTGACCA TATGGCAGAG
1021  CGTGGTATTT CATACGTTAT TTGGAAACAG CGATTCTATG CGCCATTTGC AAGTATTTAC
1081  GGACCAGCCT ACACATGGAA CCCCATGCCA GATCGCGGCA GTATTACAGA AAACCATTAT
1141  GATCATGTTC ATGTCTCCTT TAATGCTTAA (SEQ ID NO:5)
```

Figure 6

```
   1  MIITKKSLFV TSVALSLVPL ATAQAQEWTP RSVTEIKSEL VLVDNVFTYT VKYGDTLSTI
  61  AEAMGIDVHV LGDINHIANI DLIFPDTILT ANYNQHGQAT NLTVQAPASS PASVSHVPSS
 121  EPLPQASATS QPTVPMAPPA TPSDVPTTPF ASAKPDSSVT ASSELTSSTN DVSTELSSES
 181  QKQPEVPQEA VPTPKAAETT EVEPKTDISE APTSANRPVP NESASEEVSS AAPAQAPAEK
 241  EETSAPAAQK AVADTTSVAT SNGLSYAPNH AYNPMNAGLQ PQTAAFKEEV ASAFGITSFS
 301  GYRPGDPGDH GKGLAIDFMV PENSALGDQV AQYAIDHMAE RGISYVIWKQ RFYAPFASIY
 361  GPAYTWNPMP DRGSITENHY DHVHVSFNA* (SEQ ID NO:6)
```

Figure 7

```
   1  ATGATTATTA CTAAAAAGAG CTTATTTGTG ACAAGTGTCG CTTTGTCGTT AGCACCTTTG
  61  GCGACAGCGC AGGCACAAGA GTGGACACCA CGATCGGTTA CAGAAATCAA GTCTGAACTC
 121  GTCCTAGTTG ATAATGTTTT TACTTATACA GTAAAATACG GTGACACTTT AAGCACAATT
 181  GCTGAAGCAA TGGGGATTGA TGTGCATGTC TTAGGAGATA TTAATCATAT TGCTAATATT
 241  GACTTAATTT TTCCAGACAC GATCCTAACA GCAAACTACA ATCAACACGG TCAGGCAACG
 301  ACTTTGACGG TTCAAGCACC TGCTTCTAGT CCAGCTAGCG TTAGTCATGT ACCTAGCAGT
 361  GAGCCATTAC CCCAAGCATC TGCCACCTCT CAACCGACTG TTCCTATGGC ACCATCTGCG
 421  ACACCATTAG CATCTGCAAA GCCAGATAGT TCTGTGACAG CGTCATCTGA GCTCACATCG
 481  TCAACGAATG ATGTTTCGAC TGAGTCGTCT AGCGAATCAC AAAAGCAGCC AGAAGTACCA
 541  CAAGAAGCAG TTCCAACTCC TAAAGCAGCT GAAACGACTG AAGTCGAACC TAAGACAGAC
 601  ATCTCAGAAG ACCCAACTTC AGCTAATAGG CCTGTACCTA ACGAGAGTGC TTCAGAAGAA
 661  GTTTCTTCTG CGGCCCCAGC ACAAGCCCCA GCAGAAAAAG AAGAAACCTC TGCGCCAGCA
 721  GCACAAAAAG CTGTAGCTGA CACCACAAGT GTTGCAACCT CAAACGGCCT TTCTTACGCT
 781  CCAAACCATG CCTACAATCC AATGAATGCA GGGCTTCAAC CACAAACAGC AGCCTTCAAA
 841  GAAGAAGTGG CTTCTGCCTT TGGTATTACG TCATTTAGTG GTTACCGTCC AGGTGACCCA
 901  GGAGATCATG GTAAAGGTTT GGCCATTGAT TTTATGGTGC CTGAAAATTC TGCTCTTGGT
 961  GATCAAGTTG CTCAATATGC CATTGACCAT ATGGCAGAGC GTGGTATTTC ATACGTTATT
1021  TGGAAACAGC GATTCTATGC GCCATTTGCA AGTATTTACG GACCAGCTTA CACATGGAAC
1081  CCCATGCCAG ATCGCGGCAG TATTACAGAA AACCATTATG ATCATGTTCA TGTCTCCTTT
1141  AATGCTTAA (SEQ ID NO:7)
```

Figure 8

```
   1  MIITKKSLFV TSVALSLAPL ATAQAQEWTP RSVTEIKSEL VLVDNVFTYT VKYGDTLSTI
  61  AEAMGIDVHV LGDINHIANI DLIFPDTILT ANYNQHGQAT TLTVQAPASS PASVSHVPSS
 121  EPLPQASATS QPTVPMAPSA TPLASAKPDS SVTASSELTS STNDVSTESS SESQKQPEVP
 181  QEAVPTPKAA ETTEVEPKTD ISEDPTSANR PVPNESASEE VSSAAPAQAP AEKEETSAPA
 241  AQKAVADTTS VATSNGLSYA PNHAYNPMNA GLQPQTAAFK EEVASAFGIT SFSGYRPGDP
 301  GDHGKGLAID FMVPENSALG DQVAQYAIDH MAERGISYVI WKQRFYAPFA SIYGPAYTWN
 361  PMPDRGSITE NHYDHVHVSF NA* (SEQ ID NO:8)
```

Figure 9

1 CAAGAGTGGA CACCACGATC GGTTACAGAA ATCAAGTCTG AACTCGTCCT AGTTGATAAT

61 GTTTTTACTT ATACTGTAAA ATACGGTGAC ACTTTAAGCA CAATTGCTGA AGCAATGGGA

121 ATTGATGTGC ATGTCTTAGG AGATATTAAT CATATTGCTA ATATTGACTT AATTTTTCCA

181 GACACGATCC TAACAGCCAA CTACAACCAA CACGGTCAGG CAACGACTTT GACGGTTCAA

241 GCGCCTGCTT CTAGTCCAGC TAGCGTTAGT CATGTACCTA GCAGTGAGCC ATTACCCCAA

301 GCATCTGCCA CCTCTCAATC GACTGTTCCT ATGGCACCAT CTGCGACACC ATCTGATGTC

361 CCAACGACAC CATTCGCATC TGCAAAGCCA GATAGTTCTG TGACAGCGTC ATCTGAGCTC

421 ACATCGTCAA CGAATGATGT TTCGACTGAG TTGTCTAGCG AATCACAAAA GCAGCCAGAA

481 GTACCACAAG AAGCAGTTCC AACTCCTAAA GCAGCTGAAA CGACTGAAGT CGAACCTAAG

541 ACAGACATCT CAGAGGATTC AACTTCAGCT AATAGGCCTG TACCTAACGA GAGTGCTTCA

601 GAAGAAGTTT CTTCTGCGGC CCCAGCACAA GCCCCAGCAG AAAAAGAAGA AACCTCTGCG

661 CCAGCAGCAC AAAAAGCTGT AGCTGACACC ACAAGTGTTG CAACCTCAAA TGGCCTTTCT

721 TACGCTCCAA ACCATGCCTA CAATCCAATG AATGCAGGGC TTCAACCACA AACAGCAGCC

781 TTCAAAGAAG AAGTGGCTTC TGCCTTTGGT ATTACGTCAT TTAGTGGTTA CCGTCCAGGT

841 GATCCAGGAG ATCATGGTAA AGGTTTGGCC ATTGATTTTA TGGTGCCTGA AAATTCTGCT

901 CTTGGTGATC AAGTTGCTCA ATATGCCATT GACCATATGG CAGAGCGTGG TATTTCATAC

961 GTTATTTGGA AACAGCGATT CTATGCGCCA TTTGCAAGTA TTTACGGACC AGCCTACACA

1021 TGGAACCCCA TGCCAGATCG CGGCAGTATT ACAGAAAACC ATTATGATCA TGTTCATGTC

1081 TCCTTTAATG CTTAA **(SEQ ID NO:9)**

Figure 10

1 QEWTPRSVTE IKSELVLVDN VFTYTVKYGD TLSTIAEAMG IDVHVLGDIN HIANIDLIFP

61 DTILTANYNQ HGQATTLTVQ APASSPASVS HVPSSEPLPQ ASATSQSTVP MAPSATPSDV

121 PTTPFASAKP DSSVTASSEL TSSTNDVSTE LSSESQKQPE VPQEAVPTPK AAETTEVEPK

181 TDISEDSTSA NRPVPNESAS EEVSSAAPAQ APAEKEETSA PAAQKAVADT TSVATSNGLS

241 YAPNHAYNPM NAGLQPQTAA FKEEVASAFG ITSFSGYRPG DPGDHGKGLA IDFMVPENSA

301 LGDQVAQYAI DHMAERGISY VIWKQRFYAP FASIYGPAYT WNPMPDRGSI TENHYDHVHV

361 SFNA* **(SEQ ID NO:10)**

Figure 11

1 CAAGAGTGGA CACCACGATC GGTTACAGAA ATCAAGTCTG AACTCGTCCT AGTTGATAAT

61 GTTTTTACTT ATATAGTAAA ATACGGTGAC ACTTTAAGCA CAATTGCTGA AGCAATGGGG

121 ATTGATGTGC ATGTCTTAGG AGATATTAAT CATATTGCTA ATATTGACTT AATTTTTCCA

181 GACACGATCC TAACAGCAAA CTACAACCAA CACGGTCAGG CAACGACTTT GACGGTTCAA

241 GCACCTGCTT CTAGTCCATC TAGCGTTAGT CATGTACCTA GCAGTGAGCC ATTACCCCAA

301 GCATCTGCCA CCTCTCAACC GACTGTTCCT ATGGCACCAT CTGCGACACC ATCTGATGTC

361 CCAACGACAC CATTCGCATC TGCAAAGCCA GATAGTTCTG TGACAGCGTC ATCTGAGCTC

421 ACATCGTCAA CGAATGATGT TTCGACTGAG TTGTCTAGCG AATCACAAAA GCAGCCAGAA

481 GTACCACAAG AAGCAGTTCC AACTCCTAAA GCAGCTGAAC CGACTGAAGT CGAACCTAAG

541 ACAGACATCT CAGAAGACCC AACTTCAGCT AATAGGCCTG ACCTAACGA GAGTGCTTCA

601 GAAGAAGCTT CTTCTGCGGC CCCAGCACAA GCTCCAGCAG AAAAAGAAGA AACCTCTCAG

661 ATGTTAACTG CGCCAGCAGC ACAAAAAGCT GTAGCTGACA CCACAAGTGT TGCAACCTCA

721 AACGGCCTTT CTTACGCTCC AAACCATGCC TACAATCCAA TGAATGCAGG GCTTCAACCA

781 CAAACAGCAG CCTTCAAAGA AGAAGTGGCT TCTGCCTTTG GTATTACGTC ATTTAGTGGT

841 TACCGTCCAG GAGATCCAGG AGATCATGGT AAAGGATTAG CCATTGACTT TATGGTACCG

901 GTTAGCTCTA CGCTTGGTGA TCAAGTTGCT CAATATGCCA TTGACCATAT GGCAGAGCGT

961 GGTATTTCAT ACGTTATTTG GAAACAGCGA TTCTATGCGC CATTTGCAAG TATTTACGGA

1021 CCAGCCTACA CATGGAACCC CATGCCAGAT CGCGGCAGTA TTACAGAAAA CCATTATGAT

1081 CATGTTCATG TCTCCTTTAA TGCTTAA **(SEQ ID NO:11)**

Figure 12

1 QEWTPRSVTE IKSELVLVDN VFTYIVKYGD TLSTIAEAMG IDVHVLGDIN HIANIDLIFP

61 DTILTANYNQ HGQATTLTVQ APASSPSSVS HVPSSEPLPQ ASATSQPTVP MAPSATPSDV

121 PTTPFASAKP DSSVTASSEL TSSTNDVSTE LSSESQKQPE VPQEAVPTPK AAEPTEVEPK

181 TDISEDPTSA NRPVPNESAS EEASSAAPAQ APAEKEETSQ MLTAPAAQKA VADTTSVATS

241 NGLSYAPNHA YNPMNAGLQP QTAAFKEEVA SAFGITSFSG YRPGDPGDHG KGLAIDFMVP

301 VSSTLGDQVA QYAIDHMAER GISYVIWKQR FYAPFASIYG PAYTWNPMPD RGSITENHYD

361 HVHVSFNA* **(SEQ ID NO:12)**

Figure 13

1 CAAGAGTGGA CACCACGATC GGTTACAGAA ATCAAGTCTG AACTCGTCCT AGTTGATAAT

61 GTTTTTACTT ATACTGTAAA ATACGGTGAC ACTTTAAGCA CAATTGCTGA AGCAATGGGG

121 ATTGATGTGC ATGTCTTAGG AGATATTAAT CATATTGCTA ATATTGACCT AATTTTTCCA

181 GACACGATCC TAACAGCAAA CTACAATCAA CACGGTCAGG CAACGAATTT GACGGTTCAA

241 GCACCTGCTT CTAGTCCAGC TAGCGTTAGT CATGTACCTA GCAGTGAGCC ATTACCCCAA

301 GCATCTGCCA CCTCTCAACC GACTGTTCCT ATGGCACCAC CTGCGACACC ATCTGATGTC

361 CCAACGACAC CATTCGCATC TGCAAAGCCA GATAGTTCTG TGACAGCGTC ATCTGAGCTC

421 ACATCGTCAA CGAATGATGT TTCGACTGAG TTGTCTAGCG AATCACAAAA GCAGCCAGAA

481 GTACCACAAG AAGCAGTTCC AACTCCTAAA GCAGCTGAAA CGACTGAAGT CGAACCTAAG

541 ACAGACATCT CAGAAGCCCC AACTTCAGCT AATAGGCCTG TACCTAACGA GAGTGCTTCA

601 GAAGAAGTTT CTTCTGCGGC CCCAGCACAA GCCCCAGCAG AAAAAGAAGA AACCTCTGCG

661 CCAGCAGCAC AAAAAGCTGT AGCTGACACC ACAAGTGTTG CAACCTCAAA TGGCCTTTCT

721 TACGCTCCAA ACCATGCCTA CAATCCAATG AATGCAGGGC TTCAACCACA AACAGCAGCC

781 TTCAAAGAAG AAGTGGCTTC TGCCTTTGGT ATTACGTCAT TTAGTGGTTA CCGTCCAGGT

841 GATCCAGGAG ATCATGGTAA AGGTTTGGCC ATTGATTTTA TGGTGCCTGA AAATTCTGCT

901 CTTGGTGATC AAGTTGCTCA ATATGCCATT GACCATATGG CAGAGCGTGG TATTTCATAC

961 GTTATTTGGA AACAGCGATT CTATGCGCCA TTTGCAAGTA TTTACGGACC AGCCTACACA

1021 TGGAACCCCA TGCCAGATCG CGGCAGTATT ACAGAAAACC ATTATGATCA TGTTCATGTC

1081 TCCTTTAATG CTTAA **(SEQ ID NO:13)**

Figure 14

1 QEWTPRSVTE IKSELVLVDN VFTYTVKYGD TLSTIAEAMG IDVHVLGDIN HIANIDLIFP

61 DTILTANYNQ HGQATNLTVQ APASSPASVS HVPSSEPLPQ ASATSQPTVP MAPPATPSDV

121 PTTPFASAKP DSSVTASSEL TSSTNDVSTE LSSESQKQPE VPQEAVPTPK AAETTEVEPK

181 TDISEAPTSA NRPVPNESAS EEVSSAAPAQ APAEKEETSA PAAQKAVADT TSVATSNGLS

241 YAPNHAYNPM NAGLQPQTAA FKEEVASAFG ITSFSGYRPG DPGDHGKGLA IDFMVPENSA

301 LGDQVAQYAI DHMAERGISY VIWKQRFYAP FASIYGPAYT WNPMPDRGSI TENHYDHVHV

361 SFNA* **(SEQ ID NO:14)**

Figure 15

1 CAAGAGTGGA CACCACGATC GGTTACAGAA ATCAAGTCTG AACTCGTCCT AGTTGATAAT

61 GTTTTTACTT ATACAGTAAA ATACGGTGAC ACTTTAAGCA CAATTGCTGA AGCAATGGGG

121 ATTGATGTGC ATGTCTTAGG AGATATTAAT CATATTGCTA ATATTGACTT AATTTTTCCA

181 GACACGATCC TAACAGCAAA CTACAATCAA CACGGTCAGG CAACGACTTT GACGGTTCAA

241 GCACCTGCTT CTAGTCCAGC TAGCGTTAGT CATGTACCTA GCAGTGAGCC ATTACCCCAA

301 GCATCTGCCA CCTCTCAACC GACTGTTCCT ATGGCACCAT CTGCGACACC ATTAGCATCT

361 GCAAAGCCAG ATAGTTCTGT GACAGCGTCA TCTGAGCTCA CATCGTCAAC GAATGATGTT

421 TCGACTGAGT CGTCTAGCGA ATCACAAAAG CAGCCAGAAG TACCACAAGA AGCAGTTCCA

481 ACTCCTAAAG CAGCTGAAAC GACTGAAGTC GAACCTAAGA CAGACATCTC AGAAGACCCA

541 ACTTCAGCTA ATAGGCCTGT ACCTAACGAG AGTGCTTCAG AAGAAGTTTC TTCTGCGGCC

601 CCAGCACAAG CCCCAGCAGA AAAAGAAGAA ACCTCTGCGC CAGCAGCACA AAAAGCTGTA

661 GCTGACACCA CAAGTGTTGC AACCTCAAAC GGCCTTTCTT ACGCTCCAAA CCATGCCTAC

721 AATCCAATGA ATGCAGGGCT TCAACCACAA ACAGCAGCCT TCAAAGAAGA AGTGGCTTCT

781 GCCTTTGGTA TTACGTCATT TAGTGGTTAC CGTCCAGGTG ACCCAGGAGA TCATGGTAAA

841 GGTTTGGCCA TTGATTTTAT GGTGCCTGAA AATTCTGCTC TTGGTGATCA AGTTGCTCAA

901 TATGCCATTG ACCATATGGC AGAGCGTGGT ATTTCATACG TTATTTGGAA ACAGCGATTC

961 TATGCGCCAT TTGCAAGTAT TTACGGACCA GCTTACACAT GGAACCCCAT GCCAGATCGC

1021 GGCAGTATTA CAGAAAACCA TTATGATCAT GTTCATGTCT CCTTTAATGC TTAA **(SEQ ID NO:15)**

Figure 16

1 QEWTPRSVTE IKSELVLVDN VFTYTVKYGD TLSTIAEAMG IDVHVLGDIN HIANIDLIFP

61 DTILTANYNQ HGQATTLTVQ APASSPASVS HVPSSEPLPQ ASATSQPTVP MAPSATPLAS

121 AKPDSSVTAS SELTSSTNDV STESSSESQK QPEVPQEAVP TPKAAETTEV EPKTDISEDP

181 TSANRPVPNE SASEEVSSAA PAQAPAEKEE TSAPAAQKAV ADTTSVATSN GLSYAPNHAY

241 NPMNAGLQPQ TAAFKEEVAS AFGITSFSGY RPGDPGDHGK GLAIDFMVPE NSALGDQVAQ

301 YAIDHMAERG ISYVIWKQRF YAPFASIYGP AYTWNPMPDR GSITENHYDH VHVSFNA*

(SEQ ID NO:16)

Figure 17

```
12384          1 ATGATTATTACTAAAAAGAGCTTATTTGTGACAAGTGTCGCTTTGTCGTT   50
2699           1 ATGATTATTACTAAAAAGAGCTTATTTGTGACAAGTGTCGCTTTGTCGTT   50
B514           1 ATGATTATTACTAAAAAGAGCTTATTTGTGACAAGTGTCGCTTTGTCGTT   50
Spy57          1 ATGATTATTACTAAAAAGAGCTTATTTGTGACAAGTGTCGCTTTGTCGTT   50
U09352         1 ATGATTATTACTAAAAAGAGTTTATTTGTGACAAGTGTCGCTTTGTCGTT   50
Oklahoma       1 ATGATTATTACTAAAAAGAGCTTATTTGTGACAAGTGTCGCTTTGTCGTT   50
                 ********************* ****************************

12384         51 AGCACCTTTGGCGACAGCACAGGCACAAGAGTGGACACCACGATCGGTTA  100
2699          51 AGCACCTTTGGCGACAGCGCAGGCACAAGAGTGGACACCACGATCGGTTA  100
B514          51 AGCACCTTTGGCGACAGCGCAGGCACAAGAGTGGACACCACGATCGGTTA  100
Spy57         51 AGTACCTTTGGCGACAGCGCAGGCACAAGAGTGGACACCACGATCGGTTA  100
U09352        51 AGCACCTTTGGCGACAGCGCAGGCACAAGAGTGGACACCACGATCGGTTA  100
Oklahoma      51 AGTACCTTTGGCGACAGCGCAGGCACAAGAGTGGACACCACGATCGGTTA  100
                 ** ***************** ****************************

12384        101 CAGAAATCAAGTCTGAACTCGTCCTAGTTGATAATGTTTTTACTTATACT  150
2699         101 CAGAAATCAAGTCTGAACTCGTCCTAGTTGATAATGTTTTTACTTATATA  150
B514         101 CAGAAATCAAGTCTGAACTCGTCCTAGTTGATAATGTTTTTACTTATACA  150
Spy57        101 CAGAAATCAAGTCTGAACTCGTCCTAGTTGATAATGTTTTTACTTATACT  150
U09352       101 CACAAATCAAGTCTGAACTCGTCCTAGTTGATAATGTTTTTACTTATACA  150
Oklahoma     101 CAGAAATCAAGTCTGAACTCGTCCTAGTTGATAATGTTTTTACTTATACT  150
                 ** ******************************************

12384        151 GTAAAATACGGTGACACTTTAAGCACAATTGCTGAAGCAATGGGAATTGA  200
2699         151 GTAAAATACGGTGACACTTTAAGCACAATTGCTGAAGCAATGGGGATTGA  200
B514         151 GTAAAATACGGTGACACTTTAAGCACAATTGCTGAAGCAATGGGGATTGA  200
Spy57        151 GTAAAATACGGTGACACTTTAAGCACAATTGCTGAAGCAATGGGGATTGA  200
U09352       151 GTAAAATACGGTGACACTTTAAGCACAATTGCTGAAGCAATGGGGATTGA  200
Oklahoma     151 GTAAAATACGGTGACACTTTAAGCACAATTGCTGAAGCAATGGGGATTGA  200
                 ************************************** *****

12384        201 TGTGCATGTCTTAGGAGATATTAATCATATTGCTAATATTGACTTAATTT  250
2699         201 TGTGCATGTCTTAGGAGATATTAATCATATTGCTAATATTGACTTAATTT  250
B514         201 TGTGCATGTCTTAGGAGATATTAATCATATTGCTAATATTGACTTAATTT  250
Spy57        201 TGTGCATGTCTTAGGAGATATTAATCATATTGCTAATATTGACCTAATTT  250
U09352       201 TGTGCATGTCTTAGGAGATATTAATCATATTGCTAATATTGACTTAATTT  250
Oklahoma     201 TGTGCATGTCTTAGGAGATATTAATCATATTGCTAATATTGACCTAATTT  250
                 ****************************************** ******

12384        251 TTCCAGACACGATCCTAACAGCCAACTACAACCAACACGGTCAGGCAACG  300
2699         251 TTCCAGACACGATCCTAACAGCAAACTACAACCAACACGGTCAGGCAACG  300
B514         251 TTCCAGACACGATCCTAACAGCAAACTACAATCAACACGGTCAGGCAACG  300
Spy57        251 TTCCAGACACGATCCTAACAGCAAACTACAATCAACACGGTCAGGCAACG  300
U09352       251 TTCCAGACACGATCCTAACAGCAAACTACAACCAACACGGTCAGGCAACG  300
Oklahoma     251 TTCCAGACACGATCCTAACAGCAAACTACAATCAACACGGTCAGGCAACG  300
                 ********************** ******** ******************

12384        301 ACTTTGACGGTTCAAGCGCCTGCTTCTAGTCCAGCTAGCGTTAGTCATGT  350
2699         301 ACTTTGACGGTTCAAGCACCTGCTTCTAGTCCATCTAGCGTTAGTCATGT  350
B514         301 ACTTTGACGGTTCAAGCACCTGCTTCTAGTCCAGCTAGCGTTAGTCATGT  350
Spy57        301 AATTTGACGGTTCAAGCACCTGCTTCTAGTCCAGCTAGCGTTAGTCATGT  350
U09352       301 ACTTTGACGGTTCAAGCGCCTGCTTCTAGTCCAGCTAGCGTTAGTCATGT  350
Oklahoma     301 AATTTGACGGTTCAAGCACCTGCTTCTAGTCCAGCTAGCGTTAGTCATGT  350
                 * ***************** ***************** ****************
```

```
12384       351 ACCTAGCAGTGAGCCATTACCCCAAGCATCTGCCACCTCTCAATCGACTG  400
2699        351 ACCTAGCAGTGAGCCATTACCCCAAGCATCTGCCACCTCTCAACCGACTG  400
B514        351 ACCTAGCAGTGAGCCATTACCCCAAGCATCTGCCACCTCTCAACCGACTG  400
Spy57       351 ACCTAGCAGTGAGCCATTACCCCAAGCATCTGCCACCTCTCAACCGACTG  400
U09352      351 ACCTAGCAGTGAGCCATTACCCCAAGCATCTGCCACCTCTCAATCGACTA  400
Oklahoma    351 ACCTAGCAGTGAGCCATTACCCCAAGCATCTGCCACCTCTCAACCGACTG  400
                ************************************** *****

12384       401 TTCCTATGGCACCATCTGCGACACCATCTGATGTCCCAACGACACCATTC  450
2699        401 TTCCTATGGCACCATCTGCGACACCATCTGATGTCCCAACGACACCATTC  450
B514        401 TTCCTATGGCACCATCTGCGACACCAT----------------------TA  429
Spy57       401 TTCCTATGGCACCACCTGCGACACCATCTGATGTCCCAACGACACCATTC  450
U09352      401 TTCCTATGGCACCATCTGCGACACCATCTGATGTCCCAACGACACCATTA  450
Oklahoma    401 TTCCTATGGCACCACCTGCGACACCATCTGATGTCCCAACGACACCATTC  450
                ************** ************             *

12384       451 GCATCTGCAAAGCCAGATAGTTCTGTGACAGCGTCATCTGAGCTCACATC  500
2699        451 GCATCTGCAAAGCCAGATAGTTCTGTGACAGCGTCATCTGAGCTCACATC  500
B514        430 GCATCTGCAAAGCCAGATAGTTCTGTGACAGCGTCATCTGAGCTCACATC  479
Spy57       451 GCATCTGCAAAGCCAGATAGTTCTGTGACAGCGTCATCTGAGCTCACATC  500
U09352      451 GCATCTGCAAAGCCAGATAGTTTTGTGACAGCGTCATCTGAGCTCACATC  500
Oklahoma    451 GCATCTGCAAAGCCAGATAGTTCTGTGACAGCGTCATCTGAGCTCACATC  500
                ********************** ****************************

12384       501 GTCAACGAATGATGTTTCGACTGAGTTGTCTAGCGAATCACAAAAGCAGC  550
2699        501 GTCAACGAATGATGTTTCGACTGAGTTGTCTAGCGAATCACAAAAGCAGC  550
B514        480 GTCAACGAATGATGTTTCGACTGAGTCGTCTAGCGAATCACAAAAGCAGC  529
Spy57       501 GTCAACGAATGATGTTTCGACTGAGTTGTCTAGCGAATCACAAAAGCAGC  550
U09352      501 ATCAACGAATGATGTTTCGACTGAGTTGTCTAGCGAATCACAAAAGCAGC  550
Oklahoma    501 GTCAACGAATGATGTTTCGACTGAGTTGTCTAGCGAATCACAAAAGCAGC  550
                ************************** ************************

12384       551 CAGAAGTACCACAAGAAGCAGTTCCAACTCCTAAAGCAGCTGAAACGACT  600
2699        551 CAGAAGTACCACAAGAAGCAGTTCCAACTCCTAAAGCAGCTGAACCGACT  600
B514        530 CAGAAGTACCACAAGAAGCAGTTCCAACTCCTAAAGCAGCTGAAACGACT  579
Spy57       551 CAGAAGTACCACAAGAAGCAGTTCCAACTCCTAAAGCAGCTGAAACGACT  600
U09352      551 CAGAAGTACCACAAGAAGCAGAACCAACTCCTAAAGCAGCTGAAAGCACT  600
Oklahoma    551 CAGAAGTACCACAAGAAGCAGTTCCAACTCCTAAAGCAGCTGAAACGACT  600
                ********************  **********************   ***

12384       601 GAAGTCGAACCTAAGACAGACATCTCAGAGGATTCAACTTCAGCTAATAG  650
2699        601 GAAGTCGAACCTAAGACAGACATCTCAGAAGACCCAACTTCAGCTAATAG  650
B514        580 GAAGTCGAACCTAAGACAGACATCTCAGAAGACCCAACTTCAGCTAATAG  629
Spy57       601 GAAGTCGAACCTAAGACAGACATCTCAGAAGCCCCAACTTCAGCTAATAG  650
U09352      601 GAAGTCGAACCTAAGACAGACATCTCAGAAGATTCAACTTCAGCTAATAG  650
Oklahoma    601 GAAGTCGAACCTAAGACAGACATCTCAGAAGCCCCAACTTCAGCTAATAG  650
                ***************************** *   ****************

12384       651 GCCTGTACCTAACGAGAGTGCTTCAGAAGAAGTTTCTTCTGCGGCCCCAG  700
2699        651 GCCTGTACCTAACGAGAGTGCTTCAGAAGAAGCTTCTTCTGCGGCCCCAG  700
B514        630 GCCTGTACCTAACGAGAGTGCTTCAGAAGAAGTTTCTTCTGCGGCCCCAG  679
Spy57       651 GCCTGTACCTAACGAGAGTGCTTCAGAAGAAGTTTCTTCTGCGGCCCCAG  700
U09352      651 GCCTGTACCTAACGGAAGTGCTTCAGAAGAAGCTTCTTCTGCGGCCCCAG  700
Oklahoma    651 GCCTGTACCTAACGAGAGTGCTTCAGAAGAAGTTTCTTCTGCGGCCCCAG  700
                **************  ***************** *****************

12384       701 CACAAGCCCCAGCAGAAAAAGAAGAAACCTCT-----------GCGCCA  738
2699        701 CACAAGCTCCAGCAGAAAAAGAAGAAACCTCTCAGATGTTAACTGCGCCA  750
B514        680 CACAAGCCCCAGCAGAAAAAGAAGAAACCTCT-----------GCGCCA  717
Spy57       701 CACAAGCCCCAGCAGAAAAAGAAGAAACCTCT-----------GCGCCA  738
U09352      701 CACAAGCTCCAGCAGAAAAAGAAGAAACCTCTCAGATGTTAACTGCGCCA  750
Oklahoma    701 CACAAGCCCCAGCAGAAAAAGAAGAAACCTCT-----------GCGCCA  738
                ******* ************************             ******
```

```
12384       739 GCAGCACAAAAAGCTGTAGCTGACACCACAAGTGTTGCAACCTCAAATGG  788
2699        751 GCAGCACAAAAAGCTGTAGCTGACACCACAAGTGTTGCAACCTCAAACGG  800
B514        718 GCAGCACAAAAAGCTGTAGCTGACACCACAAGTGTTGCAACCTCAAACGG  767
Spy57       739 GCAGCACAAAAAGCTGTAGCTGACACCACAAGTGTTGCAACCTCAAATGG  788
U09352      751 GCAGCACAAAAAGCTGTAGCTGACACCACAAGTGTTGCAACCTCAAACGG  800
Oklahoma    739 GCAGCACAAAAAGCTGTAGCTGACACCACAAGTGTTGCAACCTCAAATGG  788
                ********************************************** **

12384       789 CCTTTCTTACGCTCCAAACCATGCCTACAATCCAATGAATGCAGGGCTTC  838
2699        801 CCTTTCTTACGCTCCAAACCATGCCTACAATCCAATGAATGCAGGGCTTC  850
B514        768 CCTTTCTTACGCTCCAAACCATGCCTACAATCCAATGAATGCAGGGCTTC  817
Spy57       789 CCTTTCTTACGCTCCAAACCATGCCTACAATCCAATGAATGCAGGGCTTC  838
U09352      801 CCTTTCTTACGCTCCAAACCATGCCTACAATCCAATGAATGCAGGGCTTC  850
Oklahoma    789 CCTTTCTTACGCTCCAAACCATGCCTACAATCCAATGAATGCAGGGCTTC  838
                **********************************************

12384       839 AACCACAAACAGCAGCCTTCAAAGAAGAAGTGGCTTCTGCCTTTGGTATT  888
2699        851 AACCACAAACAGCAGCCTTCAAAGAAGAAGTGGCTTCTGCCTTTGGTATT  900
B514        818 AACCACAAACAGCAGCCTTCAAAGAAGAAGTGGCTTCTGCCTTTGGTATT  867
Spy57       839 AACCACAAACAGCAGCCTTCAAAGAAGAAGTGGCTTCTGCCTTTGGTATT  888
U09352      851 AACCACAAACAGCAGCCTTCAAAGAAGAAGTG-CTTCTGCCTTTGGTATT  899
Oklahoma    839 AACCACAAACAGCAGCCTTCAAAGAAGAAGTGGCTTCTGCCTTTGGTATT  888
                ********************************** ******************

12384       889 ACGTCATTTAGTGGTTACCGTCCAGGTGATCCAGGAGATCAT-GGTAAAG  937
2699        901 ACGTCATTTAGTGGTTACCGTCCAGGAGATCCAGGAGATCAT-GGTAAAG  949
B514        868 ACGTCATTTAGTGGTTACCGTCCAGGTGACCCAGGAGATCAT-GGTAAAG  916
Spy57       889 ACGTCATTTAGTGGTTACCGTCCAGGTGATCCAGGAGATCAT-GGTAAAG  937
U09352      900 ACGTCATTTAGTGGTTACCGTCCAGGAGATCCAGGAGATCATTGGTAAAG  949
Oklahoma    889 ACGTCATTTAGTGGTTACCGTCCAGGTGATCCAGGAGATCAT-GGTAAAG  937
                ***************************** ** ************ *******

12384       938 GTTTGGCCATTGATTTTATGGTGCCTGAAAATTCTGCTCTTGGTGATCAA  987
2699        950 GATTAGCCATTGACTTTATGGTACCGGTTAGCTCTACGCTTGGTGATCAA  999
B514        917 GTTTGGCCATTGATTTTATGGTGCCTGAAAATTCTGCTCTTGGTGATCAA  966
Spy57       938 GTTTGGCCATTGATTTTATGGTGCCTGAAAATTCTGCTCTTGGTGATCAA  987
U09352      950 GATTAGCCATTGACTTTATGGTACCGGTTAGCTCTACGCTTGGTGATCAA  999
Oklahoma    938 GTTTGGCCATTGATTTTATGGTGCCTGAAAATTCTGCTCTTGGTGATCAA  987
                * ** ******** ******** ** *  *  *** * ************

12384       988 GTTGCTCAATATGCCATTGACCATATGGCAGAGCGTGGTATTTCATACGT 1037
2699       1000 GTTGCTCAATATGCCATTGACCATATGGCAGAGCGTGGTATTTCATACGT 1049
B514        967 GTTGCTCAATATGCCATTGACCATATGGCAGAGCGTGGTATTTCATACGT 1016
Spy57       988 GTTGCTCAATATGCCATTGACCATATGGCAGAGCGTGGTATTTCATACGT 1037
U09352     1000 GTTGCTCAATATGCCATTGACCATATGGCAGACGGTGGTATTTCATACGT 1049
Oklahoma    988 GTTGCTCAATATGCCATTGACCATATGGCAGAGCGTGGTATTTCATACGT 1037
                ********************************  ****************

12384      1038 TATTTGGAAACAGCGATTCTATGCGCCATTTGCAAGTATTTACGGACCAG 1087
2699       1050 TATTTGGAAACAGCGATTCTATGCGCCATTTGCAAGTATTTACGGACCAG 1099
B514       1017 TATTTGGAAACAGCGATTCTATGCGCCATTTGCAAGTATTTACGGACCAG 1066
Spy57      1038 TATTTGGAAACAGCGATTCTATGCGCCATTTGCAAGTATTTACGGACCAG 1087
U09352     1050 TATTTGGAAACAGCGATTCTATGCGCCATTTGCAAGTATTTACGGACCAG 1099
Oklahoma   1038 TATTTGGAAACAGCGATTCTATGCGCCATTTGCAAGTATTTACGGACCAG 1087
                **********************************************
```

```
12384      1088 CCTACACATGGAACCCCATGCCAGATCGCGGCAGTATTACAGAAAACCAT 1137
2699       1100 CCTACACATGGAACCCCATGCCAGATCGCGGCAGTATTACAGAAAACCAT 1149
B514       1067 CTTACACATGGAACCCCATGCCAGATCGCGGCAGTATTACAGAAAACCAT 1116
Spy57      1088 CCTACACATGGAACCCCATGCCAGATCGCGGCAGTATTACAGAAAACCAT 1137
U09352     1100 CCTACACATGGAACCCCATGCCAGATCGCGGCAGTATTACAGTTTTCCAT 1149
Oklahoma   1088 CCTACACATGGAACCCCATGCCAGATCGCGGCAGTATTACAGAAAACCAT 1137
                * ************************************    ****

12384      1138 TATGATCATGTTCATGTCTCCTTTAATGCTTAA 1170
2699       1150 TATGATCATGTTCATGTCTCCTTTAATGCTTAA 1182
B514       1117 TATGATCATGTTCATGTCTCCTTTAATGCTTAA 1149
Spy57      1138 TATGATCATGTTCATGTCTCCTTTAATGCTTAA 1170
U09352     1150 TATGATCATGTTCATGTCTCCTTTAATGCTTAA 1182
Oklahoma   1138 TATGATCATGTTCATGTCTCCTTTAATGCTTAA 1170
                ********************************
```

Figure 18

```
12384          1 MIITKKSLFVTSVALSLAPLATAQAQEWTPRSVTEIKSELVLVDNVFTYT   50
2699           1 MIITKKSLFVTSVALSLAPLATAQAQEWTPRSVTEIKSELVLVDNVFTYI   50
B514           1 MIITKKSLFVTSVALSLAPLATAQAQEWTPRSVTEIKSELVLVDNVFTYT   50
Spy57          1 MIITKKSLFVTSVALSLVPLATAQAQEWTPRSVTEIKSELVLVDNVFTYT   50
U09352         1 MIITKKSLFVTSVALSLAPLATAQAQEWTPRSVTQIKSELVLVDNVFTYT   50
Oklahoma       1 MIITKKSLFVTSVALSLVPLATAQAQEWTPRSVTEIKSELVLVDNVFTYT   50
                 ****************** ****************.**************

12384         51 VKYGDTLSTIAEAMGIDVHVLGDINHIANIDLIFPDTILTANYNQHGQAT 100
2699          51 VKYGDTLSTIAEAMGIDVHVLGDINHIANIDLIFPDTILTANYNQHGQAT 100
B514          51 VKYGDTLSTIAEAMGIDVHVLGDINHIANIDLIFPDTILTANYNQHGQAT 100
Spy57         51 VKYGDTLSTIAEAMGIDVHVLGDINHIANIDLIFPDTILTANYNQHGQAT 100
U09352        51 VKYGDTLSTIAEAMGIDVHVLGDINHIANIDLIFPDTILTANYNQHGQAT 100
Oklahoma      51 VKYGDTLSTIAEAMGIDVHVLGDINHIANIDLIFPDTILTANYNQHGQAT 100
                 **************************************************

12384        101 TLTVQAPASSPASVSHVPSSEPLPQASATSQSTVPMAPSATPSDVPTTPF 150
2699         101 TLTVQAPASSPSSVSHVPSSEPLPQASATSQPTVPMAPSATPSDVPTTPF 150
B514         101 TLTVQAPASSPASVSHVPSSEPLPQASATSQPTVPMAPSATP-------L 143
Spy57        101 NLTVQAPASSPASVSHVPSSEPLPQASATSQPTVPMAPPATPSDVPTTPF 150
U09352       101 TLTVQAPASSPASVSHVPSSEPLPQASATSQSTIPMAPSATPSDVPTTPL 150
Oklahoma     101 NLTVQAPASSPASVSHVPSSEPLPQASATSQPTVPMAPPATPSDVPTTPF 150
                 .**********.********************* *.**** ***

12384        151 ASAKPDSSVTASSELTSSTNDVSTELSSESQKQPEVPQEAVPTPKAAETT 200
2699         151 ASAKPDSSVTASSELTSSTNDVSTELSSESQKQPEVPQEAVPTPKAAEPT 200
B514         144 ASAKPDSSVTASSELTSSTNDVSTESSSESQKQPEVPQEAVPTPKAAETT 193
Spy57        151 ASAKPDSSVTASSELTSSTNDVSTELSSESQKQPEVPQEAVPTPKAAETT 200
U09352       151 ASAKPDSFVTASSELTSSTNDVSTELSSESQKQPEVPQEAEPTPKAAEST 200
Oklahoma     151 ASAKPDSSVTASSELTSSTNDVSTELSSESQKQPEVPQEAVPTPKAAETT 200
                 ******* ****************** ************** ******* *

12384        201 EVEPKTDISEDSTSANRPVPNESASEEVSSAAPAQAPAEKE----ETSAP 246
2699         201 EVEPKTDISEDPTSANRPVPNESASEEASSAAPAQAPAEKEETSQMLTAP 250
B514         194 EVEPKTDISEDPTSANRPVPNESASEEVSSAAPAQAPAEKE----ETSAP 239
Spy57        201 EVEPKTDISEAPTSANRPVPNESASEEVSSAAPAQAPAEKE----ETSAP 246
U09352       201 EVEPKTDISEDSTSANRPVPNGSASEEASSAAPAQAPAEKEETSQMLTAP 250
Oklahoma     201 EVEPKTDISEAPTSANRPVPNESASEEVSSAAPAQAPAEKE----ETSAP 246
                 **********  ********* ***** ************       .**

12384        247 AAQKAVADTTSVATSNGLSYAPNHAYNPMNAGLQPQTAAFKEEVASAFGI 296
2699         251 AAQKAVADTTSVATSNGLSYAPNHAYNPMNAGLQPQTAAFKEEVASAFGI 300
B514         240 AAQKAVADTTSVATSNGLSYAPNHAYNPMNAGLQPQTAAFKEEVASAFGI 289
Spy57        247 AAQKAVADTTSVATSNGLSYAPNHAYNPMNAGLQPQTAAFKEEVASAFGI 296
U09352       251 AAQKAVADTTSVATSNGLSYAPNHAYNPMNAGLQPQTAAFKEEVLLPLVL 300
Oklahoma     247 AAQKAVADTTSVATSNGLSYAPNHAYNPMNAGLQPQTAAFKEEVASAFGI 296
                 ****************************************** .

12384        297 TSFSGYRPGDPGDHGKGLAIDFMVPENSALGDQVAQYAIDHMAERGISYV 346
2699         301 TSFSGYRPGDPGDHGKGLAIDFMVPVSSTLGDQVAQYAIDHMAERGISYV 350
B514         290 TSFSGYRPGDPGDHGKGLAIDFMVPENSALGDQVAQYAIDHMAERGISYV 339
Spy57        297 TSFSGYRPGDPGDHGKGLAIDFMVPENSALGDQVAQYAIDHMAERGISYV 346
U09352       301 RHLVVTVQEIQEIIGKGLAIDFMVPVSSTLGDQVAQYAIDHMADGGISYV 350
Oklahoma     297 TSFSGYRPGDPGDHGKGLAIDFMVPENSALGDQVAQYAIDHMAERGISYV 346
                           *********** *.***************. *****
```

```
12384      347 IWKQRFYAPFASIYGPAYTWNPMPDRGSITENHYDHVHVSFNA 389
2699       351 IWKQRFYAPFASIYGPAYTWNPMPDRGSITENHYDHVHVSFNA 393
B514       340 IWKQRFYAPFASIYGPAYTWNPMPDRGSITENHYDHVHVSFNA 382
Spy57      347 IWKQRFYAPFASIYGPAYTWNPMPDRGSITENHYDHVHVSFNA 389
U09352     351 IWKQRFYAPFASIYGPAYTWNPMPDRGSITVFHYDHVHVSFNA 393
Oklahoma   347 IWKQRFYAPFASIYGPAYTWNPMPDRGSITENHYDHVHVSFNA 389
               ******************************  ***********
```

Figure 19

```
   1 ATGAAGAAAA GAATGTTATT AGCGTCAACA GTAGCCTTGT CATTTGCCCC
  51 AGTATTGGCA ACTCAAGCAG AAGAAGTTCT TTGGACTGCA CGTAGTGTTG
 101 AGCAAATCCA AAACGATTTG ACTAAAACGG ACAACAAAAC AAGTTATACC
 151 GTACAGTATG GTGATACTTT GAGCACCATT GCAGAAGCCT TGGGTGTAGA
 201 TGTCACAGTG CTTGCGAATC TGAACAAAAT CACTAATATG GACTTGATTT
 251 TCCCAGAAAC TGTTTTGACA ACGACTGTCA ATGAAGCAGA AGAAGTAACA
 301 GAAGTTGAAA TCCAAACACC TCAAGCAGAC TCTAGTGAAG AAGTGACAAC
 351 TGCGACAGCA GATTTGACCA CTAATCAAGT GACCGTTGAT GATCAAACTG
 401 TTCAGGTTGC AGACCTTTCT CAACCAATTG CAGAAGTTAC AAAGACAGTG
 451 ATTGCTTCTG AAGAAGTGGC ACCATCTACG GGCACTTCTG TCCCAGAGGA
 501 GCAAACGACC GAAACAACTC GCCCAGTTGA AGAAGCAACT CCTCAGGAAA
 551 CGACTCCAGC TGAGAAGCAG GAAACACAAG CAAGCCCTCA AGCTGCATCA
 601 GCAGTGGAAG TAACTACAAC AAGTTCAGAA GCAAAAGAAG TAGCATCATC
 651 AAATGGAGCT ACAGCAGCAG TTTCTACTTA TCAACCAGAA GAGACGAAAA
 701 TAATTTCAAC AACTTACGAG GCTCCAGCTG CGCCCGATTA TGCTGGACTT
 751 GCAGTAGCAA AATCTGAAAA TGCAGGTCTT CAACCACAAA CAGCTGCCTT
 801 TAAAGAAGAA ATTGCTAACT TGTTTGGCAT TACATCCTTT AGTGGTTATC
 851 GTCCAGGAGA CAGTGGAGAT·CACGGAAAAG GTTTGGCTAT CGACTTTATG
 901 GTACCAGAAC GTTCAGAATT AGGGGATAAG ATTGCGGAAT ATGCTATTCA
 951 AAATATGGCC AGCCGTGGCA TTAGTTACAT CATCTGGAAA CAACGTTTCT
1001 ATGCTCCATT CGATAGCAAA TATGGGCCAG CTAACACTTG GAACCCAATG
1051 CCAGACCGTG GTAGTGTGAC AGAAAATCAC TATGATCACG TTCACGTTTC
1101 AATGAATGGA TAA (SEQ ID NO:17)
```

Figure 20

```
   1 MKKRMLLAST VALSFAPVLA TQAEEVLWTA RSVEQIQNDL TKTDNKTSYT
  51 VQYGDTLSTI AEALGVDVTV LANLNKITNM DLIFPETVLT TTVNEAEEVT
 101 EVEIQTPQAD SSEEVTTATA DLTTNQVTVD DQTVQVADLS QPIAEVTKTV
 151 IASEEVAPST GTSVPEEQTT ETTRPVEEAT PQETTPAEKQ ETQASPQAAS
 201 AVEVTTTSSE AKEVASSNGA TAAVSTYQPE ETKIISTTYE APAAPDYAGL
 251 AVAKSENAGL QPQTAAFKEE IANLFGITSF SGYRPGDSGD HGKGLAIDFM
 301 VPERSELGDK IAEYAIQNMA SRGISYIIWK QRFYAPFDSK YGPANTWNPM
 351 PDRGSVTENH YDHVHVSMNG * (SEQ ID NO:18)
```