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(54) Title: GROUP B STREPTOCOCCUS VACCINE

(57) Abstract: This application relates to improved Group B Streptococcus ("GBS") saccharide-based vaccines comprising combinations of GBS polysaccharides with polypeptide antigens, and *vice versa*, such that the polypeptide and the saccharide each contribute to the immunological response in a recipient. The combination is particularly advantageous where the saccharide and polypeptide are from different GBS serotypes. The combined antigens may be present as a simple combination where separate saccharide and polypeptide antigens are administered together, or they may be present as a conjugated combination, where the saccharide and polypeptide antigens are covalently linked to each other. Preferably, the immunogenic compositions of the invention comprise a GBS saccharide antigen and at least two GBS polypeptide antigens, wherein said GBS saccharide antigen comprises a saccharide selected form GBS serotype Ia, Ib, and III, and wherein said GBS polypeptide antigens comprise a combination of at least two polypeptide or fragments thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.



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## GROUP B STREPTOCOCCUS VACCINE

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This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/410,839, filed September 13, 2002, which application is incorporated herein by reference in its entirety.

### TECHNICAL FIELD

10 This invention relates to polysaccharides from the bacteria *Streptococcus agalactiae* (GBS) and to their use in immunisation.

### BACKGROUND ART

Once thought to infect only cows, the Gram-positive bacterium *Streptococcus agalactiae* (or "group B streptococcus", abbreviated to "GBS" (Ref. 1) is now known to cause serious disease, bacteremia and meningitis, in immunocompromised individuals and in neonates. There are two types of neonatal infection. The first (early onset, usually within 5 days of birth) is manifested by bacteremia and pneumonia. It is contracted vertically as a baby passes through the birth canal. GBS colonises the vagina of about 25% of young women, and approximately 1% of infants born via a vaginal birth to colonised mothers will become infected. Mortality is between 50-70%. The second 15 is a meningitis that occurs 10 to 60 days after birth. If pregnant women are vaccinated with type III capsule so that the infants are passively immunised, the incidence of the late onset meningitis is reduced but is not entirely eliminated. 20

The "B" in "GBS" refers to the Lancefield classification, which is based on the antigenicity of a carbohydrate which is soluble in dilute acid and called the C carbohydrate. Lancefield identified 13 types of C carbohydrate, designated A to O, that could be serologically differentiated. The organisms that most commonly infect humans are found in groups A, B, D, and G. Within group B, strains can be divided into at least 9 serotypes (Ia, Ib, Ia/c, II, III, IV, V, VI, VII and VIII) based on the structure of their polysaccharide capsule. In the past, serotypes Ia, Ib, II, and III were equally prevalent in normal vaginal carriage and early onset sepsis in newborns. Type V GBS has emerged 25 as an important cause of GBS infection in the USA, however, and strains of types VI and VIII have become prevalent among Japanese women. 30

The genome sequence of a serotype V strain 2603 V/R has been published (Ref. 2) and various polypeptides for use as vaccine antigens have been identified (Ref. 3). The vaccines currently in clinical trials, however, are based on polysaccharide antigens. These suffer from serotype-specificity and poor immunogenicity, and so there is a need for effective vaccines against 35 *S.agalactiae* infection.

It is an object of the invention to provide further and improved GBS vaccines.

## DISCLOSURE OF THE INVENTION

The inventors have realised that saccharide-based vaccines can be improved by using them in  
5 combination with polypeptide antigens, and *vice versa*, such that the polypeptide and the saccharide  
each contribute to the immunological response in a recipient. The combination is particularly  
advantageous where the saccharide and polypeptide are from different GBS serotypes.

The combined antigens may be present as a simple combination where separate saccharide  
and polypeptide antigens are administered together, or they may be present as a conjugated  
10 combination, where the saccharide and polypeptide antigens are covalently linked to each other.

Thus the invention provides an immunogenic composition comprising (i) one or more GBS  
polypeptide antigens and (ii) one or more GBS saccharide antigens. The polypeptide and the  
polysaccharide may advantageously be covalently linked to each other to form a conjugate.

Between them, the combined polypeptide and saccharide antigens preferably cover two or  
15 more GBS serotypes (*e.g.* 2, 3, 4, 5, 6, 7, 8 or more serotypes). The serotypes of the polypeptide and  
saccharide antigens may or may not overlap. For example, the polypeptide might protect against  
serogroup II or V, while the saccharide protects against either serogroups Ia, Ib, or III. Preferred  
combinations protect against the following groups of serotypes: (1) serotypes Ia and Ib, (2) serotypes  
Ia and II, (3) serotypes Ia and III, (4) serotypes Ia and IV, (5) serotypes Ia and V, (6) serotypes Ia and  
20 VI, (7) serotypes Ia and VII, (8) serotypes Ia and VIII, (9) serotypes Ib and II, (10) serotypes Ib and  
III, (11) serotypes Ib and IV, (12) serotypes Ib and V, (13) serotypes Ib and VI, (14) serotypes Ib and  
VII, (15) serotypes Ib and VIII, (16) serotypes II and III, (17) serotypes II and IV, (18) serotypes II  
and V, (19) serotypes II and VI, (20) serotypes II and VII, (21) serotypes II and VIII, (22) serotypes  
III and IV, (23) serotypes III and V, (24) serotypes III and VI, (25) serotypes III and VII, (26)  
25 serotypes III and VIII, (27) serotypes IV and V, (28) serotypes IV and VI, (29) serotypes IV and VII,  
(30) serotypes IV and VIII, (31) serotypes V and VI, (32) serotypes V and VII, (33) serotypes V and  
VIII, (34) serotypes VI and VII, (35) serotypes VI and VIII, and (36) serotypes VII and VIII.

Still more preferably, the combinations protect against the following groups of serotypes: (1)  
serotypes Ia and II, (2) serotypes Ia and V, (3) serotypes Ib and II, (4) serotypes Ib and V, (5)  
30 serotypes III and II, and (6) serotypes III and V. Most preferably, the combinations protect against  
serotypes III and V.

Protection against serotypes II and V is preferably provided by polypeptide antigens.  
Protection against serotypes Ia, Ib and/or III may be polypeptide or saccharide antigens.

Preferably, the immunogenic composition comprises one or more serogroup V antigens or  
35 fragments thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS  
147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358,

GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691. Preferably, the composition comprises a composition of at least two of these GBS antigens or a fragment thereof.

In one embodiment, the immunogenic composition comprises a GBS saccharide antigen and at least two GBS polypeptide antigens or fragments thereof, wherein said GBS saccharide antigen  
5 comprises a saccharide selected from GBS serotype Ia, Ib, and III, and wherein said GBS polypeptide antigens comprise a combination of at least two polypeptide or a fragment thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.

10 Preferably, the combination comprises GBS 80 or a fragment thereof. In one embodiment, the GBS polypeptide antigens comprise a combination of two GBS antigens or fragments thereof selected from the antigen group consisting of (1) GBS 80 and GBS 91, (2) GBS 80 and GBS 104, (3) GBS 80 and GBS 147, (4) GBS 80 and GBS 173, (5) GBS 80 and GBS 276, (6) GBS 80 and GBS 305, (7) GBS 80 and GBS 313, (8) GBS 80 and GBS 322, (9) GBS 80 and GBS 328, (10) GBS 80  
15 and GBS 330, (11) GBS 80 and GBS 338, (12) GBS 80 and GBS 358, (13) GBS 80 and GBS 361, (14) GBS 80 and GBS 404, (14) GBS 80 and GBS 404, (15) GBS 80 and GBS 656, (16) GBS 80 and GBS 690, and (17) GBS 80 and GBS 691.

Still more preferably, the combination is selected from the antigen group consisting of (1) GBS 80 and GBS 338; (2) GBS 80 and GBS 361, (3) GBS 80 and GBS 305, (4) GBS 80 and GBS  
20 328, (5) GBS 80 and GBS 690, (6) GBS 80 and GBS 691 and (7) GBS 80 and GBS 147. Even more preferably, the combination comprises GBS 80 and GBS 691.

In one embodiment, the composition comprises a combination at least three GBS polypeptide antigens. Preferably, this combination comprises GBS 80 and GBS 691.

Preferably, the immunogenic composition further comprises a GBS polypeptide or a  
25 fragment thereof of serogroup II.

### ***The polypeptide antigen***

The polypeptide is preferably: (a) a polypeptide comprising an amino acid sequence selected from the group consisting of the even-numbered SEQ IDs 2-10966 from Ref. 3; (b) a polypeptide comprising an amino acid sequence having sequence identity to an amino acid sequence from in (a);  
30 or (c) a polypeptide comprising a fragment of an amino acid sequence from (a).

Within (a), preferred SEQ IDs are those which encode GBS1 to GBS689 (see Table IV of reference 3).

Within (b), the degree of sequence identity may vary depending on the amino acid sequence (a) in question, but is preferably greater than 50% (*e.g.* 60%, 70%, 80%, 90%, 95%, 99% or more).  
35 Polypeptides within (b) include homologs, orthologs, allelic variants and functional mutants of (a). Typically, 50% identity or more between two proteins is considered to be an indication of functional

equivalence. Identity between proteins is preferably determined by the Smith-Waterman homology search algorithm as implemented in the MPSRCH program (Oxford Molecular), using an affine gap search with parameters *gap open penalty=12* and *gap extension penalty=1*.

5 Within (c), the length of the fragment may vary depending on the amino acid sequence (a) in question, but the fragment is preferably at least 7 consecutive amino acids from the sequences of (a) *e.g.* 8, 10, 12, 14, 16, 18, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more. Preferably the fragment comprises one or more epitopes from the sequence. Other preferred fragments are the N-terminal signal peptides of SEQ IDs 1-10966 from Ref. 3, SEQ IDs 1-10966 from Ref. 3 without their N-terminal signal peptides, and SEQ IDs 1-10966 from Ref. 3 wherein up to 10 amino acid  
10 residues (*i.e.* 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 residues) are deleted from the N-terminus and/or the C-terminus *e.g.* the N-terminal amino acid residue may be deleted.

The polypeptides can, of course, be prepared by various means (*e.g.* recombinant expression, purification from GBS, chemical synthesis *etc.*) and in various forms (*e.g.* native, fusions, glycosylated, non-glycosylated *etc.*). They are preferably prepared in substantially pure form (*i.e.* substantially free from other streptococcal or host cell proteins) or substantially isolated form.  
15

Preferred polypeptide antigens are: GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691, including polypeptides having amino acid sequences with sequence identity thereto *etc.*

20 The nucleotide and amino acid sequences of GBS80 in Ref. 3 are SEQ ID 8779 and SEQ ID 8780. These sequences are set forth below as SEQ ID NOS 1 and 2:

**SEQ ID NO. 1**

ATGAAATTATCGAAGAAGTTATTGTTTTTCGGCTGCTGTTTTAACAATGGTGGCGGGTCAACTGTTGAACCAGTAGCTCAGTTTGC  
GACTGGAAATGAGTATTGTAAAGAGCTGCAGAAGTGTCAAGAACGCCAGCGAAAAACAACAGTAAATATCTATAAATTACAAGCTG  
25 ATAGTTATAAATCGGAAATTAATCTTAATGGTGGTATCGAGAATAAAGACGGCGAAGTAATATCTAACTATGCTAAACTTTGGTGAC  
AATGTAAGAAGGTTTGCAGGTGTACAGTTTAAACGTTATAAAGTCAAGACGGATATTTCTGTTGATGAATGAAAAAATGACAAC  
AGTTGAAGCAGCAGATGCAAAAAGTTGGAACGATTCTTGAAGAAGGTGTACAGTCTACCTCAAAAACTAATGCTCAAGGTTTGGTTCG  
TCGATGCTCTGGATTCAAAAAGTAATGTGAGATACTTGATGTAGAAAGATTAAAGAATTCACCTTCAAAACATTACCAAAGCTTAT  
GCTGTACCGTTTGTGTTGGAATTACCAAGTTGCTAAGTCTACAGGTACAGGTTTCTTCTGAAATTAATATTTACCTAAAAACGT  
30 TGTAACTGATGAACCAAAAACAGATAAAGATGTAAAAAATTAGGTGAGGACGATGCAGGTTATACGATTGGTGAAGAATTCAAAT  
GGTCTTGAATCTACAATCCCTGCCAATTTAGGTGACTATGAAAAATTTGAAATTAATGATGAAATTTGCAGATGGCTTGACTTAT  
AAATCTGTTGGAATAATCAAGATTGGTTCGAAAACACTGAATAGAGATGAGCACTACACTATTGATGAACCAACAGTTGATAACCA  
AAATACATTAATAAATACCTTAAACAGAGAAATTTAAAGAAATTTGCTGAGCTACTTAAAGGAATGACCTTGTAAAAATCAAG  
ATGCTCTTGATAAAGCTACTGCAAAATACAGATGATGCGGCATTTTTGGAATTCAGTTGCATCAACTATTAATGAAAAAGCAGTT  
35 TTAGGAAAAGCAATGAAAAACTTTTGAACCTCAATAATGACCAATACTCTGATAAAGCTGACAAATCCAAAACCATCTAATCCTCC  
AAGAAAACAGAAAGTTCATACTGGTGGGAAACGATTTGTAAGAAAGACTCAAAGAAAACAAACACTAGGTGGTGTGAGTTTGG  
ATTTGTTGGCTTCTGATGGGACAGCAGTAAAAATGGACAGATGCTCTTATTAAGCGAATACTAATAAAAACTATATGCTGGAGAA  
GCTGTTACTGGGCAACCAATCAAATGAAATCACATAAGACGGTACGTTTGGAGATTAAAGGTTTGGCTTATGCAAGTTGATGCGAA  
40 TGCAGAGGGTACAGCAGTAACTTACAAATTAAGAAGAAACAAAGCACCAGAAGGTTATGTAATCCCTGATAAAGAAATCGAGTTTA  
CAGTATCAAAAACATCTTATAATACAAAACCAACTGACATCACGGTTGATAGTGCTGATGCAACACCTGATACAAATTAATAAACAAC  
AAACGTCCTTCAATCCCTAATACTGGTGGTATTGGTACGGCTATCTTTGTCGCTATCGGTGCTGCGGTGATGGCTTTTGTGTTAA  
GGGATGAAGCGTCTACAAAAGATAAC

**SEQ ID NO: 2**

45 MKLSKLLFSAAVLTMVAGSTVPEVPAQFATGMSIVRAAEVQERPAKTTVNIYKLDQADSYKSEITSNNGIENKDGVEVINSYAKLGD  
NVKGLQGVQFKRYKVKTDISVDELKLLTVEAADAKVGTILEEGVSLPQKTNAQGLVVDALDSKSNVRVLYVEDLKNSPSNTTKAY  
AVPFVLELVPVANSTGTGFLSEINIYPKNVVTDPEKTDKDKVKKLQDDAGYTTIGEEFKWFLKSTIPANLGDYEFKFEITDKFADGLTY  
KSVGKIKIGSKTLNRDEHYTIDEPTVDNQNTLKITFKPEKFKEIAELLKGMVLVKNQDALDKATANTDDAAFLVAVASTINEKAV

LGKAIENTFELQYDHTPDKADNPKPSNPPRPKEVHTGGKRFVKKDSTETQTLGGAEFDLLASDGTAVKWTDALIKANTNKNYIAGE  
AVTGPQPIKLKSHDTGTFEIKGLAYAVDANAEGTAVTYKLIKETKAPYVYI PDKELEBFTVSQTSYNTKPTDITVDSADATPDPTIKNN  
KRPSIPNTGGIGTAFVAIGAAVMAFAVKGMKRRTKDN

5 The nucleotide and amino acid sequences of GBS 91 in Ref. 3 are SEQ ID 8937 and SEQ ID  
8938. These sequences are set forth below as SEQ ID NOS 3 and 4:

**SEQ ID NO. 3**

ATGAAAAAGGACAAAGTAAATGATACTAAGCAATCTTACTCTCTACGTAAATAATAAATTTGGTTAGCATCAGTAATTTTAGGGTCA  
10 ATTCATAATGGTCAACAAGTCTGTTTTGCGGATCAAACACATCGGTTCAAGTTAATAATCAGACAGGCACTAGTGTGGATGCTA  
ATAATTCCTTCCAATGAGACAAGTGCCTCAAGTGTGATTACTTCCAATAATGATAGTGTCAAGCGTCTGATAAAGTTGTAATAGT  
CAAAATACGGCAAACAAGGACATTACTACTCTTTAGTAGAGCAAAGCCAATGGTGGAAAAACATTACTGAACAAGGGAAATTA  
TGTTTATAGCAAAGAAACCGAGGTGAAAAATACACCTTCAAAATCAGCCCAGTAGCTTTCTATGCAAAGAAAGGTGATAAAGTTT  
15 TCTATGACCAAGTATTTAATAAAGATAAATGTGAAATGGATTTTCATATAAAGTCTTTTTTGTGGCGTACGTCGATACGCAGCTATTGAG  
TCACTAGATCCATCAGGAGGTTTCAAGACTAAAGCACCTACTCTGTAAACAAATTCAGGAAGCAATAATCAAGAGAAAATAGCAAC  
GCAAGGAAATATATACATTTTACATAAAGTAGAAGTAAAAAATGAAGCTAAGGTAGCGAGTCCAACCTCAATTTACATTGGACAAAG  
GAGACAGAAATTTTTACGACCAAATACTAACTATTGAAGGAAATCAGTGGTTATCTTATAAATCATTCAATGGTGTTCGTCGTTTT  
20 GTTTTGTAGGTAAGCATCTTCAGTAGAAAAAATGAAGATAAAGAAAAAGTGTCTCCTCAACCAAGCCCGTATTACTAAAAAC  
TGGTAGACTGACTATTTCTAACGAAACAACACTACAGGTTTTGATATTTAATTAAGAATATAAAGATGATAACGGTATCGCTGCTG  
TTAAGGTACCGTTTTGGACTGAACAAGGAGGCAAGATGATATTAATGGTATACAGCTGTAACTACTGGGGATGGCAACTACAAA  
GTAGCTGTATCATTTGCTGACCATAGAATGAGAAGGGTCTTTAATAATTCATTTATACTACCAAGAAGCTAGTGGGACACTTGT  
AGGTGTAACAGGAACTAAAGTGACAGTAGCTGGAACCTAATCTTCTCAAGAACCTATGAAAAATGGTTTAGCAAAGACTGGTGT  
25 AATAATATTATCGGAAGTACTGAAGTAAAAAATGAAGCTAAAAATCAAGTCAGACCCAATTTACTTTAGAAAAAGGTGACAAAATA  
AATTATGATCAAGTATTGACAGCAGATGGTTACCAAGTGGATTTCTTACAATCTTATAGTGGTGTTCGTCGCTATATTCCTGTGAA  
AAAGCTAACTACAAGTAGTGAAGGCGAAAGATGAGGCGACTAAACCGACTAGTTATCCCAACTTACCTAAAAAGGTACCTATA  
CATTTACTAAAACTGTAGATGTGAAAAGTCAACCTAAAGTATCAAGTCCAGTGGAAATTTAATTTTCAAAGGGTGAAAAATAACAT  
TATGATCAAGTGTTAGTAGTAGATGGTATCAGTGGATTTTCATACAAGAGTTATTTCCGGTATTTCGTCGCTATATTGAAATT

**SEQ ID NO. 4**

MKKQGVNDTKQSYSLRKYKFGLASVILGSFIMVTPSPVFADQTTTQVNNQGTSTVDANNSSNETSASSVI TSNNDVQASDKVNS  
30 QNTATKDIITPLVETKPMVEKTLPEQGNVYVSKETEVKNTPSKSPVAFYAKKGDVFDQVFNKDNVWVSYKSFVGRVYAAIE  
SLDPGSGSETKAPTPTVNSGNNQEKIATQGNVYFVSHKVEVKNEAKVASPTQFTLDKGDRIFYDQILTIENQWLSYKSFNGVRRF  
VLLGKASSVEKTEDKEKVSPPQARI TKTGRLTISNETTTGFDILLI TNIKDDNGIAAVKVPVWTEQGGQDDIKWYTAVTGDNKY  
VAVSFADHKNEKGLYNIHLYQEAAGTLVGVGTGKVTVAGTNSQEP IENGLAKTGVIYNIIGSTEVKNEAKISSQQTFTLEKGDKI  
25 NYDQVL TADGYQWISYKSYSGVRRYI PVKLLTTSSEKAKDEATKPTSYPNL PKTGTVYFTTKTVDVKSQPKVSSPVEFNFQKGEKIH  
YDQVLVVDGHWISYKSYSGIRRYIEI

The nucleotide and amino acid sequences of GBS 104 in Ref. 3 are SEQ ID 8777 and SEQ  
ID 8778. These sequences are set forth below as SEQ ID NOS 5 and 6:

**SEQ ID NO. 5**

ATGAAAAAGAGACAAAAATATGGAGAGGGTTATCAGTTACTTTACTAATCCTGTCCAAATTCATTTGGTATATTGGTACAAGG  
40 TGAACCCCAAGATACCAATCAAGCAC TTGAAAAAGTAATGTTAAAAAACCGGGAGACAATGCTACACCATTAGGCAAAGCGACTT  
TTGTGTTAAAAAATGACAATGATAAGTCAAGAAACAAGTCA CGAAACCGGTAGAGGGTTCTGGAGAAGCAACCTTTGAAAAATAAAA  
CCTGGAGACTACACATTAAGAGAAGAAACAGCACCAATTTGGTTA TAAAAAACTGATAAAAACCTGGAAAGTTAAAGTTGCAGATAA  
45 CGGAGCAACAATAATCGAGGGTATGGATGCAGATAAAGCAGAGAAA CGAAAAGAAGTTTGAATGCCCAATATCCAAAATCAGCTA  
TTTATGAGGATACAAAAGAAATTAACCCATTAGTTAATGTAGAGGGTTCCAAAAGTTGGTGAACAATAACAAGCATTGAATCCAATA  
AATGAAAAAGATGGTCAAGAGAGATTGCTGAAGGTTGGTTATCAAAAAAATACAGGGGTCAATGATCTCGATAAGAAATAAATA  
50 TAAAATTGAATTAACCTGTTGAGGGTAAAAACCACTGTTGAAACGAAAGAACTTAATCAACCACTAGATGTCGTTGTGCTATTAGATA  
ATTCAAATAGTATGAATAATGAAAGAGCCAATAATCTCAAAGAGCATTA AAAAGCTGGGGAAGCAGTTGAAAAGCTGATTGATAAA  
AATTACATCAATAAAGACAATAGAGTAGCTCTTGTGACATATGCCTCAACCATTTTGGATGGTACTGAAGCCACCGTATCAAAGGG  
AGTTGCCGATCAAAATGGTAAAGCGCTGAATGATAGTGTATCATGGGATTA TCATAAACTACTTTTACAGCAACTACACATAATT  
55 ACAGTTATTTAAATTTAACAAATGATGCTAACGAAAGTTAATATTCTAAAGTCAAGAAATTCCAAAGGAAGCGGAGCATATAAATGGG  
GATCGCACGCTCTATCAATTTGGTGCAGCATTTACTCAAAAAGCTCTAATGAAAGCAAAATGAAATTTTAGAGACACAAAGTTCTAA  
TGCTAGAAAAAACTATTTTTACGTAACCTGATGGTGTCCCTACGATGCTTATGCCATAAAATTTAATCCTTATATATCAACAT  
60 CTTACCAAAACCAAGTTAATCTTTTTTAAATAAATAACGATAAGAAAGTGGTATTCTCAAAGAGGATTTTATAATCAATGGTGTGAT  
GATTATCAAAATAGTAAAGGAGATGGAGAGAGTTTTAAACTGTTTTCGGATAGAAAAGTTCCTGTTACTGGAGGAACGACACAAGC  
55 AGCTTATCGAGTACCGCAAAATCAACTCTCTGTAATGAGTAATGAGGGATATGCAATTAATAGTGGATATATTTATCTCTATTGGA  
GAGATTACAACCTGGGTCTATCCATTTGATCCTAAGACAAGAAAGTTTCTGCAACGAAAACAAATCAAAAACCTCATGGTGAGCCAACA  
ACATTTACTTTAATGGAAATAAAGACCTAAAGGTTATGACATTTTTTACTGTTGGATTGGTGTAAACGGAGATCCTGGTCAAC  
TCCTCTTGAAGCTGAGAAATTTATGCAATCAATATCAAGTAAAAACAGAAAATTTATACTAATGTTGATGATACAAAATAAAATTTATG  
60 ATGAGCTAAAATAAATACTTTAAAACAATTTGTTGAGGAAAAACATTTCTATTGTTGATGAAAATGTGACTGATCCTATGGGAGAGATG  
ATTGAATTCCAATTA AAAAATGGTCAAAGTTTTACACATGATGATACGTTTTGGTTGGAAATGATGGCAGTCAATTA AAAAATGG  
TGTGGCTCTTGGTGGACCAACAGTGTGAGGGGAAATTTAAAAGATGTTACAGTGACTTATGATAAGACATCTCAAACCATCAAAA

5 TCAATCATTTGAACTTAGGAAGTGGACAAAAGTAGTCTTACCTATGATGTACGTTTAAAAGATAACTATAAAGTAAACAAATTT  
 TACAATACAAATAATCGTACAACGCTAAGTCCGAAGAGTGAAAAAGAACCAAATACTATTCGTGATTTCCCAATTCACAAAATTCG  
 TGATGTTTCGTGAGTTTCCGGTACTAACCATCAGTAATCAGAAGAAAATGGGTGAGGTTGAATTTATTAAGTTAATAAAGACAAAC  
 ATTCAGAATCGCTTTTGGGAGCTAAGTTTCAACTTCAGATAGAAAAGATTTTCTGGGTATAAGCAATTTGTTCCAGAGGGAAGT  
 10 GATGTTACAACAAAGAATGATGGTAAAAATTTATTTTAAAGCACTTCAAGATGGTAACTATAAAATATATGAAATTTCAAGTCCAGA  
 TGGCTATATAGAGGTTAAAACGAAACCTGTTGTGACATTTACAATTCAAAATGGAGAAGTACGAACTCGAAAGCAGATCCAAATG  
 CTAATAAAAATCAAAATCGGGTATCTTGAAGGAAATGGTAAACACTCTTATTACCAACACTCCCAAACGCCACCGAGGTTTTCCT  
 AAAACAGGGGAATGGTACAATGTCTATATAATTAGTTGGTCTACTTTTATGATACTTACCATTGTCTTTCCTCGTAAACA  
 ATTG

10 SEQ ID NO. 6

15 MKKRQKIWRGLSVTLILLSQIPFGILVQGETQDTNQLGKVIKKTGDNATPLGKATFVLKNDNDKSETSHETVEGSGEATFENIK  
 PGDYTLREFTAPIGYKTKDKWVKVADNGATTIEGMDADKAEKRKEVLNAQYPKSAIYEDTKENYPLVNVVSGSKVGEQYKALNPI  
 NGKDGREIAEGWLSKKITGVNDLDKNKYKIELTVEGKTTVETKELNQPLDVVLLDNSNSMNERANNSQRALKAGEAVEKLDIK  
 20 DRTLYQFGAFTTQKALMKANEILETQSSNARKKLI FHVTDGVPTMSYAINFPNPISTSYQNQFNSFLNKIPDRSGILQEDFIINGD  
 DYQIVKGDGSEFKLFSDRKVPVTTGGTQAA YRV PQNQLS VMSNEGYA INSGYI YLYWRDYNWVY PFDPKTKKVSATKQIKTHGEPT  
 TLYFNGNIRPKGYDIFTVGIVGNDP GATPLEAEKFMQSISSKTENYTNVDDTNKIYDELNKYFKTIVEEKHSIVDGNVTDPMGEM  
 IEFQLKNGQSFTHDDVVLVGNDSQLKNGVALGPNSDGGILKDVITTYDKTSQTIKINHLNLGSGQKVVLTVDVRLKDNYSINKF  
 25 YNTNMRNTTLLSPKSEKEPNTIRDFPIPKIRDVREFVLTISNQKKMGEVEFIVKNDKHSESLGAKFQLQLEKDFS GYKDFVPEGS  
 DVTTKNDGKIYFKALQDGNLYEISSPDGYIEVKTTPVVTFTIQNGEVTNLKADPNANKNQIGYLEGNGKHLITNTPKRPPGVFP  
 KTGIGITTVILVGSFTMILTICSFRRKQL

25 The nucleotide and amino acid sequences of GBS 147 in Ref. 3 are SEQ ID 8525 and SEQ  
 ID 8526. These sequences are set forth below as SEQ ID NOS 7 and 8:

SEQ ID NO. 7

30 GTGGATAAACATCACTCAAAAAGGCTATTTTAAAGTTAACACTTATAACAAC TAGTATTTATTAATGCATAGCAATCAAGTGAATGCAGAGGAG  
 CAAGAATTA AAAAACCAAGAGCAATCACCTGTAATGCTAATGTTGCTCAACAGCCATCGCCATCGGTA ACTACTAATACTGTTGAAAAACATCT  
 GTAACAGCTCCTCTGCTAGTAATACAGCGAAAAGAAATGGGTGATACATCTGTAAAAAATGACAAAA CAGAAGATGAATTTATAGAAGAGTTATCT  
 35 AAAAACTTGATACGCTCTAATTTGGGGGCTGATCTGAAGAGAATATCCCTCTAAAC CAGAGACAACCAACAATAAAGAAAGCAATGTAGTAACA  
 AATGCTTCAACTGC AATAGCACAGAAAGTCCCTCAGCATATGAAGAGGTGAAGCCAGAAGCAAGT CATCGCTTCTGTTCTTGATACATCTAAA  
 ATAACAAAATTA CAGCCATAAGCCAAACCCAAAGAGGAAATGTAGTAGCTATTTATGATACTGGCTTTGATATTAACCATGATTTTTCTGTTTA  
 GATAGCCAAAAGATGATAAGCACAGCTTTAAA ACTAAGACAGAATTTGAGGAATTTAAAGCAAACATAATATCACTTATGGGAAATGGGTTAAC  
 40 GATAAGATTTGTTTTGCACATAACTACGCCAA CAATACAGAAACGGTGGCTGATATTCAGCAGCTATGAAAGATGGTTATGTTT CAGAAGCAAG  
 AATATTTCCGATGGTACACACGCTTGGTGGTATTTTGGTAGGTAATAGTAAACCTCAGCAATCAATGGTCTCTTTTAGAAGGTGCAGCGCCAAAT  
 GCTCAAGTCTTATTAATCGGTATTCAGATAAAAATGATTTCGGACAAAATTTGGTGAAGCATATGCTAAAGCAATCACAGACGCTGTTAATCTAGGA  
 45 GCAAAAACGATTAATATGAGTATGGAAAACAGCTGATTCTTTAATTGCTCTCAATGATAAAGTTAATTAGCAC TTAATTAGCTTCTGAGAAG  
 GCGCTTGCAGTTGTGTGGCTCCCGAAATGAAGCGCATTTGGTATGAGTATATAGCAAACCATTA TCACTAATCCTGACTACGGTACCGTTAAT  
 AGTCCAGTATTTCTGAAGTACTTTGAGTGTGCTAGCTATGAATCACTTAAAACTATCAGTGAGGTCGTTGAAAACAACATTTGAAGGTAAAGTTA  
 50 GTTAAGTTGCCGATTTGTGACTTCTAAACCTTTTGACA AAGGTAAAGCCCTACGATGTGGTTTATGCCAATFATGGTGC AAAAAAAGACTTTGAGGT  
 AAGGACTTTAAAGGTAAGATTGCATTAATGAGCGTGGTGGTGGACTTGATTTTATGACTAAAATCACTCATGCTACAAATGCAGGTGTTGTTGGT  
 ATCGTTATTTTAAACGATCAAGAAAACCTGGAAATTTCTAATTCCTTACCGTGAATTA CCGTGGGGATTATAGTAAAGTAGATGGCCAGCGT  
 55 ATAAAAAATACTCAAGTCAGTTAACATTTAAC CAGAGTTTGAAGTAGTTGATAGCCAAGGTGGTAAATCGTATGCTGGAACAATCAAGTTGGGGC  
 GTGACAGCTGAAGGAGCAATCAAGCTGATGTAACAGCTTCTGGCTTTGAAATTTATTTCTTCAACCTATAATAATCAATACCAAA CAATGTCTGGT  
 ACAAGTATGGCTTCA CCAACATGTTGCAGGATTAATGACAATGCTTCAAAGTCAATTTGGCTGAGAAATAAAAAGGGATGAATTTAGATTTCTAAAAA  
 TTGCTAGAATTTGCTAAAACATCCTCATGAGCTCAGCAACAGCATTATATAGTGAAGAGGATAAGGCGTTT TATTACCACGTCAGCAAGGTGCA  
 60 GGTGTAGTTGATGCTGAAAAAGCTATCCAGCTCAATATTAATTACTGGAACCGATGGCAAAGCTAAAATTAATCTCAAACGAAATGGGAGATAAA  
 TTTGATATCACAGTCAAAATTCATAA ACTTGTAGAAGGTGTCAAAAGAAATTTGATTAATCAAGCTAATGTAGCAGCAACAGCAATAAAGGTA  
 TTTGCCCTTAAAACCAAGCCTTGCTAGATACTAATTTGCCAGAAAGTAATTTCTCGTGATAAAGAAACACAAGTTCGATTTACTATTGATGCTAGT  
 65 CAATTTAGTCAGAAATTAAGAAGACAGATGGCAAATGGTATTTCTTAGAAGGTTTGTACGTTT TAAAGAGCCAAAGGATAGTAATCAGGAGTTA  
 ATGAGTATTCCTTTGFPAGGATTTAATGGTGAATTTGCGAACTTACAAGCATTGAAACACCGATTTATAAGACGCTTCTAAAGGTAGTCTTAC  
 TATAAACCAAATGATACAACCTATAAAGCAAATGGAGTACAATGAATCAGTCTCCTTTTGAAGCAACAACATATACCTGCTTGTAAACAATCA  
 CGCTCTTGGGGCTATGTTGATTTATGTC AAAAATGGTGGGGAGTTAGAATTAGCACCGGAGAGTCCAAAAGAAATTTT TAGGAACTTTGAGAAT  
 AAGGTTGAGGATAAAAACAAATTCATCTTTTGGAAAAGAGATGCAGCGAATAATCATATTTTGCCATTTCTCAAATAAAGATGGAATAGGGACGAA  
 70 ATCACTGCCAGGCAACTTCTTAAGAAATGTTAAGGATATTTCTGCTCAAGTCTAGATCAAATGGAAATGTTATTTGGCAAAGTAAGGTTTTA  
 CCATCTTATCGTAAAAATTTCCATAATAATCAAAGCAAAGTGATGGTCATTAATCGTATGGATGCTCTTCAGTGGAGTGGTTTAGATAAGGATGGC  
 AAAGTTGTAGCAGATGTTTATATACTTATCGCTTACGTTACACACCGTAGCAGAAGGAGCAATAGTCAGGAGTCAGACTTTAAAGTACAAGTA  
 AGTACTAAGTCACCAAATCTTCTT CACGAGCTCAGTTTGTAGTAAACTAATCGAACATTAAGCCTTAGCCATGCCTAAGGAAAGTAGTTATGTTCT  
 ACATATCGTTTACAATTAGTTTATCTCATGTTGTA AAGATGAAGAATATGGGGATGAGACTTCTTACCATTATTTCCATATAGATCAAGAAGGT  
 75 AAAGTGACACTTCTTAAACCGTTAAGATGAGGAGAGTGAAGGTTGCGGTAGAACCTAAGGCCCTTGACACTTGTGTGGAAGATAAAGCTCGTAAT  
 TTCGCAACCGTAAATTTGCTGATCTCTTGAATAGGCAGTAGTATCAGAAAAGAAACCGCTATAGTAATTTCTAACAGTTC AATATTTGAT  
 AACTTGAAAAAAGAACCTATGTTTATTTCTAAA AAGAAAAGTAGTAAAACAAGAAATCTAGAAGAAAATAATAGTTAGTAGCCGCAAACTACAGT  
 ACTACTCAATCATTTGCTTAAAGAAAATAACTAAAATCAGGAAATGAGAAAGTCCCTCACTTCTACAACAATAATAGTAGCAGAGTAGCTAAGATCATA  
 TCACCTAAACATAACGGGGATTCTGTTAACCATACCTTACCTAGTACATCAGATAGAGCAACGAATGGTCTATTTGTTGGTACTTTGGCATTGTTA  
 TCTAGTTTACTTCTTTATTTGAAACCCAAAAGACTAAAATAATAGTAAA

SEQ ID NO. 8

VDKHSHKAILKLTITTSILLMHSNQVNAEBEQELKNQEQSPVIANVAQQPSPSVTINTVEKTSVTAASASNTAKEMGDTSVKNDKTEDELLEELS  
 KNLDTSNLGDLEEEYPSKPEPTNNKNESVNVNASTAIAQKVP SAYEBVKPESKSSLA VLDTSKI TKLQAITQRGKGNVVAI IDTGF DINHDI FRL

DSPKDDKHSFKTKTEFEELKAKHNI TYGKWNNDKI VFAHNYANNETVADIAAAMKDGYSSEAKNI SHGTHVAGI FVGNKRPAINGLLEGAAPN  
 AQVLLMRI PDKIDSDKFGGEAYAKAITDAVNLGAKT INMSIGKTADSLIALNDKVKLALKLASEKGVAVVVAAGNRGAFMGDYSKPLSTNPDYGTWN  
 SPAISEDLSVASYESLKI I SEVVETTI EGKLVKLP I VTSKPFDKGKAYDVVYANYGAKKDFEGKDFKGI ALI ERGGGLDFMTKI THATNAGVVG  
 5 I VI FNDQEBKRGNF LI PYRELPVGI I SKVDGERI KNTSSQLTFNQSFVVD SQGGNRMLEBQSSWGVTAEGA I KPDVTASGFEI YSSYNNQYQTMG  
 TSMASPHVAGLMTMLQSHLAEKYKGMNLDKLLLELSKNI LMSATALYSEEDKAFYS PRQQGAGVVDAAEKA IQAQYYITGNDGKAKINLKRMDK  
 PDITVTI HKLVEGVKELYQANVATEQVNWKGFKALKPQALLDNTWQKVI LRDKETQVRFTI DASQFSQKLEQMANGYFLEGFVRFKEAKDSNOEL  
 MSIPFVGFNGDFANLQALETP I YKFLSKGSFY YKPNDDTHKDQLEYNESAPFESNNYTALLTQSASWGYVDYVKNNGELELAPESPKRI I LGTFEN  
 10 KVEDKTI HLLERDAANNPYFAI SPNKDGNRDEITPQATFLRNVDI SAQVLDQNGNVI WQSKVLP SYRKNFHNPKQSDGHYRMDALQWSGLDKDG  
 KVVADGFYTYRLRYTPVAEGANSQESDFKQVSTKSPNLPSRAQFDETNRLSLAMPKESYVPTYRLQLVLSHVVKDEEYGDETSYHYFHIDQEG  
 KVTLPKTVKI GESEVAVDPKALT LVVEDKAGNFATVKLSDLLNKAVVSEKENA I VINSFKYFDNLKKEPME I SKKEKVVKNKLEBI I LVKPKQTTV  
 TTQSLSKBITKSGNEKVLSTNNNSSRVAKI I SPKHNGDSVNHTLPSTSDRATNGLFVGTLLALLSSLLLYLKP KTKNNK

The nucleotide and amino acid sequences of GBS 173 in Ref. 3 are SEQ ID 8787 and SEQ ID 8788. These sequences are set forth below as SEQ ID NOS 9 and 10:

15 **SEQ ID NO. 9**

ATGAAACGTAAACTTTATCTTAATACGGTGACGGTTTTAACGTTAGCTGCTGCAATGAATACTAGCAGTATCTATGCTAATAGTACTGAGACA  
 AGTGCCTCAGTAGTCTCTACTACAATACTATCGTTCAAAC TAATGACAGTAATCCTACCGCAAATTTGTATCAGAATCAGGACAATCTGTAATA  
 GGTCAAGTAAAAACAGATAAATCTGCGGCGCTTACAACAGTTGACACGCCCTCATCATATTCAGCTCCAGATGCTTTAAAAACAACCTCAATCAAGT  
 20 CCTGTCGTTGAGAGTACTTCTACTAAGTTAACTGAAGAGACTTACAAACAAAAGATGGTCAAGATTAGCCAAACATGGTGAGAAGTGGTCAAGTT  
 ACTAGTGAGGAACCTGTTAATATGGCATAACGATATTAATGCTTAAAGAAAACCCATCTTTAAATGCAGTCATTACTAGACGCCAAGAAGCTATT  
 GAAGAGGCTAGAAAACCTTAAAGATACCAATCAGCCGTTTTTAGTGTTCCTTTGTTAGTCAAGGGGTTAGGCGACAGTATTAAGGTTGTAACCC  
 AATAATGGCTTGATCTATGCAGATGGAAAATTAGCACATTTGACAGTAGCTATGTCAAAAATATAAAGATTTAGGATTTATATTTTAGGACAA  
 ACGAATCTTCCAGAGTATGGTGGCGTAATATAACAGATTCTAAATATACGGTCTAACGCATAATCCTTGGGATCTTGCTCATAATGCTGGTGGC  
 TCTTCTGGTGGAGTGAGCAGCAGCCATTTGCTAGCGGAATGACGCCAATTTGCTAGCCGTAAGTGTATGCTGGTGGTCTATCCGATTTCCATCTTCTTGG  
 25 ACGGCTTGGTAGGTTTAAACCAACAAGAGGATTGGTGAGTAATGAAAGCCAGATTCGTATAGTACAGCAGTTCATTTCCATTAAGTAACTAAGTCA  
 TCTAGAGACGCAGAAACATTTAATCTTATCTAAAGAAAAGCGATCAAACGCTAGTATCAGTTAATGATTTAAAACTTTACCAATTTGCTTATACT  
 TTGAAATCACC AATGGGACAGAAAGTTAGTCAAGATGCTAAAACGCTATTATGGACAACGTCACATCTTAAGAAAACAAGGATTCAAAGTAAACA  
 GAGATAGACTTACCAATTGATGGTAGAGCATTAAATGCGTGATTTTCAACCTTGGCTATGGCATGGGAGGAGCTTTTTCAACAATTTGAAAAGAC  
 TTAATAAACAATGGTTTTACTAAAGAAAGCGTTGATCCTATTACTTGGGCGTTCATGTTATTTATCAAAATTCAGATAAGGCTGAACCTTAAGAAA  
 30 TCTATTATGGAAGCCCAAAAACATATGGATGATTTATCGTAAGGCAATGGAGAGCTTCAACAAGCAATTTCCATTTTCTTATCGCCACACGCCGCA  
 AGTTTTAGCCCTCTAAATACAGATCCATATGTAACAGAGGAAAGATAAAAAGAGCGATTTATAATATGGAAAACCTTGAGCCAAAGAAAGAAATGCT  
 CTCTTAAATCGCCAGTGGGAGCCTATGTTGCGTAGAACACCTTTTACACAAATGCTAATATGACAGGACTCCAGCTATCAGTATCCCGACTTAC  
 TTATCTGAGTCTGGTTTACCATAGGGACGATGTTAATGGCAGGTGCAAACTATGATATGGTATTAATTAATTTGCAACTTTCTTTGAAAACAT  
 CATGTTTTAATGTTAAATGGCAAAAGATAAATAGATAAAGAAGTGAACCTTACTGGCCTAATAACAGCCTTAACTTCTTTAAAGCTCAT  
 35 TCACTATTAGTAAATTTAGAAGAAATTCACAAGTTACTCAAGTATCTATCTTAAAAAATGGATGAAATCGTCTGTTAAAAATAAACCATCCGTA  
 ATGGCATATCAAAGCACTTCTTAAAAACAGGTGATACAGAAATCAAGCCTATCTCCAGTTTTAGTAGTAACCTTTTATAGCTTGTTTTAGCTTT  
 GTAACAAAAGAAATCAGAAAAGT

**SEQ ID NO. 10**

MKRKYFI LNTVTVLTLAAMNTSSI YANSTETASVVPNTNT I VQINDSNPTAKFVSESGQSVI QVVKPDNSAALTTVDTPHHI SAPDALKITQSS  
 PVVESTSTKLTEETYKQKDGQDLANMVRSGQVTSEELVNMAFYI IAKENPSLNAV I TTRQEA I BEARKLKDNTNQPFLGVPLLVKGLGHSI I KGGET  
 NNGLI YADGKI STFDSSYVVKYKDLGFI I LGQTNFPPEYGRWNI TDSKLYGLTHNPWDLAHNAGSSGGSAAA I ASGMT P I ASGSDAGGSI I RI PSSH  
 TGLVLKPTRGLVSNKPDYSYTAHVHFPITKSSRDAETLLTYLKKSDQTLVSVNDLKLSP I IAYTLKS PMGTBVSQDAKNA IMDNVTFLRKQGFKVT  
 40 EIDLPI DGRALMRDYSTLAI GMGAFST I BKDLKKGFTKEDVDP I TWAVHVI YQNSDKAELKKS I MBEAQKHMDYR KAMEKHLKQFP I FLSPTTA  
 SLAPLNTDYPVTEBCKRAIYNMENLSQEER I ALFNQRQWEPMLRRTPFTQIANMTGLPAI S I PLYLSEGLPI G TMLMAGANYDMVLI KFAITFFBKH  
 45 HGFNVKQRI I DKEVKPSTGLI QPTNSLFPKAHSSLVNLNLEENSQVTQVSI SKKWKMSVKNKPSVMAYQKALPKTGDTESSLSPVLVVTLLLACFSF  
 VTKKNQKS

The nucleotide and amino acid sequences of GBS 276 in Ref. 3 are SEQ ID 8941 and SEQ ID 8942. These sequences are set forth below as SEQ ID NOS 11 and 12:

50 **SEQ ID NO. 11**

TTGCGTAAAAACAAAACACTACCATTGATAAACTTGCCATTGCGCTTATATCTACAGGATCTTGCTCAATGCACAATCAGACATTAAGCAAAT  
 ACTGTGACAGAAGACACTCCTGCTACCGAACAAGCCGTAGAACCCCAACCAATAGCAGTTTCTGAGGAATCAGCATCATCAAAGGAAACTAAA  
 55 ACCTCAAAACTCCTAGTGATGATAGGAGAAACAGTAGCAGATGACGCTAATGATCTAGCCCTCAAGCTCCTGCTAAAACCTGCTGATACACCAGCA  
 ACCTCAAAAGCGACTATTAGGATTGAAACGACCCCTTCTCATGTCAAACCTGACAGGAAAAAGCAGGCAAGGAGCTGGGACCGTTGTTGCAGTG  
 ATTGATGCTGTTTTGATAAAAATCATGAAGCGTGGCGCTTACAGACAAAACCTAAAGCAGTTACCAATCAAAGAAAATCTTGAAAAGCTAAA  
 AAAGAGCACGGTATTACCTATGGCAGTGGGTCAATGATAAGGTTGCTTATTACCAGACTATAGTAAAGATGGTAAAAACGCTGTTGATCAAGAA  
 CACGGCACACAGCTGTGAGGATCTTGTGAGGAAATGCTCATCTGAAATGAAAGAACCTTACCGCTTAGAAGGTGCGATAGCCTGAGGCTCAATTG  
 60 CTTTTGATGCGTGTGCAAAATGTAATGGACTAGCAGACTATGCTCGTAACTACGCTCAAGCTATCAGAGATGCTGTCAACTGGGAGCTAAGGTG  
 ATTAATATGAGCTTTGTTAATGCTGCACTAGCTTACGCCAACCTTCCAGACGAAACAAAAGGCTTTGACTATGCCAAATCAAAGGTTGTTAGC  
 ATTTGTGACCTCAGCTGGTAAATGATAGTAGCTTTGGGGGCAAGCCCGCTCACTCTAGCAGATCATCTGATTTATGGGGTGGTGGGACCTGCA  
 CGCGCAGATTCACATTCACAGTTGCTTCTTACAGCCAGATAAACCTCACTGAAAACCTGCTACGGTCAAAAACAGAGCATCATCAAGATAAAGAA  
 ATGCTGTTATTTCAACAACCGTTTTGAGCCAAACAAGGCTTACGACTATGCTTATGCTAATCGTGTACGAAAGAGGATGATTTTAAAGATGTC  
 GAAGTAAAGATTGCCCTTATTGAACGTGGCGATATTGATTTCAAAGATAAGATTGCAACGCTAAAAAGCTGGTGTGCTAGGGGCTTGTATCAT  
 65 GACAATCAAGACAAGGCTTCCCGATTGAATGCAAAATGTTGACAGATGCTCGCCGCTTTATCAGTCAAGAGAGACGCTCTTATTAAGAGAC  
 AATCCCCAAAACCAATTAACCTCAATGCGACACCTAAGGTATTGCCAACAGCAAGTGGCACCACCAACTAAGCCGCTTCTCAAGCTGGGGTCTGACA  
 GCTGACGGCAATATTAAACCGGATATTGACGACCCCGCCCAAGATATTTGTCATCAGTGGCTAAACAACAGTATGCCAAACTTTCTGGAAGTATG  
 ATGCTGACCATTTGCTAGCGGATCATGAGACTGTTGCAAAAGCAATATGAGACACAGTATCCTGATATGACACCATCAGGCTCTTGATTTA  
 GCTAAGAAAGTATTGATGAGCTCAGCACTGCCCTATATGATGAAGATGAAAAGCTTATTTTTCTCTCGCCACAGGAGCAGGAGCAGTGCAT



GCTAAAAAGCTTCAGCAGCAACGATGTATGTAAACAGATAAGGACAATACCTCAAGCAAGGTTCACTGAACAATGTTTCTGATAAAATTTGAAGTA  
 ACAGTAACAGTTTCAACAACTCTGATAAACCTCAAGAGTTGTATTTACCAAGTAACTGTTCAAACAGATAAAGTAGATGGAAAAACACTTTGCCTTG  
 GCTCCATAAGCATTTGATGAGACATCATGGCAAAAAATCACAATTCAGCCAATAGCAGCAAAACAGTACCAGTTCCAATCGATGCTAGTCCGATTT  
 5 AGCAAGGACTTGCTTGCCCAAATGAAAAATGGCTATTTCTTAGAAGGTTTTGTTCGTTTCAAACAAGATCCCTACAAAAGAAGAGCTTATGAGCATT  
 CCATATATTTGGTTTCCGAGGTGATTTTGGCAATCTGTGAGCTTAGAAAAACCAATCTATGATAGCAAAAGACGGTAGCAGCTACTATCATGAAGCA  
 AATAGTGATGCCAAAGACCAATTAGATGGTGATGGATTACAGTTTTACGCTCTGAAAAATAACTTTACAGCAGCTTACCACAGAGTCTAACCCATGG  
 ACCGATTTATAAGCTGTCAAAGAAGGGGTTGAAAAACATAGAGGATATCGAATCTTCAGAGATCACAGAAACCAATTTTTCAGGTTACTTTTGCAAAA  
 CAAGACGATGATAGCCACTACTATATCCACCGTACGCTAATGGCAAAACCAATATGCTGCGATCTTCCAAATGGGGACGGTAAACAGAGATTATGTC  
 10 CAATTCAGGTTACTTTCTTGGTAATGCTAAAAACCTTGTGGCTGAAGTCTTGGACAAAGAAGGAAAATGTTGTTTGGACAAGTGAGGTAACCGAG  
 CAAGTTGTTAAAACTACAAATGACTTGGCAAGCACACTTGGTTCAACCCGTTTTGAAAAACCGGTTGGGACGGTAAAGATAAAGACGGGCAA  
 GTTGTGCTAACGGAACCTACCTATCGTGTTCGCTACACGCCGATTAGCTCAGGTGCAAAAGAACAACACTGATTTTGTATGTGATTTGTAGAC  
 AATACGACACCTGAAGTCGCAACATCGGCAACATTTCTCAACAGAAAGATAGTCGTTTGCACACTTGCACTTAAACCAAAAACCGCAACCGGTTTAC  
 CGTGAGCGTATTTGCTTACTTATATGGATGAGGATCTGCCAACACAGAGTATATTTCTCCAATGAAGATGGTACCTTTACTCTTCTCTGAAGAG  
 15 GCTGAACAATGGAAGCGCTACTGTTCCATTGAAAAATGTCAGACTTTACTTATGTTGTAAGATATGGCTGGTAAACATCACTTATACACCGAGT  
 CTAAGCTATTTGGAGGGCCACTCTAATAAGCCGAAACAAGCGGTTAGATCAAGCACCAGCAAGAAACCAAGGCTAAACAGAAACAAGACCGGT  
 TCAGGTCAAACAGATAAAAAAGAACTAAACAGAAAAAGATAGTTTCAAGTCAAACACAGGTAACCTCTCAAAAAGGTCAATCTTCT  
 CGTACTCTAGAGAACGATCTTCTAAGCGTGTCTTAGCTACAAAAGCATCAACAGAGATCAGTTACCAACGACTAATGACAAGGATACAAATCGT  
 TTACATCTCCTTAAGTTAGTTATGACCACCTTCTTCTTGGGA

20 SEQ ID NO. 12

MRKKQKLPFDKLAIALISTSIILLNAQSDIKANTVTEPTATEQAVEPQPIAVSEESRSKSKETKTSQTPSDVGETVADDANDLAPQ  
 APAKTADTPATSKATIRDLNDP SHVKTLEKAGKAGT VVAVIDAGFDKNHEAWRLTDKTKARYQSKENLEKAKKEHGIYGEWVN  
 DKVAYYHDYKDGKNAVQEHGTHVSGILSGNAPSEMKEPYRLEGAMPEAQLLLMRVEIVNGLADYARNYAQAIRDAVNLGAKVIN  
 25 MSFGNAALAYANLPDETKKAFDYAKSKGVSIVTSAGNDSFSGGKRLPLADHPDYGVVGTAAADSLTVAASYSPDKQLTETATVK  
 DDDHQDKEMPVISTNRFEPNKAYDYAYANRGTKEDDFKDVVEGKIALIERGDIIDFKDKIANAKKAGAVGVLIYDNQDKGFPIELPNV  
 DQMPAAFI SRRDGLLLKDNPKTITFNATPKVLPASGTLKSRFSSWGLTADGNIKPDIAPGQDILSSVANNKYAKLSGTSMSAP  
 LVAGIMGLLQKQYETQYPMTPSERL DLAKKVLMSATALYDEDEKAYFSPRQGGAGAVDAKKASAATMYVTDKNTSSKVLHNNV  
 SDKFEVTVTVHNSDKPQELYYQVTVQTDKVDGKHFALAPKALYETSWQKTIIPANSKQVTVPIDASRFKDLLAQMKNKYFLEG  
 30 FVRFKQDPTKEELMSIPIYIGFRGDFGNLSALEKPIYDSKDGSSYYHEANSDAKDQLDGDGLQFYALKNNFTALTTESENPTWIIKAV  
 KEGVENIEDIBSSEITETIFAGTFAKQDDDSHYIHRHANGKPYAALSPNGDGNRDYVQFQGTFLRNKLNVAEVLDKEGNVVWTS  
 EVTEQVVKNYNNDLASTLGS TRFEKTRWDGKDKGKVVANGTYTYRVRYTPISSGAKEQHTDFDVIVDNTPPEVATSATFSTEDSR  
 LTTLASKPKTSQPVYRERLAIYTYMDEDLPTTEYISPNEGDFTLPEEAETMEGATVPLKMSDFTYVVEDMAGNIYTPVTKLLEGHS  
 NKPEQDGSQAPDKKPEAKPEQDGSQTPDKKKEKPEKDSGQTPGKTPQKQSSRTLEKRSSKRALATKASTRDQLPTTNDKDT  
 35 NRLHLLKLVMTFFFLG

The nucleotide and amino acid sequences of GBS 305 in Ref. 3 are SEQ ID 207 and SEQ ID 208. These sequences are set forth below as SEQ ID NOS 13 and 14:

SEQ ID NO. 13

ATGGGACGAGTAATGAAAACAATAACAACATTTGAAAATAAAAAAGTTTTAGTCTTGGTTTACGACGATCTGGAGAAGCTGCTGC  
 40 ACGTTTGTAGCTAAGTTAGGAGCAATAGTGACAGTTAATGATGGCAAACCAATTTGATGAAAATCCAACAGCACAGTCTTTGTTGG  
 AAGAGGGTATTAAGTGGTTTGTGGTAGTCATCCTTTAGAATTTGATAGAGGATTTTGTACATGATTAATAAATCCAGGAATA  
 CCTTATAACAATCCATAGGTCAAAAAAGCATTAAGAAAAACAATCCTGTTTTGACTGAAGTGGAAATAGCATACTTAGTTTCAGA  
 ATCTCAGCTAATAGGTATTAAGGCTCTAACGGGAAAAACGACAACGACAAACGATGATTCAGAAAGTCTTAAATGCTGGAGGTGAGA  
 45 GAGTTTGTAGCTGGGAATATCGGCTTCTCTGCTAGTGAAGTTGTTCAAGCTGCGAATGATAAAGATACTTAGTTATGGAATTA  
 TCAAGTTTTTCAAGTAAATGGGAGTTAAGGAATTTCTGCTCATATTTGACAGTAATTAATAATTTAATGCAACTATTAGATTATCA  
 TGGGCTTTTTGAAGATATGTTGCTGCAAAATGGAATATCCTAAATCAAATGCTTCTCATCTGATTTTTTGGTACTTAATTTTAATC  
 AAGTATTTCTAAAGAGTTAGCTAAACTACTAAAGCAACAATCGTTCCTTTCTCTACTACGGAAAAAGTTGATGGTGCTTACGTA  
 50 CAAGACAAGCACTTTTCTATAAAGGGGAGAATATATGTCAGTAGATGACATTTGGTGTCCAGGAAGCCATAACGTAGAGAAATGC  
 TCTAGCAACTATTTGCGGTTGCTAAACTGGCTGGTATCAGTAATCAAGTTAATAGAGAAACTTTAAGCAATTTTGGAGGTGTTAAAC  
 ACCGCTTGCAATCACTCGGTAAGGTTATGTTTCTATAACGACAGCAAGTCAACTAATAATTTGGCAACTCAAAAAGCA  
 TTAATCTGGCTTTGATAATACTAAAGTTATCCTAATTCAGGAGGTTTATGATCGCGGTAATGAGTTTGTGATGAATGATACCAGATAT  
 CACTGGACTTAAACATATGTTGTTTGGGGAATCGGCATCTCGAGTAAACGTTGCTGCAAAAAAGCAGGAGTAACTTATAGCG  
 55 ATGCTTTAGATGTTAGAGATCGGTCACATAAAGCTTATGAGGTGGCAACAAGGGCGATGTTATCTTGTAAAGTCTGCAAAATGCA  
 TCATGGGACATGTAATAAGAAATTCGAAGTCCGTTGATGAATTCATTTGATACTTTTCAAGGCTTACAGGAGAG

SEQ ID NO. 14

MGRVMKTIITFENKVLVGLARSGEAARLLAKLGAIVTVNDGKPFDENPTAQSLLEEGIKVVCVSHPLELLEDDFCYMIKNPGI  
 PYNPNMVKKALEKQIPVLTVEVELAYLVSESLIGITGNSGKTTTTMIAEVLNAGGQRLLAGNIGFPASEVVAANDKDTLVMEL  
 60 SSFQLMGVKEFRPHIAVITNLMPHLDYHGSFEDYVAAKWNIQNQSSSDFLVLFNFQGISKELAKTTKATVFPSTTEKVDGAYV  
 QDKQLFYKGENIMSVDIGVPGSHNVENALATTAVALLAGISNOVIRETLNFGVVKHRLQSLKGVHGISFYNDKSTNILLATQKA  
 LSGFDNTKVLIIAGGLDRGNEFDELIPTITGLKHMVVLGESASRVKRAAQKAGVTVSDALDVRDAVHKAYEVAQQGDVILLSPANA  
 SWDMYKNFEVVRGDEFIDTFESLRGE

The nucleotide and amino acid sequences of GBS 313 are in Ref. 3 are SEQ ID 4089 and SEQ ID 4090. These sequences are set forth as SEQ ID NOS 15 and 16 below:

SEQ ID NO. 15

ATGAAACGTATTGCTGTTTAACTAGTGGTGGTACGCCCTGGTATGAACGCTGCTATCCGTGCAGTTGTTGCGTAAAGCAATTTCTGAAGGTATG
GAAGTTTACGGCATCAACCAAGGTTACTATGGTATGGTGACAGGGGATATTTCCCTTTGGATGCTAATTCGTTGGGGATACTATCAACCGTGGG
5 GGAACGTTTTTACGTTCCAGCACGTTATCCTGAATTTGCTGAACTTGAAGGTGAGCTTAAAGGGATGAAACAGCTTAAAAACACGGTATTGAAGGT
GTAGTAGTTATCGGTGGTGGTGGTCTTATCATGGTGGTATGCGTCTAACTGAGCACGGTTTCCAGCTGTTGGTTTGGCGGGTACAAATTGATAAC
GATATCGTTGGCACTGACTATACTATTGGTTTGGACACAGCAGTTGCGACAGCAGTTGAGAATCTTGACCGCTCTCGTGATACATCAGCAAGTCAAT
AACCGTACTTTTGTGTTGAGGTTATGGGAAGAAATGCAGGAGATATCGCTCTTTGGTTCAGGTTATCGCTGCAGGTGCAGATCAAAATATTGTTCTCT
GAAGAAGAGTTCAATATTGATGAAGTTGCTCAAATGTTAGAGCTGGCTATGCGCTGGTAAACATCACCNAATCATCGTCTTGCAAGAGGTGTT
10 ATGAGTGGTGGTATGAGTTTGAACAAAACAAATGAAAGCAGCAGGAGACGATAGCGATCTTGGTGGACGAATTTAGGACATCTGCTCCGTGGTGGTATG
CCGACGGCTCGTATCGTGTCTTAGCATCTCGTATGGGAGCGTACGCTGTTCAATTTGTTGAAAGAAGGTCGTGGTGGTGGTGGTGGTGGTGGTGGTGGT
AACGAAGAAATGTTGAAAGTCCAATTTTAGGTTTAGCAGAAAGAGGTTGCTTTGTTGAGCTTGACTGATGAGGAAAAATCGTTGTTAATAATCCG
CATAAAGCGGACCTTCGCTTGGCAGCACTTAATCGTGACCTTGCCAACCAAGTAGTAAA

SEQ ID NO. 16

MKRIAVLTSGGDAPGMNAAIRAVVRKAI SEGMVEYGINQGYGMVTDI FPLDANSVGDITNRGGTFLRSARYPEFALEGGQLKGI EQLKKHGI EG
VVVIGDGSYHGMARLFEHGFPAVGLPGTIDNDIVGTDYTI GFDTAVATAVENLDRDRDSASHNRTFVVEVMGRNAGDIALWSGI AAGADQI IVP
EEEFNIDEVSVNRVAGYAAGKHQI I VLAEGVMSGDEFATKMKAAAGDSDLRVNLGHLLRGGSPTRDRVLAASRMGAYAVQLLKEGRGGLAVGVH
NEEMVESPILGLAEBEGALFSLTDEGKI VVNNPHKADLRLLAALNRDLANQSSK

20 The nucleotide and amino acid sequences of GBS 322 in Ref. 3 are SEQ ID 8539 and SEQ
ID 8540. These sequences are set forth below as SEQ ID NOS 17 and 18:

SEQ ID NO. 17

ATGAATAAAAAGGTTACTATTGACATCGACAATGGCAGCTTCGCTATTATCAGTCGCAAGTGTTCAGCACAAAGAAACAGATACGACGTTGGACAGCA
CGTACTGTTTTCAGAGGTTAAAGGCTGATTTGGTAAAGCAAGACAATAAATCATCATATACTGTGAAATATGGTGATACACTAAAGCGTTATTTTCAGAA
25 GCAATGTCAATTTGATATGAATGTCTTAGCAAAAATAAATAACATTTGCAGATATCAATCTTATTTATCCTGAGACAACACTGCAGTAACCTTACGAT
CAGAAGAGTCATACTGCCACTTCAATGAAAATAGAAACACAGCAGCAAAATGCTGCTGGTCAAACAACAGCTACTGGTGGATTTGAAAACCAATCAA
GTTTTCTGTTGCAGACAAAAGTTTCTCTCAATACAATTTCCGGAAGGTATGACACCAGAAGCAGCAACAACGATTGTTTCCGCAATGAAGACATAT
TCTTCTGCGCCAGCTTTGAAATCAAAGAAGTATTAGCACAAAGAGCAAGCTGTTAGTCAAGCAGCAGCTAATGAACAGGTATCACCAGCTCCTGTG
AAGTCCGATTACTT CAGAAGTTCAGCAGCTTAAAGAGGAACTTAAACCAACTCAGACGCTCAGTCAGTCAACCAACAGTATCACCAGCTTCTGTT
30 GCCGCTGAAACACCAGCTCCAGTAGCTAAAGTAGCACCGGTAAGAAGTGTAGCAGCCCTAGAGTGGCAAGTGTAAAGTAGTCACTCCTAAAGTA
GAAACTGGTGCATCACCAGAGCATGTATCAGCTCCAGCAGTTCCTGTGACTACGACTTACCAGCTACAGACAGTAAAGTTACAAGCGACTGAAAGTT
AAGAGCGTTCCGGTAGCACAAAAGCTCCAACAGCAACACCGGTAGCACAAACAGCTTCAACAACAATGACAGTACTGCACATCTTGAAAATGCA
GGGCTCCAACCTCATGTTGCAGCTTATAAAGAAAAAGTAGCGTCAACTTATGGAGTTAATGAATTCAGTACATACCGTGCGGGAGATCCAGGTGAT
CATGGTAAAGGTTTAGCAGTTGACTTATTTGTAGGTAATAAACAAGCCTTGGTAATAAAGTTGCACAGTACTCTACACAAAATATGGCAGCAAAAT
35 AACATTTCAATATGTTATCTGGCAACAAAAGTTTACTCAAATACAACAGTATTTATGGACCTGCTAATACTTGGAAATGCAATGCCAGATCGTGGT
GGCGTTACTGCGCAACCACTATGACCACGTTCCAGTATCATTTAACAAAATAATATAAAAAGGAAGCTATTTGGCTCTCTTTTATATGCTTGAAT
AGACTTTCAAGGTTCTTATATAATTTTTATTA

SEQ ID NO. 18

MNKKVLLTSTMAASLLSVASVQAQETDITWTARTVSEVKADLVKQDNKSSYTVKYGDTLSVI SEAMS IDMNVLAKINNIADINLI YPETTLTIVTYD
QKSHATATSMKIEPTATNAGQTTATVDLKTQVSVADQKVS LNTI SEGMTPEAATTVI VSPMKTYSSAPALKSKEVLQAQVSSQAANEQVSPAPV
KSITSEVPAAKEVVKPQTSTVSQSTTVSPASVAEETPAPVAKVAPVPTVAAPRVASVKKVPTPKVETGASPEHVSAPAVPVTSTPATD SKLQATEV
KSVPVQAQKAPTATPVAQPASTTNAVAAHPENAGLQPHVAAYKEKVASTYGVNFBSTYRAGDPGDHKGKLAVDFI VGTNQALGNKVAQYSTQNMAAN
40 NISYVIWQQKFYSNTNSI YGPANTWNAMPDRGGVTANHYDHVHVSFNK

45 The nucleotide and amino acid sequences of GBS 328 in Ref. 3 are SEQ ID 6015 and SEQ
ID 6016. These sequences are set forth below as SEQ ID NOS 19 and 20:

SEQ ID NO. 19

ATGAAAAGAAAATATTTTGAAGTAGTGTCTTGGTTTGTAGTCGCTGGACTTCTATTATGTTCTCAAGCGTGTTCGCGGACCAAGTCGGTGTCT
CAAGTTATAGGCGTCAATGACTTTTATGGTGCACCTTGACAATACTGGAACAGCAAAATATGCTGATGAAAAGTTGCTAATGCTGGTACTGCTGCT
CAATTAGATGCTTATATGGATGACGCTCAAAAAGATTTCAAACAACCTAACCTTAATGGTGAAGCATTAGGGTTCAAGCAGGCGATATGGTTGGA
50 GCAAGTCCAGCCAACCTCGGGCTTCTTCAAGATGAACCAACTGTCAAAAATTTAATGCAATGAATGTTGAGTATGGCACATTTGGGTAACCATGAA
TTTGATGAAGGGTTGGCAGAAATAAATCGTATCGTTACTGGTAAAGCCCCCTGCTCCAGATTCTAATAATAATAATATTACGAAATCATACCCACAT
GAAGCTGCAAAAACAGAAATGTAGTGGCAAATGTTATTGATAAAGTTAACAAACAATTCCTTACAATTTGGAAGCCTTACGCTATTAAAAATATT
CCTGTAATAAACAAGTGTGAACGTTGGCTTTATCGGGATGTCAACAAAGACATCCCAACCTTGTCTTACGTAAAAATTTATGAACAATATGAA
55 TTTTATAGTGAAGCTGAAAACAAATCGTTAAATACGCCAAAGAAATTAACAAGCTAAAAATGTCAAAGCTATTTGAGTCTCGCACATGTACCTGCAACA
AGTAAAAATGATAATTGCTGAAGGTGAAGCAGCAGAAATGATGAAAAAGTCAATCAACTCTCCCTGAAAATAGCGTAGATATTGCTCTTGGCTGGA
CACAACTCATCAATATACAAAATGGTCTTGTGGTAAAACCTCGTATTGTACAAGCGCTCTCTCAAGGAAAAGCCTATGCTGATGTACGTTGGTGTCTTA
GATACTGATACACAAGATTTCAATGAGACCCCTCAGCTAAAGTAATTCAGTGTGCTCCTGGTAAAAAACAGGTFAGTCCGATATTCAAGCCATT
60 GTTGACCAAGCTAATACTATCGTTAAACAAGTAACAGAAAGCTAAAATTTGGTACTGCGGAGGTAAGTGTCTATGATTACCGGTTCTGTTGATCAAGAT
AATGTTAGTCCGTTAGGAGCCCTCATCACAGAGGCTCAACTAGCAATTTGCTCGAAAAGCTGGCCAGATATCGAATTTTGGCATTGACAAAATATGTT
GGCATTGCTGCTGACTTACTCATCAAAACAGATGGAACAAATCACCTGGGGAGCTGCACAAGCAGTTCAACCTTTTGGTAAATATCTTACAAGTCGTC
GAAAATTAAGTGGTAGAGATCTTTATAAAGCACTCAACGAAACAATAAGCAACAAAACAAAATTTCTTCTTCAAATAGCTGGTCTGCGATACACTTAC
65 ACAGATAATAAAGAGGGCGGGAAGAAACACCAATTTAAAGTTGTAAAAGCTTATAAATCAAATGGTGAAGAAATCAATCCTGATGCAAAAATACAAA
TTAGTTATCAATGACTTTTATTCGGT
TTTATGGCCCTATATCACTGATTTAGAAAAGCTGGTAAAAGAGTGAGCGGTTCCAAAATAATAAACCTAAAATCTATGTCTACTATGAGAGTGGTAAAT
GAAACTATTACACAAAATGATGGTACACATAGCATTATTAAGAACTTTATTTAGATCGACAAGGAAATATTGTAGCACAAAGATTTGATCAGAC

ACTTTAAACCAAAACAAAATCAAATCTACAAAATCAACCTGTAACTACAATTACAAAAACAATTACACCAATTTACAGCTATTAACCTATG
AGAAATTTAGGCAAAACCATCAAATCCACTACTGTAAAATCAAAACAATTACAAAAACAACCTCTGAATATGGACAATCATTCCTTATGTCTGTC
TTTGGTGTGGACTTATAGGAATTGCTTTAAATACAAAGAAAAACATATGAAA

5 SEQ ID NO. 20

MKKKI ILKSSVLGLVAGTSMFSSVFADQVGVQVI GVNDFHGLDNTGTANMPDGKVANAGTAAQLDAYMDDAQKDFKQTNPNGESIRVQAGDMVG
ASPANSGLLQDEPTVKNFNAMNVEYGTGLNHEFDEGLAEYNNRIVTGKAPAPDSNINNI TKSYPHEAAKQEVVANVIDKVNKQIPYNWKPYAIKNI
PVNNKSVNVGFIGIVTKDIPNLVLRKNYEQYEFLEAETIVKYAKELQAKNVKAVVLAHVPAATSKNDIAEGEAAEMMKVNLFPENSVDIVFAG
10 HNHQYTNGLVGVKTRIVQALSQKAYADVRGVLDTDTQDFIETPSAKVIAVAPGKKTGSADIQAVDQANTIVKQVTEAKIGTAEVSVMI TRSVDDQ
NVSPVGSLLITEAQLA IARKSWPDI DFAMTNNGGIRADLLIKPDGTITWGAAQAVQPFNGILQVVEITGRDLYKALNEQYDQKQNFLLQIAGLRYTY
TDNRKGGEEETPFKVVKAYKSNGBEINPDAKYKLVINDFLPGGGDGFASFRNAKLLGAINPDTEVFMAIITDLEKAGKKVSPNNKPKIVYTMKMN
ETITQNDGTHSIIKKLYLDRQGNIVAQEI VSDTLNQT KSKSTKINPVTTIHKKQLHQFTA INPMRNYGKPSNSTTVKSKQLPKTNSEYQGSFLMSV
FGVGLIGIALNFKKHKM

15 The nucleotide and amino acid sequences of GBS 330 in Ref. 3 are SEQ ID 8791 and SEQ
ID 8792. These sequences are set forth below as SEQ ID NOS 21 and 22:

SEQ ID NO. 21

ATGAATAAACCGCTAAAAATCGTTGCAACACTTGGTCCCTGCGGTTGAATCCGTTGGTGGTAAGAAGTTTGGTGAGTCTGGATACTGGGGTGAAGC
CTTGACGTFAGAAGCTTCAGCAGAAAAAATTTGCTCAATTGATTAAGAAGAGGTGCTAACGTTTCCGTTTCAACTTCTCACATGGAGATCATGCTGAG
20 CAAGGAGCTCGTATGGCTACTGTTGCTGAAAGCAGAAAGATTCAGGACAAAAAGTTGGCTTCTCCTTGGATACTAAAGGACCTGAAATTCGTACA
GAACTTTTTGAAGATGGTGAGATTTCCATT CATATACAACAGGTACAAAAATTACGTGTGCTACTAAGCAAGGTATCAAATCAAATCCAGAAGTG
ATTGCATTGAATGTTGCTGGTGGACTTGACATCTTTGATGACGTTGAAAGTTGGTAAAGCAAACTCTTGTGATGATGGTAACTAGGTCTTACTGTG
TTTGCAAAAGATAAAGACACTCGTGAAATTTGAAGTAGTTGTTGAGAAATGATGGCCATTATGGTAAACAAAAAGGTGTAACATCCCTTATACTAAA
25 ATTCCTTCCAGCACTTGCAAGACGCGATAATGCTGATATCCGTTTGGACTTGAGCAAGGACTTAACTTTATGCTATCTCATTGTGACGTA
GCTAAAGATGTTAATGAAGTTCGTGCTATTGTTGAAGAACTGGSMATGGACACGTTAAGTTGTTTGGCTAAAATTGAAAATCAACAAGGTATCGAT
AATATTGATGAGATTTATCGAAGCAGCAGATGTTATGATTGCTCGTGGTGATATGGGTATCGAAGTTCCAATTTGAAATGGTTCCAGTTTACCAA
AAAATGATCATTACTAAAGTTAATGCAGCTGGTAAAGCAGTTATTACAGCAACAATATGCTTGAAACAATGACTGATAAACACACGCTGCGACTCGT
30 TCAGAAGTATCTGATGCTTCAATGCTGTTATGATGGTACTGATGCTACAAATGCTTTCAGGTGAGTCAGCTAATGGTAAATACCCAGTTGAGTCA
GTTTCGTAACAATGGCTACTATGATAAAAATGCTCAAACATTACTCAAATGAGTATGGTTCGCTTAGACTCATCTGCATTCACCAATTAACAAAAT
GATGTTATTGCATCTGCGGTTAAAGATGCAACACACTCAATGGATATCAAACCTGTTGTAACAATTACTGAAACAGGTAATACAGCTCGTGCCATT
TCTAAATTCCTCCAGATGCAGACATTTTGGCTGTACATTTGATGAAAAAGTACAACGTTTCAATGATGATTAACCTGGGGTGTATCCCTGTCTT
35 GCAGACAAACGACTCTACAGATGATATGTTGAGGTTGCAGAACGTTGAGTACACTTGAAGCAGGATTTGTTGAATCAGGCGATAATATCGTTATC
GTTGCGAGGTGTTCTGTAGGTACAGGTGAACTAACCAATGCGTGTTCGTACTGTTAAA

35 SEQ ID NO. 22

MNKRVKIVATLGPVAFRGGKKGESGYWGESLDVEASAQKIAQLIKEGANVFRFNFSGHDHAEQGMATVRKAEIAGQKVGFLDITKGPRI RT
ELFEDGADFHSTTTGPKLRVATKQGIKSTPEVIALNVAGGLDIFDDVEVGQILVDDGKLGTLVFAKDKDTREFEVVENDGLIGKQKGVNIPYTK
I PFPALAEERDADIRFLEQGLNFIAISFVRTAKDVNEVRAICBETGXGHVLFKAKIENQGGIDNIDEIIEAADGIMIARGDMGIEVPPFEMVPPYQ
40 KMIITKVNAAAGKAVITATNMLETMTDKPRATRSEVSDVFNVAVIDGTDATMLSGESANGKYPVBSVRTMATIDKNAQTLNNEYGRDSSAPFRNNKT
DVIASAVKDATHSMDIKLVVFTITETGNTARAI SKFRPADDILAVTFDEKVRSLMINWGVIPVLADKPASTDDMFEVAERVALEAGFVSEGDNIIVI
VAGVPVGTGGTNTMRVRTVK

The nucleotide and amino acid sequences of GBS 338 in Ref. 3 are SEQ ID 8637 and SEQ
ID 8638. These sequences are set forth below as SEQ ID NOS 23 and 24:

45 SEQ ID NO. 23

TTGTCTGCTATAATAGACAAAAAGGTGGTGATATTTATGATTTTAGCATTAAATCGGTGATATCATTAATTCAAAAAGATACTTGA
ACGTGAAACTTTCCAAAGCTCTTTTCAGCAACTAATGACCGAACTATCTGATGATATGGTGAAGAGCTGATTTCTCCATTCACCTA
TTACAGCTGGTGAATTTCAAGCTTTTATGAAACCAACAAAAAGGTAATTTCAAATTTGACCATATTTCAACTAGCTCTAAAA
50 CCTGTTAATGTAAGGTTCCGCTCGGTACAGGAAACATATAAATCCATCAATCAAATGAAAAGTATCGGTGCTGATGGTCCCTGC
CTACTGGCATGCTCGCTCAGCTATTAATCATATACATGATAAAAAATGATTATGGAACAGTTCAAGTAGCTATTTGCCTTGATGATG
AAGACAAAACTTGAATTAACACTAAATAGTCTCAATTCAGCTGGTGAATTTATCAAGTCAAATGGACTACAAAACCATTTTCAA
ATGCTTGAGCACTTAATACTTCAAGATAATTAACAAGAACAAATTTCAACATCAAAAAGTTAGCCCACTGGAAAAATATTGAACCTAG
TGCGCTGACTAAACGCCTTAAAGCAAGCGGTCTGAAGATTTACTTAAGAACGAGAACACAGGACGCCGATCTATTAGTTAAAAGTT
55 GCACTCAAACCTAAAGGGGGAAGCTATGATTTT

SEQ ID NO. 24

MSAIDDKKVVIFMYLALIGDIINSKQILERETFQOSFQQLMTELSDEVYEEELISPFITITAGDEFQALLKPSKKVFIIDHILQALPKPVNVRFLGTG
NIIITSINSNESIGADGPAYWHARSAINHIDKNDYGTVQVAICLDDDEQNLLELTLNLSLISAGDFIKSKWTTNHFQMLBHLILQDNVQEQQHQKLAQ
60 LENIEPSALTKRLKASGLKILYLRTRTQAADLLVKSCTQTRKGSYDF

The nucleotide and amino acid sequences of GBS 358 in Ref. 3 are SEQ ID 3183 and SEQ
ID 3184. These sequences are set forth below as SEQ ID NOS 25 and 26:

SEQ ID NO. 25

5 ATGTTTTATACAATTGAAGAGCTGGTAGAGCAAGCTAATAGCCAACATAAGGGTAAACATAGCAGAGCTCATGATCCAACCGGAAATGAAATGACT  
 GGTAGAAGTCGTGAAGAAATCGTTATATATGTCGCCGAATCTTGAAGTCATGAAAGCTTCTGTTATGATGGATTAAACCCCTAGTAAATCAATC  
 AGTGGTTTAAACAGCGCGTGATGCTGTCAAGATGGATCAATATTTACAATCAGGAAAACTATTTAGATACCACAATCCTAGCTGCGGTTAGGAAT  
 GCTATGGCTGTTAATGAGTTAAATGCTAAGATGGGACTGGTCTGTGCAACCACTGCAGGTAGTGCAGGATGTTTACCAGCTGTGATTTCTACA  
 10 GCCATTGAAAAGCTTAATTTAACAGAAGAAGAGCAACTTGATTTTCTATTACAGCCGGCGCATTTGGTCTCGTCATTGGTAATAATGCCCTTATC  
 TCAGGTGCAGAAGGAGTTGCCAAGCTGAAGTTGGGTGAGTGTGCTATGGCTGCGGCTGCTTTAGTTATGGCTGCTGGAGTACTCCTTTCCAA  
 GCTAGCCAAGCTATAGCATTTGTTTATTAATAATATGCTTGGACTTATCTGTGACCCCTGTTGACAGGTTTAGTTGAAGTCCCTTGTGTGAAGCGGAAT  
 GCTCTTGGATCAAGTTTGCACCTTGTGCTGCTGATGGCTTGGCTGGTATGAATCGCAAATCCAGTAGATGAAGTTATGATGCAATGTAT  
 CAAGTTGGATCAAGTTTACCAGCTGCTTTTCTGTGAGACTGCAGAAGGAGGACTTGTGCCACGCCGACAGGAAGCGTTATAGTAAAGAAATTTTT  
 GGGGAA

**SEQ ID NO. 26**

15 MFYTIIEELVEQANSQHKGNIAELMIQTEIEMTGRSREEIRYIMSRNLEVMKASVIDGLTPSKSISGLTGGDAVKMDQYLQSGKTI SDTTIILAAVRN  
 AMAVNELNARKMLVCATPTAGSAGCLPAVISTAI EKLNLTBEEQLDFLFTAGAFGLVIGNNASISGABGGCQAEVGSASAMAAALVMAAGGTPFQ  
 ASQAI AFVINKMLGLICDPVAGLVEVPCVKNRNLGSSFALVAADMALAGIESQIPVDEVIDAMYQVGSLSLPTAFRETAEGGLAATPTGRYSKEIF  
 GE

The nucleotide and amino acid sequences of GBS 361 in Ref. 3 are SEQ ID 8769 and SEQ ID 8770. These sequences are set forth below as SEQ ID NOS 27 and 28:

**SEQ ID NO. 27**

20 ATGAGCGTATATGTTAGTGGAAATAGGAATTAATTTCTTCTTTGGGAAAGAATTATAGCGAGCATAAACAGCATCTCTTCGACTTAAAAGAAGGAATTT  
 CTAACATTTATATAAAAAATCAGACTCTATTTTGAATCTTATACAGGAAGCATAACTAGTGACCCAGAGGTTCTCTGAGCAATACAAAGATGAGAC  
 ACGTAATTTTAAATTTGCTTTTACCGCTTTTGAAGAGGCTCTTGCTTCTCAGGTGTTAATTTAAAAGCTTATCATAATATTGCTGTGTGTTTAGGG  
 25 ACCTCACTGGGGGAAAGAGTGTGGTCAAAAATGCCTTGTATCAATTTGAAGAAGGAGAGCGTCAAGTAGATGCTAGTTTATAGAAAAGCATCTG  
 TTTACCATATGCTGATGAATGATGGCTTATCATGATATGTTGGGAGCTTCGTATGTTTATTCACCCGCTGTTCTGCAAGTAATAATGCCGTAAT  
 ATTAGGAACAACAATTAATCAAGATGGCGATTGTGATTAGCTATTTGTTGGTGGCTGTGATGATTAAGTGAATATTTCTTAGCAGGCTTACATCA  
 CTAGGAGCTATTAATACAGAATGGCATGTCAGCCCTATTCTTCTGAAAAGGAATCAATTTGGGTGAGGGCGCTGGTTTGTGTTCTGTCAAAG  
 ATCAGTCCCTAGCTAAAATATGAAAAAATATCGGTGGTCTTATTACTTCAGATGGTTATCATATAACAGCACCTAAGCCAACAGGTGAAGGGGGCGC  
 ACAGATTGCAAAGCAGCTAGTGACTCAAGCAGGTATTGACTACAGTGAGATTGACTATATTAACGGTCACGGTACAGGTAATCAAGCTAATGATAAA  
 30 ATGAAAAAATATGATGTTAGTTTCCCAGACAACGACATTTGATCAGCAGTACCAAGGGGCAACCGGTATACTCTAGGGGCTGAGGTATTA  
 TCGAATGATTAATGTTTAGCGCAATAGAGGAACAGACTGTACCAGCACTAAAATGAGATTGGGATAGAAGGTTTCCAGAAAAATTTGTCTA  
 TCATCAAAGAGAGAATAACCAATAAGAATGCTTAAATTTTCTGTTGCTTTGGTGGAAATAAATGTTGCTCTTATTGCTATCTTTAGATTCA  
 CCTCTAGAACATTAACCTGCTAGAGAAAATCTTAAATGGCTATCTTATCATCTGTTGCTTCCATTTCTAAGAATGAATCACTTTCTATAACCTATG  
 AAAAAAGTTGCTAGTAATTTCAACGACTTTGAAGCATTACGCTTTAAAGGGGCTAGACCACCCAAAATGTCACCCAGCACAATTTAGGAAAATGGA  
 35 TGATTTTCCAAAATGGTTGCCGTAACAACAGCTCAAGCACTAATAGAAGCAATTAATCTAAAAAACAAGATTAATCTAAAAAGTAGGAATGTA  
 TTTACAACACTTTCTGGACAGTTGAGGTTGTTGAAGGTAATGAAAAGCAATCACAACAGAAGGATATGCACATGTTCTGCTTACAGATTCCCCT  
 TTACAGTAATGAATGCAGCAGCTGGTATGCTTTCTATCATTTTTAAAATAACAGGTCCTTTATCTGTGATTTGACAAAATAGTGGAGCGCTTGATGG  
 TATACAATATGCCAAGGAAATGATGCGTAACGATAATCTAGACTATGTGATTTCTGTTTCTGCTAATCAGTGGACAGACATGAGTTTATGTTGGTGG  
 CAACAATTAACCTATGATAGTCAAAATGTTTCTCGGTTCTGATTTATGTTTACAGCACAAGTCCCTCTCTCGTCAAGCATTTGGATAATTTCTCTATAATAT  
 40 TAGGTAGTAAACAATTAATAATAGCCATAAAAACATTACAGATGTGATGACTATTTTGTATGCTGCGCTTCAAATTTATATCAGACTTAGGACT  
 AACCAAAAAGATATCAAGGTTTCTGTTTGAAGTGAAGGAGGAGGAGGCTAGTTTATGATTTCTTAGCGAACTTGTCTGAGTATTATAAT  
 ATGCCAAACCTTGGCTTCTGGTCAAGTTTGGATTTTCTATCAATGTTGCTGGTGGGAGAACTGGACTATACTGTTAATGAAAGTATAGAAAAGGGCTATT  
 ATTTAGTCTATCTTATTCGATCTTCTGGTGGTATCTCTTTTGTCTATTATTGAAAAAAGG

**SEQ ID NO. 28**

50 MSVYVSGIGI ISSLGNKYSEHKQHLFDLKEGISKHLYKNHDSILESYSITSDPEVPEQYKDETRNFKFAFTA FBEALASSGVNLKAYHNI AVCLG  
 TSLGGKSAGQNALYQFEBGERQVDASLLEKASVYHIADELMAYHDI VASVYI STACASNNNAVLLGTQLLQDGDCLAI CGGDELDSDI SLAGFTS  
 LGAINTEMACQPPYSSGKGINLGEAGFVVLVKDQSLAKYGI IGGIITSDGYHITAPKPTGEGAAQIAKQLVQAGIDYSEIDY INGHGTGTQANDK  
 MEKNMYGKFFPTTLLISSTKGQTHLGAAGI IELINCLAAIEEQVPAKNEIGIEGFPENFVYHQREYPI RNALNFSFAFGNNNSGVLSSSLDS  
 55 PLETL PARENLMKAILSSVASISKNESLSITYEKVASNFNDFEALRFKGRARPKTVNPAQFRKMDDFS KMVAVTTAQA LI RSNINLKKQDTSKVGIV  
 FTTLSPVEVVEGIEKQITTEGYAHVSARFPPTVMNAAAGMLS I IFKITGPLSVISTNSGALDGI QYAKEMMRNNDNLDYVILV SANQWTDMSFMWW  
 QQLNYDSQMPFVSDYCSAQLSRQALDNSPI ILLGSKQLKYSHKTFDVMTI FDAALQNLSDLGLTI KDIKGFVWNERKKA VSDYDFLANLSEYIN  
 MPNLASGQGFSSNGAGEELDYTVNESIEKGYLVLSYSIFGGISFAI IEKR

The nucleotide and amino acid sequences of GBS 404 in Ref. 3 are SEQ ID 8799 and SEQ ID 8800. These sequences are set forth below as SEQ ID NOS 29 and 30:

**SEQ ID NO. 29**

60 ATGAAAATAGATGACCTAAGAAAAGCGACAATGTTGAAGATCGTCTCAGTAGCGGAGGTTTATTCTCTAGCGGAGGAAGTGATTACCGATT  
 CTTCACCTTTTATGCTCGGAGGGAGTTGAAAAACCAAGCTTGTGGTTTTAATCATCTTACTGCTACTTGGCGGAGGGGACTAACCGCATTTTT  
 AATGACTCATCTCACCCTTAGTTACCAATCTCAGAAATGTCCTACGTTCTGTATAATAGCGCAACAGAGAGAACAATCGATTTCTGTTAATAAA  
 CTCTTGGCTCAACTGAGGATTTCTGGTCAACAAGAAATCCAAACCAAGGTTTTGGAATTTATAAGGAACCAAACTTGTCTTTACACCAATTCA  
 65 ATTCAAACAGGTTGTGGTATAGGTGAATCTGCTTCAAGACCAATTTATTGTTGAGCAGATAAAAAAATCTATCTGATATTTCTTTTACAATGAA  
 TTATCACATAAATATGGTGTACTGGTGAATTTGCTATGGCTACGTCATCGCCCAGAGTTGGTCAACACATTCAAACAGAGTTAGGCATTTATG  
 GATAAGTATAAAGAAATCGCACAGGACTTACTAAGAAAGAAAGCAAATGCTTTAAATGTTTGGCTAGAACTTCAAGCAGATTTATGACGGGGTA  
 TGGGCTCACTACATCAGGGGAAAAATCTCTTAGAACAGGAGACTTTGAAGAGGCTATGAATGCTGCCACGCCGCTCGGAGACGATACCCCTCAG  
 AAAGAACCTACGGAAAATTAGTGCTGATAGCTTTACCCATGGAACAGCTGAACAACGCCAACGTTGGTTTAAACAAAGGCTTTCAATATGGTGAC  
 ATCCAACACGGTGATCTTTCTCCGTAGAACATCTA

SEQ ID NO. 30

MKIDDLRKSNDVDRSSSSGGSSFGSSGSLPILQLLLLRGSKWTKLVVLI I LLLLGGGGLTSI FNDSSSPSSYSQSNVSRSDNSATREQIDFVNK
VLGSTEDFWSQEFQTOGFGNYKEPKLVLYTNSIQTCGIGESASGPFYCSADKKI YLDISFYNELSHKYGATGDFAMAYVIAHEVGHHIQTELGIM
DKYNRMRHGLTKKEANALNVRLBELQADYYAGVWAHYIRGNLLEQGDFFEEAMNAHAHVGD DTLQKETYGKLVPSFTHTGTABRQRWFNKGFPQYGD
IQHGDTFSVEHL

5

The nucleotide and amino acid sequences of GBS 656 in Ref. 3 are SEQ ID 9323 and SEQ ID 9324. These sequences are set forth below as SEQ ID NOS 31 and 32:

SEQ ID NO. 31

ATGAAAAGATTACATAAACTGTTTATAACCGTAATTGCTACATTAGGTATGTTGGGGGTAATGACCTTTGGTCTTCCAACGCAGCCGCAAAACGTA
ACGCCGATAGTACATGCTGATGTC AATTCAATCTGTTGATACGAGCCAGGAATTTCAAAAATAATTTAAAAATGCTATTGGTAACCTACCATTTCAA
TATGTTAATGGTATTTATGAATTAATAATAATCAGACAAATTTAAATGCTGATGTC AATGTTAAAGCGTATGTTCAAATACAATTGACAAATCAA
AAAGACTATCAACTGCTAATGCAATGCTTGATAGAACCATTCGTC AATATCAAAATCGCAGAGATACCACTCTTCCCGGATGCAAAATGGAAACCA
TTAGGTTGGCATCAAGTAGCTACTAATGACCATTTATGGACATGCAAGTGCACAAGGGGCATTTAATGCTATGCTTTAGCTGGAAATTTCAAAGGT
TGGGATGCTTCCGTGTC AAAATCCTCAAAATGTTGTCACACAAACAGCTCATTCCAACCAATCAAATCAAAAAATCAATCGTGGACAAAATTTATTAT
GAAAGCTTAGTTTCGTAAGCGGTTGACCAAAAACAAACGTTTCGTTACCGTGAACCTCCATTGTACCGTAATGATACTGATTTAGTTCATTTGCA
ATGCACCTAGAAGCTAAATCAAGATGGCACATTAGAAATTAATGTTGCTATTCCAACACACAAGCATCATACACTATGGATTATGCAACAGGA
GAAATAACACTAAAT

10

15

SEQ ID NO. 32

MKRLHLKFIITVIATLGLMGLVMTFGLPTQPQNVTFPIVHADVNSSVDTSQBFQNLKNAIGNLPFYVNGIYELNNTQNLNADVNVKAYVQNTIDNQ
QRLSTANAMLDRTIRQYQNRDITLDPANWKPLGWHQVATNDHYGHAVDKGLHIAIALAGNFKGWDASVSNPQNVVTTQAHNSQNSQKINRGQNY
EQLVRKAVDQNKRVRYRVTPLYRNDTDLVFPAMHLEAKSQDGTLEFNVAIPTQASYTMDYATGEITLN

20

The nucleotide and amino acid sequences of GBS 690 in Ref. 3 are SEQ ID 9965 and SEQ ID.9966. These sequences are set forth as SEQ ID NOS 33 and 34 below:

SEQ ID NO. 33

ATGAGTAAACGCAAAAATTTAGGAATTAGTAAAAAGGAGCAATTATATCAGGGCTCTCAGTGGCACTAATGTAGTAATAGGTGGCTTTTATGG
GTACAATCTCAACCTAATAAGAGTGCAGTAAAACTAACTACAAAAGTTTTTAAATGTTAGAGAAGGAAGTGTTCGTCCTCACTCTTTTGACAGGA
AAAGCTAAGGCTAATCAAGAACAGTATGTATTTTGTATGCTAATAAAGGTAATCGAGCAACTGTCAAGTTAAAGTGGGTGATAAAAATCACAGCT
GGTCAAGCAGTTAGTTC AATATGATACAACAACCTGCACAAGCAGCCTACGACACTGCTAATCGTCAATTAATAAAGTAGCCGCTCAGATTAATAAT
CTAAAGACAAACGGAAGTCTTCCAGCTATGGAATCAAGTATCAATCTTCTTCATCATCAAGGACAAGGGACTCAATCGACTAGTGGTGGCAGC
AATCGTCTACAGCAAAAATTTAACAAGTCAAGCTAATGCTTCATACAACCAACAACCTTCAAGATTTGAATGATGCTTATGCAGATGCACAGGCAGAA
GTAATAAAGCACAAAAGCATTGAATGATACTGTTATTACAAGTGACGATCAGGGACAGTTGTTGAAGTTAATAGTGATATTGATCCAGCTTCA
AAAAGTGTCAAGTACTTGTCCATGTAGCAACTGAAAGGTAACCTCCAAGTACAAGGAAACGATGAGTGAATGATTGGCTAATGTTAAAAAAGAC
CAGGCTGTTAAAAATAAATCTAAGGCTCTATCCTGCACAGGAATGGGAAGGTAATAATTTCAATATCTCAAAATTTCCAGAAGCAGAAGCAAAACAC
AATGACTCTAATAACCGGCTTAGTGTCTGTAATATAAATAAATAAAGTAGATATTACTAGCCCTCTCGATGCATTAATAACAGGTTTACCCTATCA
GTTGAAAGTAGTTAATGAGATAAGCACCTTATGTCCCTACAAGTCTGTGATAAACAAGATAATAAACACTTTGTTGGGTATACAATGATTCT
AATCGTAAAAATTTCCAAGTTGAAGTCAAAATTTGGTAAAGCTGATGCTAAGACACAAGAAATTTTATCAGGTTTGAAGCAGGACAAATCGTGGT
ACTAATCCAAGTAAAACCTTCAAGGATGGGCAAAAATTTGATAAATTTGAATCAATCGATCTTAACTCTAATAAGAAATCAGAGGTGAAA

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SEQ ID NO. 34

MSKRQNLGISKKGAIISGLSVALIVVIGGFLWVQSQPNKSAVKTKYKFNVRGSSVSSSTLLTGKAKANQEQVYVFDANKGNRATVTVKVGDKITAG
QQLVQYDTTTTAAAYDTANRQLNKVARQINNLKTTGSLPAMESDQSSSSSQGGTQSTSGATNRLQNYQSQANASYNQQLQDLNDAYADAQAEVN
KAQKALNDVITVISEVSGTVVEVNSIDIPASKTSQVLVHVATEGKLVQVQGTMEYDLANVKDQAVKIKSKVYPDKKEWEGKISYISNYPEABANNNS
NNGSSAVNYKYKVDITSPLDALKQGFVSVVEVNGDKHLIVPTSSVINKDNKHFVWVYVNDNSNRKISKVEVKIKGAKAQEILSGLKAGQIVVNTNPS
KTFKDGQKIDNIESIDLNSNKKSEVK

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The nucleotide and amino acid sequences of GBS 691 in Ref. 3 are SEQ ID 3691 and SEQ ID 3692. These sequences are set forth as SEQ ID NOS 35 and 36 below:

SEQ ID NO. 35

ATGAAAAAATTTGGAATTATTGCTCCTCACACTACTGACCTTCTTTTTGGTATCTTGCGGACAACAACTAAACAAGAAAGCACTAAAACACTATT
TCTAAAATGCCTAAAATTTGAAGGCTTCACTATTTATGAAAAAATTCCTGAAAAATCGGAAAAAAGTAAATAATTTTACATATTTTACACTGGGTAT
TTATTTAAACTAGGTGTTAATGTTCAAGTTACAGTTTAGACTTAGAAAAAGATAGCCCGTTTTTGGTAAACAACCTGAAAGAAAGCTAAAAAATTA
ACTGCTGATGATACAGAAGCTATTGCCGCACAAAAACCTGATTTAATCATGTTTTTCGATCAAGATCCAACATCAATACTCTGAAAAAATTTGCA
CCAACCTTAGTTTATAATATGGTGCACAAAATTTATTAGATATGATGCCAGCCTTGGGAAAGTATTCGGTAAAGAAAAAGAAAGCTAATCAGTGG
GTTAGCCAATGAAAACTAAAACCTCGCTGTCAAAAAGATTTACACCATATCTTAAAGCCTAACACTACTTTTACTATTATGGATTTTATGAT
AAAAATATCTATTTATATGGTAATAATTTGGACGCGGTGGAGAATAATCTATGATTTCACTAGTTTATGCTGCCCCAGAAAAAGTCAAAAAGAT
GTCTTTAAAAAAGGGTGGTTTACCCTTTCGCAAGAAGCAATCGTGTATTACGTTGGAGATTATGCCCTTGTTAATATAACAACCAAGCTAAAAA
GCAGCTTATCACTTAAAGAAAGTATGCTGGAAAGATTTACCAGCTGTCAAAAAGGGCACATCATAGAAAGTAACTACGACGTGTTTTATTTCT
TCTGACCCTCTATCTTTAGAAGCTCAATTAATAATCAATTAACAAGGCTATCAAGAAAAATACAAT

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SEQ ID NO. 36

MKKIGIIVLTLTFFLVSCGQQTQKQESTKTTISKMPKIEGFTYYGKIPENPKKVINFTYSYTGYYLLKLVNVSYSYSLDLEKDSVPVF  
GKQLKEAKKLTADDTEAIAAQKPDLMVFDQDPNINILKKIAPTLVIKYGAQNYLDMMPALGKVFVGEKEBANQWVSQWKTITLAVK  
KDLHHLLKPNNTTFTIMDFYDKNIYLYGNFGRGGELIYDSLGYAAPEKVKKDVFKKGFVTVSQAIGDYVGDYALVNINKTTKAA  
SSLKESDVWKNLPAVKKGHIIESNYDVVYFSDPLSLEAQLKSFTKAIKENIN

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Other preferred polypeptide antigens include: GBS4 (SEQ ID 2 from Ref. 3); GBS22 (SEQ ID 8584 from Ref. 3); and GBS85 (SEQ ID 216 from Ref. 3), including polypeptides having amino acid sequences with sequence identity thereto *etc.*

The polypeptide is preferably not a C protein (alpha or beta or epsilon) or a R protein (Rib).

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The nucleotide and amino acid sequences of GBS 4 in Ref. 3 are SEQ ID 1 and SEQ ID 2.

These sequences are set forth below as SEQ ID NOS 37 and 38:

**SEQ ID NO. 37**

ATGAAAGTAAAAATAAGATTTTAAACGATGGTAGCACTTACTGTCTTAAACATGTGCTACTTATTCATCAATCGGTTATGCTGATACAAGTGATAAGA  
ATACTGACACGAGTGTCTGACTACGACCTTATCTGAGGAGAAAAGATCAGATGAACTAGACCAGTCTAGTACTGGTTCTTCTCTGAAAATGAATC  
15 GAGTTCATCAAGTGAACCAGAAACAAATCCGTCACCTAATCCACCTACAACAGAACCCATCGCAACCCTCACCTAGTGAAGAGAAACAAGCCTGATGGT  
AGAACGGAAGACAGAAATTTGGCAATAATAAGGATATTTCTAGTGGAAACAAAAGTATTAATTTTTCAGAAGATAGTATTAAGAATTTTAGTAAAGCAAGTA  
GTGATCAAGAAGTGGATCGCGATGAATCATCATCTTCAAAGCAATGATGGGAAAAAGGCCACAGTAAGCCTAAAAGGAACTTCTCAAAC  
AGGAGATAGCCACTCAGATACTGTAATAGCATCTACGGGAGGATTATTTCTGTTATCATTAAAGTTTTTACAATAAGAAAATGAACTTTAT

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**SEQ ID NO. 38**

MKVKNKILTMVALTVLTCATYSSIGYADTSKNDTDSVVTTLSEKRSDELQDSSSTGSSSENESSSSSEPETNPSTNPPTTEPSPSPSEENKPDG  
RTKTEIGNNKDISSGTKVLISEDSIKNFSKASSDQBEVDRESSSKANDGKKGHSKPKKELPKTGDSHSDTVIASTGGIILLLSLSPFNKMKLY

The nucleotide and amino acid sequences of GBS 22 in Ref. 3 are SEQ 8583 and SEQ ID

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8584. These sequences are set forth below as SEQ ID NOS 39 and 40:

**SEQ ID NO. 39**

ATGAAAAGGATACGGAAGCCCTTATTTTGTCTCGGAGTAGTTACCTAATTTGCTTATGTGCTTGTACTAAACAAAGCCAGCAAAAAATGGCT  
TGTCAAGTAGTACAGTCTTTTATCCAGTATATCCATTAACAAAGCAGTTTCTGGTGATTTGAATGATATTAATAATGATTCGATCACAGTCAGGTAT  
30 TCATGGTTTTTGAAACCTCATCAAGTGATGTTGCTGCCATTTATGATGCTGATCTATTTCTTTATCATTCGCACACACTAGAAGCTTGGGCGAGACGT  
TTGGAACCTAGTTTGCATCACTCTAAAGTATCTGTAATGAAGCTTCAAAGGTATGACTTTGGATAAAGTTTATGGCTTAGAAGATGTAGAGGCAG  
AAAAAGGATAGATGAGTCAACCTTGTATGACCTCACACTTGAAGTACCCCTGTAAAAGTATCTGAGGAAGCAAACTCATCGCTACACAAATAGC  
TAAAAGGATCCTAAAACGCTAAGTATTAACAAAAATGCTGATCAATTTAGTGACAAAGCAATGGCTATTCAGAGAAAGTATAAGCCAAAATTT  
AAAGCTGCAAGTCTAAATACTTTGTGACTTCACATACAGCATTTCTATACCTTAGCTAAGCGATACGGATTGACTCAGTTAGGTATTCAGGTGTCT  
35 CAACCGAAGCAAGACTAGTCTAAAATAATAGCCGAAATTCAGGAGTTTGTGAAACATATAAGGTTAAGACTATTTTGTGTAAGAAAGGAGTCTC  
ACCTAATAGTCTCAAGCAGTAGCTTCAGCTACTCGAGTTAAAATGCAAGTTAAGTCTTTARAAGCAGTTCCCAAAAACAATAAAGATTACTTA  
GAAAATTTGAAACTAATCTTAAGGTACTTGTCAAATCGTTAAATCAATAG

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**SEQ ID NO. 40**

MKRIRKSLIFVLGVVTLICLCACTKQSQKNGLSVVTISFYVYSITKAVSGDLNDIKMIRSQSGIHGFEPSSSDVAAYDADLFLYHSHTLEAWARR  
LEPSLHHSKVSVEASKGMTLDKVHGLEDEAEKGVDESTLYDPHTWNPVKVSEEAQLIATQLAKKDPKNAKVYQKNADQFSDKAMAIAEKYPKF  
KAAKSKYFVTSHTAFSYLAKRYGLTQLGIAGVSTEQBPSAKKLAEIQBFVKYKVKTIIFVEEGVSPKLAQAVASATRVKIASLSPLXAVPKNNKDYL  
ENLETNLKVLVKSINQ

The nucleotide and amino acid sequences of GBS 85 in Ref. 3 are SEQ ID 215 and SEQ ID

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216. These sequences are set forth below as SEQ ID NOS 41 and 42:

**SEQ ID NO. 41**

ATGCCTAAGAAGAAATCAGATACCCAGAAAAAGAAAGTTGTCTTAAACGGAATGGCAAAAGCGTAACCTTGAATTTTAAAAAACGCAAGAAAG  
ATGAAGAAGAACAAAAACGATTAACGAAAAATACGCTTAGATAAAAAGAAAGTAAATTAATATTTCTTCTCCTGAAAGAACTCAAATACTACTAA  
50 AATTAAGAAGCTTCATTTCCAAAGATTTCAAGACCTAAGATTTGAAAAGAAAACAGAAAAAAGAAAAAATAGTCAACAGCTTAGCCAAAACCTAATCGC  
ATTAGAAGTGCACCTATATTTGTAGTAGCATTCTAGTCAITTTAGTTTCCGTTTTCTACTAATCTCTTTTAGTAAAGCAAAAACAATAACAGTTA  
GTGGAAATCAGCATACACCTGATGATTTTGTATAGAGAAAACGAATATTTCAAATAAACGATTTTCTTTTCTTTAATTTTAAACATAAAGCTAT  
TGAACCAACGTTTAAAGTGCAGAAAGATGATGGGTAAAACAGCTCAGATGACTTATCAATTTCCCAATAAGTTTCATATTCAGTTCAAGAAAATAAG  
ATTATTGCATATGCACATACAAAGCAAGGATATCAACCTGTCTTGGAAACTGGAAAAAGGCTGATCCTGTAATAGTTTCAGAGCTACCAAGCACT  
55 TCTTAAACAATAACCTTGATAAGGAAGATAGTATTAAGCTATTAATTAAGATTTAAAGGCTTTAGACCCCTGATTTAATAAGTGAGATTCAGGTGAT  
AAGTTTAGCTGATTTCAAACGACACCTGACCTCTGCTGTAGATATGCACGATGGAATAGTATTAGAATACCATTATCTAATTTAAAGAAAGA  
CTTCCCTTTTACAAAACAAATTAAGAAAGAACTTAAGGAACCTTCTATTTGTTGATATGGAAGTGGGAGTTTACACAACAACAATAACCATTTGAATCAA  
CCCTGTAAAGCAGAAAGATACAAAAATAAATCAACTGATAAAAACAAAACAAAATGGTCAGGTTGCGGAAAATAGTCAAGGACAAAACAATAA  
CTCAAATACTAATCAACAAGGACAACAGATAGCAACAGAGCAGGCACCTAACCTCAAATGTTAAT

SEQ ID NO. 42

5 MPKKKSDTPEKEEVVLTEWQKRNLEFLKRRKEDEEBEQKRINEKLRRLDKRSKLNISSEPEPQNTTKIKKLHFPKISRPKIEKKQKKEKIVNSLAKTNR  
 IRTAPIFVVAFLVILVSVFLITPFSKQKTIIVSGNQHTPDDILIEKTNIQKNDYFFSLIFKHKAIEQRLLAAEDVWVKTAQMTYQFPNKFHIQVQENK  
 I IAYAHTKQGYQPVLETGKKADPVNSSELPKHFLTINLDKEDSIKLLIKDLKALDPDLISEIQVISELADSKTTPDLLLLDMHDGNSIRIPLSKFKER  
 LPPFYKQIKKNLKEPFSIVDMEVGVYTTTNTIESTPVKAEDTKNKSTDKTQTQNGQVAENSQGTNNSNTNQOQQQIATEQAPNPQNVN

GBS polypeptides of the invention may be present in the composition as individual separate polypeptides. It is preferred, however, that two or more (*i.e.* 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20) of the antigens are expressed as a single polypeptide chain (a 'hybrid' polypeptide). Hybrid polypeptides offer two principal advantages: first, a polypeptide that may be unstable or poorly expressed on its own can be assisted by adding a suitable hybrid partner that overcomes the problem; second, commercial manufacture is simplified as only one expression and purification need be employed in order to produce two polypeptides which are both antigenically useful.

The hybrid polypeptide may comprise two or more polypeptide sequences from the first antigen group. Accordingly, the invention includes a composition comprising a first amino acid sequence and a second amino acid sequence, wherein said first and second amino acid sequences are selected from a GBS antigen or a fragment thereof. Preferably, the first and second amino acid sequences in the hybrid polypeptide comprise different epitopes.

The hybrid polypeptide may comprise one or more polypeptide sequences from different GBS serotypes. Accordingly, the invention includes a composition comprising a first amino acid sequence and a second amino acid sequence, said first amino acid sequence and said second amino acid sequence selected from a GBS serotype selected from the group consisting of serotypes Ia, Ib, 25 Ia/c, II, III, IV, V, VI, VII and VIII. The first and second amino acid sequence may be from the same GBS serotype or they may be from different GBS serotypes. Preferably, the first and second amino acid sequence are selected a GBS serotype selected from the group consisting of serotypes II and V. Most preferably, at least one of the first and second amino acid sequences is from GBS serotype V. Preferably, the first and second amino acid sequences in the hybrid polypeptide comprise difference 30 epitopes.

In one embodiment, the hybrid polypeptide comprises one or more GBS antigens from serotype V. Preferably, the hybrid polypeptide comprises a first amino acid sequence and a second amino acid sequence, said first amino acid sequence and said second amino acid sequence comprising a GBS antigen or a fragment thereof selected from the group consisting of GBS 80, GBS 35 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691. Preferably, the GBS antigen or fragment thereof is selected from the group consisting of GBS 80 and GBS 691. Preferably, the first and second amino acid sequences in the hybrid polypeptide comprise difference epitopes.

Hybrids consisting of amino acid sequences from two, three, four, five, six, seven, eight, nine, or ten GBS antigens are preferred. In particular, hybrids consisting of amino acid sequences from two, three, four, or five GBS antigens are preferred.

Different hybrid polypeptides may be mixed together in a single formulation. Within such combinations, a GBS antigen may be present in more than one hybrid polypeptide and/or as a non-hybrid polypeptide. It is preferred, however, that an antigen is present either as a hybrid or as a non-hybrid, but not as both.

Preferably, the GBS antigen in one of the hybrid polypeptides is GBS 80 or a fragment thereof. Accordingly, examples of two-antigen hybrids for use in the invention may comprise: (1) GBS 80 and GBS 91, (2) GBS 80 and GBS 104, (3) GBS 80 and GBS 147, (4) GBS 80 and GBS 173, (5) GBS 80 and GBS 276, (6) GBS 80 and GBS 305, (7) GBS 80 and GBS 313, (8) GBS 80 and GBS 322, (9) GBS 80 and GBS 328, (10) GBS 80 and GBS 330, (11) GBS 80 and GBS 338, (12) GBS 80 and GBS 358, (13) GBS 80 and GBS 361, (14) GBS 80 and GBS 404, (14) GBS 80 and GBS 404, (15) GBS 80 and GBS 656, (16) GBS 80 and GBS 690, and (17) GBS 80 and GBS 691. Preferably, a two-antigen hybrid for use in the invention comprises GBS 80 and GBS 691.

Hybrid polypeptides can be represented by the formula  $\text{NH}_2\text{-A-}\{-\text{X-L-}\}_n\text{-B-COOH}$ , wherein: X is an amino acid sequence of a GBS antigen or a fragment thereof; L is an optional linker amino acid sequence; A is an optional N-terminal amino acid sequence; B is an optional C-terminal amino acid sequence; and  $n$  is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15.

If a -X- moiety has a leader peptide sequence in its wild-type form, this may be included or omitted in the hybrid protein. In some embodiments, the leader peptides will be deleted except for that of the -X- moiety located at the N-terminus of the hybrid protein *i.e.* the leader peptide of  $X_1$  will be retained, but the leader peptides of  $X_2 \dots X_n$  will be omitted. This is equivalent to deleting all leader peptides and using the leader peptide of  $X_1$  as moiety -A-.

For each  $n$  instances of  $\{-\text{X-L-}\}$ , linker amino acid sequence -L- may be present or absent. For instance, when  $n=2$  the hybrid may be  $\text{NH}_2\text{-X}_1\text{-L}_1\text{-X}_2\text{-L}_2\text{-COOH}$ ,  $\text{NH}_2\text{-X}_1\text{-X}_2\text{-COOH}$ ,  $\text{NH}_2\text{-X}_1\text{-L}_1\text{-X}_2\text{-COOH}$ ,  $\text{NH}_2\text{-X}_1\text{-X}_2\text{-L}_2\text{-COOH}$ , *etc.* Linker amino acid sequence(s) -L- will typically be short (*e.g.* 20 or fewer amino acids *i.e.* 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples comprise short peptide sequences which facilitate cloning, poly-glycine linkers (*i.e.* comprising  $\text{Gly}_n$  where  $n = 2, 3, 4, 5, 6, 7, 8, 9, 10$  or more), and histidine tags (*i.e.*  $\text{His}_n$  where  $n = 3, 4, 5, 6, 7, 8, 9, 10$  or more). Other suitable linker amino acid sequences will be apparent to those skilled in the art. A useful linker is GSGGGG (SEQ ID 1), with the Gly-Ser dipeptide being formed from a *Bam*HI restriction site, thus aiding cloning and manipulation, and the  $(\text{Gly})_4$  tetrapeptide being a typical poly-glycine linker.



-A- is an optional N-terminal amino acid sequence. This will typically be short (e.g. 40 or fewer amino acids *i.e.* 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include leader sequences to direct protein trafficking, or short peptide sequences which facilitate cloning or purification (e.g. histidine tags *i.e.* His<sub>n</sub> where *n* = 3, 4, 5, 6, 7, 8, 9, 10 or more). Other suitable N-terminal amino acid sequences will be apparent to those skilled in the art. If X<sub>1</sub> lacks its own N-terminus methionine, -A- is preferably an oligopeptide (e.g. with 1, 2, 3, 4, 5, 6, 7 or 8 amino acids) which provides a N-terminus methionine.

-B- is an optional C-terminal amino acid sequence. This will typically be short (e.g. 40 or fewer amino acids *i.e.* 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include sequences to direct protein trafficking, short peptide sequences which facilitate cloning or purification (e.g. comprising histidine tags *i.e.* His<sub>n</sub> where *n* = 3, 4, 5, 6, 7, 8, 9, 10 or more), or sequences which enhance protein stability. Other suitable C-terminal amino acid sequences will be apparent to those skilled in the art. Most preferably, *n* is 2 or 3.

### ***The saccharide antigen***

The saccharide antigen is generally the capsular polysaccharide of a GBS or a derivative thereof. Suitable derivatives include oligosaccharide (e.g. from 3 to 150, preferably 8 to 100, monosaccharide units) fragments of the polysaccharide (e.g. refs. 12 to 16), de-acetylated saccharides (Ref. 16), N-acroylated saccharides (16), saccharides with terminal aldehyde groups, *etc.*

The saccharide is preferably conjugated to a carrier molecule to enhance immunogenicity (e.g. see refs. 4 to 23 *etc.*). In some embodiments of the invention the GBS saccharide is conjugated to a GBS protein as defined above, thereby giving a polypeptide/saccharide combination of the invention in a single molecule. In other embodiments the GBS saccharide is conjugated to a non-GBS protein, in which case the conjugate will be combined with a separate GBS protein to give a polypeptide/saccharide combination of the invention.

Non-GBS carrier polypeptides include tetanus toxoid, the *N.meningitidis* outer membrane protein (24), synthetic peptides (25, 26), heat shock proteins (27, 28), pertussis proteins (29, 30), protein D from *H.influenzae* (31), cytokines (32), lymphokines (32), hormones (32), growth factors (32), toxin A or B from *C.difficile* (33), iron-uptake proteins (34) *etc.* Preferred carrier proteins are the CRM197 diphtheria toxoid (35) and tetanus toxoid.

The saccharide and polypeptide are joined covalently. This may involve a direct covalent bond between the saccharide and polypeptide, or indirect coupling via a linker or spacer may be used (e.g. via a B-propionamido linker (16), *etc.*). Any suitable conjugation chemistry may be used (e.g. reductive amination (21) *etc.*). Linkage is preferably via a terminal saccharide in the polysaccharide.

A single carrier molecule may carry saccharide antigens of a single type (*e.g.* saccharides derived from a single GBS serotype) or may carry multiple different antigens (*e.g.* saccharides derived from multiple GBS serotypes, all conjugated to the same carrier).

The saccharides can, of course, be prepared by various means (*e.g.* purification of the  
5 saccharide from GBS, chemical synthesis, *etc.*), in various sizes (*e.g.* full-length, fragmented, *etc.*) and may be derivatised for linking to carriers. They are preferably prepared in substantially pure form (*i.e.* substantially free from other streptococcal saccharides) or substantially isolated form. Processes for preparing capsular polysaccharides from GBS are well known in the art (*e.g.* refs. 36 to 39) and processes for preparing oligosaccharides from polysaccharides are also known (*e.g.*  
10 hydrolysis, sonication, enzymatic treatment, treatment with a base followed by nitrosation, *etc.* (12 to 16)).

As an alternative to using a saccharide antigen in non-conjugated combinations, a peptide mimetic of the GBS capsular polysaccharide may be used (*e.g.* 40). Suitable peptides can be selected by techniques such as phage display using protective anti-saccharide antibodies. As a further  
15 alternative, an anti-idiotypic antibody may be used instead of a saccharide antigen (*e.g.* ref. 41).

#### ***Prime/boost schedules***

Polypeptide/saccharide combinations of the invention may be given as single doses or as part of a prime/boost schedule. In a prime/boost schedule, the combinations may be used as the priming  
20 dose, the boosting dose(s), or both.

If a combination is used for both priming and boosting, it is preferred to use the same combination both times. If a combination is used for only one of priming and boosting, it is preferred that the other dose should use the polypeptide or saccharide on which the combination is based. Thus the invention provides a prime-boost schedule where either (i) one of the saccharide and  
25 polypeptide antigens is used for priming an immune response and a combination are used for boosting the response, or (ii) combined saccharide and polypeptide antigens are used for priming an immune response but only one is used for boosting the response.

Various timings for priming and boosting are suitable for use with the invention. In one embodiment, a priming dose is given to a child and a booster is given to a teenager (13-18 years) or  
30 young adult (19-25 years). In another embodiment, a priming dose is given to a teenager or young adult and a booster is given during pregnancy. In another embodiment, a priming dose is given to a female who intends to become pregnant and a booster is given during pregnancy.

#### ***Immunogenic pharmaceutical compositions***

35 Polypeptide/saccharide combinations are formulated as immunogenic compositions, and more preferably as compositions suitable for use as a vaccine in humans (*e.g.* children or adults).

Vaccines of the invention may either be prophylactic (*i.e.* to prevent infection) or therapeutic (*i.e.* to treat disease after infection), but will typically be prophylactic. Accordingly, the invention includes a method for the therapeutic or prophylactic treatment of GBS infection in an animal susceptible to GBS infection comprising administering to said animal a therapeutic or prophylactic amount of the immunogenic compositions of the invention.

The composition of the invention is preferably sterile.

The composition of the invention is preferably pyrogen-free.

The composition of the invention generally has a pH of between 6.0 and 7.0, more preferably to between 6.3 and 6.9 *e.g.* 6.6±0.2. The composition is preferably buffered at this pH.

Other components suitable for human administration are disclosed in reference 42.

Vaccines of the invention may be administered in conjunction with other immunoregulatory agents. In particular, compositions will usually include an adjuvant. Preferred further adjuvants include, but are not limited to, one or more of the following set forth below:

A. Mineral Containing Compositions

Mineral containing compositions suitable for use as adjuvants in the invention include mineral salts, such as aluminium salts and calcium salts. The invention includes mineral salts such as hydroxides (*e.g.* oxyhydroxides), phosphates (*e.g.* hydroxyphosphates, orthophosphates), sulphates, *etc.* {*e.g.* see chapters 8 & 9 of ref. 43}, or mixtures of different mineral compounds, with the compounds taking any suitable form (*e.g.* gel, crystalline, amorphous, *etc.*), and with adsorption being preferred. The mineral containing compositions may also be formulated as a particle of metal salt. See ref. 44.

B. Oil-Emulsions

Oil-emulsion compositions suitable for use as adjuvants in the invention include squalene-water emulsions, such as MF59 (5% Squalene, 0.5% Tween 80, and 0.5% Span 85, formulated into submicron particles using a microfluidizer). See ref. 45.

Complete Freund's adjuvant (CFA) and incomplete Freund's adjuvant (IFA) may also be used as adjuvants in the invention.

C. Saponin Formulations

Saponin formulations, may also be used as adjuvants in the invention. Saponins are a heterologous group of sterol glycosides and triterpenoid glycosides that are found in the bark, leaves, stems, roots and even flowers of a wide range of plant species. Saponin from the bark of the *Quillaja saponaria* Molina tree have been widely studied as adjuvants. Saponin can also be commercially obtained from *Smilax ornata* (sarsaparilla), *Gypsophilla paniculata* (brides veil), and *Saponaria officianalis* (soap root). Saponin adjuvant formulations include purified formulations, such as QS21, as well as lipid formulations, such as ISCOMs.

Saponin compositions have been purified using High Performance Thin Layer Chromatography (HP-LC) and Reversed Phase High Performance Liquid Chromatography (RP-

HPLC). Specific purified fractions using these techniques have been identified, including QS7, QS17, QS18, QS21, QH-A, QH-B and QH-C. Preferably, the saponin is QS21. A method of production of QS21 is disclosed in U.S. Patent No. 5,057,540. Saponin formulations may also comprise a sterol, such as cholesterol (see WO 96/33739).

5 Combinations of saponins and cholesterol can be used to form unique particles called Immunostimulating Complexs (ISCOMs). ISCOMs typically also include a phospholipid such as phosphatidylethanolamine or phosphatidylcholine. Any known saponin can be used in ISCOMs. Preferably, the ISCOM includes one or more of Quil A, QHA and QHC. ISCOMs are further described in EP 0 109 942, WO 96/11711 and WO 96/33739. Optionally, the ISCOMS may be  
10 devoid of additional detergent. See ref. 46.

A review of the development of saponin based adjuvants can be found at ref. 47.

C. Virosomes and Virus Like Particles (VLPs)

Virosomes and Virus Like Particles (VLPs) can also be used as adjuvants in the invention. These structures generally contain one or more proteins from a virus optionally combined or  
15 formulated with a phospholipid. They are generally non-pathogenic, non-replicating and generally do not contain any of the native viral genome. The viral proteins may be recombinantly produced or isolated from whole viruses. These viral proteins suitable for use in virosomes or VLPs include  
20 proteins derived from influenza virus (such as HA or NA), Hepatitis B virus (such as core or capsid proteins), Hepatitis E virus, measles virus, Sindbis virus, Rotavirus, Foot-and-Mouth Disease virus, Retrovirus, Norwalk virus, human Papilloma virus, HIV, RNA-phages, Q $\beta$ -phage (such as coat  
proteins), GA-phage, fr-phage, AP205 phage, and Ty (such as retrotransposon Ty protein p1). VLPs are discussed further in WO 03/024480, WO 03/024481, and Refs. 48, 49, 50 and 51. Virosomes are discussed further in, for example, Ref. 52

D. Bacterial or Microbial Derivatives

25 Adjuvants suitable for use in the invention include bacterial or microbial derivatives such as:

(1) *Non-toxic derivatives of enterobacterial lipopolysaccharide (LPS)*

Such derivatives include Monophosphoryl lipid A (MPL) and 3-O-deacylated MPL (3dMPL). 3dMPL is a mixture of 3 De-O-acylated monophosphoryl lipid A with 4, 5 or 6 acylated  
30 chains. A preferred "small particle" form of 3 De-O-acylated monophosphoryl lipid A is disclosed in EP 0 689 454. Such "small particles" of 3dMPL are small enough to be sterile filtered through a 0.22 micron membrane (see EP 0 689 454). Other non-toxic LPS derivatives include monophosphoryl lipid A mimics, such as aminoalkyl glucosaminide phosphate derivatives e.g. RC-529. See Ref. 53.

(2) *Lipid A Derivatives*

35 Lipid A derivatives include derivatives of lipid A from *Escherichia coli* such as OM-174. OM-174 is described for example in Ref. 54 and 55.

(3) *Immunostimulatory oligonucleotides*

Immunostimulatory oligonucleotides suitable for use as adjuvants in the invention include nucleotide sequences containing a CpG motif (a sequence containing an unmethylated cytosine followed by guanosine and linked by a phosphate bond). Bacterial double stranded RNA or oligonucleotides containing palindromic or poly(dG) sequences have also been shown to be immunostimulatory.

The CpG's can include nucleotide modifications/analogs such as phosphorothioate modifications and can be double-stranded or single-stranded. Optionally, the guanosine may be replaced with an analog such as 2'-deoxy-7-deazaguanosine. See ref. 56, WO 02/26757 and WO 99/62923 for examples of possible analog substitutions. The adjuvant effect of CpG oligonucleotides is further discussed in Refs. 57, 58, WO 98/40100, U.S. Patent No. 6,207,646, U.S. Patent No. 6,239,116, and U.S. Patent No. 6,429,199.

The CpG sequence may be directed to TLR9, such as the motif GTCGTT or TTCGTT. See ref. 59. The CpG sequence may be specific for inducing a Th1 immune response, such as a CpG-A ODN, or it may be more specific for inducing a B cell response, such as a CpG-B ODN. CpG-A and CpG-B ODNs are discussed in refs. 60, 61 and WO 01/95935. Preferably, the CpG is a CpG-A ODN. Preferably, the CpG oligonucleotide is constructed so that the 5' end is accessible for receptor recognition. Optionally, two CpG oligonucleotide sequences may be attached at their 3' ends to form "immunomers". See, for example, refs. 62, 63, 64 and WO 03/035836.

(4) *ADP-ribosylating toxins and detoxified derivatives thereof.*

Bacterial ADP-ribosylating toxins and detoxified derivatives thereof may be used as adjuvants in the invention. Preferably, the protein is derived from *E. coli* (i.e., *E. coli* heat labile enterotoxin "LT), cholera ("CT"), or pertussis ("PT"). The use of detoxified ADP-ribosylating toxins as mucosal adjuvants is described in WO 95/17211 and as parenteral adjuvants in WO 98/42375. Preferably, the adjuvant is a detoxified LT mutant such as LT-K63, LT-R72, and LTR192G. The use of ADP-ribosylating toxins and detoxified derivatives thereof, particularly LT-K63 and LT-R72, as adjuvants can be found in Refs. 65, 66, 67, 68, 69, 70, 71 and 72 each of which is specifically incorporated by reference herein in their entirety. Numerical reference for amino acid substitutions is preferably based on the alignments of the A and B subunits of ADP-ribosylating toxins set forth in Domenighini et al., *Mol. Microbiol* (1995) 15(6):1165 – 1167, specifically incorporated herein by reference in its entirety.

E. Human Immunomodulators

Human immunomodulators suitable for use as adjuvants in the invention include cytokines, such as interleukins (e.g. IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, etc.), interferons (e.g. interferon- $\gamma$ ), macrophage colony stimulating factor, and tumor necrosis factor.

F. Bioadhesives and Mucoadhesives

Bioadhesives and mucoadhesives may also be used as adjuvants in the invention. Suitable bioadhesives include esterified hyaluronic acid microspheres (Ref. 73) or mucoadhesives such as

cross-linked derivatives of poly(acrylic acid), polyvinyl alcohol, polyvinyl pyrrolidone, polysaccharides and carboxymethylcellulose. Chitosan and derivatives thereof may also be used as adjuvants in the invention. E.g., ref. 74.

G. Microparticles

5            Microparticles may also be used as adjuvants in the invention. Microparticles (*i.e.* a particle of ~100nm to ~150 $\mu$ m in diameter, more preferably ~200nm to ~30 $\mu$ m in diameter, and most preferably ~500nm to ~10 $\mu$ m in diameter) formed from materials that are biodegradable and non-toxic (*e.g.* a poly( $\alpha$ -hydroxy acid), a polyhydroxybutyric acid, a polyorthoester, a polyanhydride, a polycaprolactone, *etc.*), with poly(lactide-co-glycolide) are preferred, optionally treated to have a  
10 negatively-charged surface (*e.g.* with SDS) or a positively-charged surface (*e.g.* with a cationic detergent, such as CTAB).

H. Liposomes

Examples of liposome formulations suitable for use as adjuvants are described in U.S. Patent No. 6,090,406, U.S. Patent No. 5,916,588, and EP 0 626 169.

15 I. Polyoxyethylene ether and Polyoxyethylene Ester Formulations

Adjuvants suitable for use in the invention include polyoxyethylene ethers and polyoxyethylene esters. Ref. 75. Such formulations further include polyoxyethylene sorbitan ester surfactants in combination with an octoxynol (Ref. 76) as well as polyoxyethylene alkyl ethers or ester surfactants in combination with at least one additional non-ionic surfactant such as an octoxynol  
20 (Ref. 77).

Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether (laureth 9), polyoxyethylene-9-stearyl ether, polyoxyethylene-8-stearyl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether.

J. Polyphosphazene (PCPP)

25 PCPP formulations are described, for example, in Ref. 78 and 79.

K. Muramyl peptides

Examples of muramyl peptides suitable for use as adjuvants in the invention include N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-normuramyl-L-alanyl-D-isoglutamine (nor-MDP), and N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-*sn*-glycero-3-  
30 hydroxyphosphoryloxy)-ethylamine MTP-PE).

L. Imidazoquinolone Compounds.

Examples of imidazoquinolone compounds suitable for use adjuvants in the invention include Imiquamod and its homologues, described further in Ref. 80 and 81.

The invention may also comprise combinations of aspects of one or more of the adjuvants identified  
35 above. For example, the following adjuvant compositions may be used in the invention:

- (1) a saponin and an oil-in-water emulsion (ref. 82);

- (2) a saponin (e.g., QS21) + a non-toxic LPS derivative (e.g., 3dMPL) (see WO 94/00153);
- (3) a saponin (e.g., QS21) + a non-toxic LPS derivative (e.g., 3dMPL) + a cholesterol;
- (4) a saponin (e.g. QS21) + 3dMPL + IL-12 (optionally + a sterol) (Ref. 83);
- 5 combinations of 3dMPL with, for example, QS21 and/or oil-in-water emulsions (Ref. 84);
- (5) SAF, containing 10% Squalane, 0.4% Tween 80, 5% pluronic-block polymer L121, and thr-MDP, either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion.
- (6) Rib<sup>i</sup><sup>TM</sup> adjuvant system (RAS), (Ribi Immunochem) containing 2% Squalene, 0.2%  
10 Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (Detox<sup>TM</sup>); and
- (7) one or more mineral salts (such as an aluminum salt) + a non-toxic derivative of LPS (such as 3dPML).
- 15 Aluminium salts and MF59 are preferred adjuvants for parenteral immunisation. Mutant bacterial toxins are preferred mucosal adjuvants.

The composition may include an antibiotic.

GBS polypeptide(s) and saccharide(s) in the compositions of the invention will be present in 'immunologically effective amounts' *i.e.* the administration of that amount to an individual, either in  
20 a single dose or as part of a series, is effective for treatment or prevention of disease. This amount varies depending upon the health and physical condition of the individual to be treated, age, the taxonomic group of individual to be treated (*e.g.* non-human primate, primate, *etc.*), the capacity of the individual's immune system to synthesise antibodies, the degree of protection desired, the formulation of the vaccine, the treating doctor's assessment of the medical situation, and other  
25 relevant factors. It is expected that the amount will fall in a relatively broad range that can be determined through routine trials.

Typically, the compositions of the invention are prepared as injectables. Direct delivery of the compositions will generally be parenteral (*e.g.* by injection, either subcutaneously, intraperitoneally, intravenously or intramuscularly or delivered to the interstitial space of a tissue) or  
30 mucosal (*e.g.* oral or intranasal [85,86]). The compositions can also be administered into a lesion. The invention provides a syringe containing a composition of the invention.

Once formulated, the compositions of the invention can be administered directly to the subject. The subjects to be treated can be animals; in particular, human subjects can be treated. The vaccines are particularly useful for vaccinating children and teenagers, and more particularly  
35 females.

As well as GBS polypeptides and saccharides, the composition of the invention may comprise further antigens. For example, the composition may comprise one or more of the following further antigens:

- antigens from *Helicobacter pylori* such as CagA [87 to 90], VacA [91, 92], NAP [93, 94, 95],  
5 HopX [e.g. 96], HopY [e.g. 96] and/or urease.
- a saccharide antigen from *N.meningitidis* serogroup A, C, W135 and/or Y, such as the oligosaccharide disclosed in ref. 97 from serogroup C [see also ref. 98] or the oligosaccharides of ref. 99.
- a saccharide antigen from *Streptococcus pneumoniae* [e.g. 100, 101, 102].
- 10 – an antigen from hepatitis A virus, such as inactivated virus [e.g. 103, 104].
- an antigen from hepatitis B virus, such as the surface and/or core antigens [e.g. 104, 105].
- an antigen from *Bordetella pertussis*, such as pertussis holotoxin (PT) and filamentous haemagglutinin (FHA) from *B.pertussis*, optionally also in combination with pertactin and/or agglutinogens 2 and 3 [e.g. refs. 106 & 107].
- 15 – a diphtheria antigen, such as a diphtheria toxoid [e.g. chapter 3 of ref. 108] e.g. the CRM<sub>197</sub> mutant [e.g. 109].
- a tetanus antigen, such as a tetanus toxoid [e.g. chapter 4 of ref. 128].
- a saccharide antigen from *Haemophilus influenzae* B [e.g. 98].
- an antigen from hepatitis C virus [e.g. 110].
- 20 – an antigen from *N.gonorrhoeae* [e.g. 111, 112, 113, 114].
- an antigen from *Chlamydia pneumoniae* [e.g. refs. 115 to 121].
- an antigen from *Chlamydia trachomatis* [e.g. 122].
- an antigen from *Porphyromonas gingivalis* [e.g. 123].
- polio antigen(s) [e.g. 124, 125] such as OPV or, preferably, IPV.
- 25 – rabies antigen(s) [e.g. 126] such as lyophilised inactivated virus [e.g. 127, RabAvert™].
- measles, mumps and/or rubella antigens [e.g. chapters 9, 10 & 11 of ref. 128].
- influenza antigen(s) [e.g. chapter 19 of ref. 128], such as the haemagglutinin and/or neuraminidase surface proteins.
- an antigen from *Moraxella catarrhalis* [e.g. 129].
- 30 – an antigen from *Streptococcus pyogenes* (group A streptococcus) [e.g. 3, 130, 131].
- an antigen from *Staphylococcus aureus* [e.g. 132].
- an antigen from *Bacillus anthracis* [e.g. 133, 134, 135].
- an antigen from a virus in the flaviviridae family (genus flavivirus), such as from yellow fever virus, Japanese encephalitis virus, four serotypes of Dengue viruses, tick-borne  
35 encephalitis virus, West Nile virus.



- a pestivirus antigen, such as from classical porcine fever virus, bovine viral diarrhoea virus, and/or border disease virus.
- a parvovirus antigen *e.g.* from parvovirus B19.
- a prion protein (*e.g.* the CJD prion protein)
- 5 - an amyloid protein, such as a beta peptide [136]
- a cancer antigen, such as those listed in Table 1 of ref. 137 or in tables 3 & 4 of ref. 138.

The composition may comprise one or more of these further antigens.

Toxic protein antigens may be detoxified where necessary (*e.g.* detoxification of pertussis toxin by chemical and/or genetic means [107]).

10 Where a diphtheria antigen is included in the composition it is preferred also to include tetanus antigen and pertussis antigens. Similarly, where a tetanus antigen is included it is preferred also to include diphtheria and pertussis antigens. Similarly, where a pertussis antigen is included it is preferred also to include diphtheria and tetanus antigens. DTP combinations are thus preferred. Saccharide antigens are preferably in the form of conjugates. Carrier proteins for the conjugates are  
15 the same as those described above for GBS saccharide conjugation, with CRM197 being preferred.

Antigens in the composition will typically be present at a concentration of at least 1 µg/ml each. In general, the concentration of any given antigen will be sufficient to elicit an immune response against that antigen.

As an alternative to using protein antigens in the composition of the invention, nucleic acid  
20 encoding the antigen may be used. Protein components of the compositions of the invention may thus be replaced by nucleic acid (preferably DNA *e.g.* in the form of a plasmid) that encodes the protein.

#### ***Methods of treating patients***

The invention provides polypeptide/saccharide combinations of the invention for use as  
25 medicaments. The medicament is preferably able to raise an immune response in a mammal (*i.e.* it is an immunogenic composition) and is more preferably a vaccine.

The invention also provides a method of raising an immune response in a patient, comprising  
administering to a patient a composition of the invention. The immune response is preferably protective against streptococcal disease, and may comprise a humoral immune response and/or a  
30 cellular immune response.

The invention also provides the use of polypeptide/saccharide combination of the invention in the manufacture of a medicament for raising an immune response in an patient. The medicament is preferably an immunogenic composition (*e.g.* a vaccine). The medicament is preferably for the prevention and/or treatment of a disease caused by GBS (*e.g.* meningitis, sepsis, chorioamnionitis).

The invention also provides for a kit comprising a first component comprising the immunogenic compositions of the invention. The kit may further include a second component comprising one or more of the following: instructions, syringe or other delivery device, adjuvant, or pharmaceutically acceptable formulating solution.

5 The invention also provides a delivery device pre-filled with the immunogenic compositions of the invention.

The invention also provides a method for raising an immune response in a mammal comprising the step of administering an effective amount of a composition of the invention. The immune response is preferably protective and preferably involves antibodies and/or cell-mediated  
10 immunity. The method may raise a booster response.

#### ***Process for manufacturing***

The invention provides a process for preparing a composition of the invention, comprising the step of mixing (i) one or more GBS polypeptide antigens with (ii) one or more GBS saccharide antigens.

15 The process may comprise the step of covalently linking the GBS polypeptide to the GBS saccharide in order to form a conjugate.

#### ***Definitions***

The term "comprising" means "including" as well as "consisting" e.g. a composition "comprising" X may consist exclusively of X or may include something additional e.g. X + Y.

20 The term "about" in relation to a numerical value  $x$  means, for example,  $x \pm 10\%$ .

The word "substantially" does not exclude "completely" e.g. a composition which is "substantially free" from Y may be completely free from Y. Where necessary, the word "substantially" may be omitted from the definition of the invention.

#### **MODES FOR CARRYING OUT THE INVENTION**

25 GBS serotype III is grown in Todd-Hewitt broth as described in reference 36 and its capsular polysaccharide was purified. The polysaccharide is depolymerised, sized and purified as described in reference 14 to give oligosaccharide antigen. Similar procedures are used to prepare capsular polysaccharides from other GBS serotypes.

The oligosaccharide is either admixed with or covalently conjugated (directly or via a linker)  
30 to purified serotype V protein. Preferably, the protein comprises a GBS antigen or a fragment thereof selected from the group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.

It will be understood that the invention has been described by way of example only and modifications may be made whilst remaining within the scope and spirit of the invention. All documents cited herein are incorporated by reference in their entirety.

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## CLAIMS:

1. An immunogenic composition comprising a GBS saccharide antigen and at least two GBS polypeptide antigens, wherein said GBS saccharide antigen comprises a saccharide selected from GBS serotype Ia, Ib, and III, and wherein said GBS polypeptide antigens comprise a combination of at least two polypeptide or fragments thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.
2. The immunogenic composition of claim 1, wherein said GBS polypeptide antigens further comprise a GBS polypeptide or a fragment thereof of serogroup II.
3. The immunogenic composition of claim 1, wherein said GBS polypeptide antigen combination comprises GBS 80 or a fragment thereof.
4. The immunogenic composition of claim 3, wherein said GBS polypeptide antigens comprise a combination of two GBS antigens or fragments thereof selected from the group consisting of (1) GBS 80 and GBS 91, (2) GBS 80 and GBS 104, (3) GBS 80 and GBS 147, (4) GBS 80 and GBS 173, (5) GBS 80 and GBS 276, (6) GBS 80 and GBS 305, (7) GBS 80 and GBS 313, (8) GBS 80 and GBS 322, (9) GBS 80 and GBS 328, (10) GBS 80 and GBS 330, (11) GBS 80 and GBS 338, (12) GBS 80 and GBS 358, (13) GBS 80 and GBS 361, (14) GBS 80 and GBS 404, (14) GBS 80 and GBS 404, (15) GBS 80 and GBS 656, (16) GBS 80 and GBS 690, and (17) GBS 80 and GBS 691.
5. The immunogenic composition of claim 4, wherein said combination is selected from the group consisting of (1) GBS 80 and GBS 338; (2) GBS 80 and GBS 361, (3) GBS 80 and GBS 305, (4) GBS 80 and GBS 328, (5) GBS 80 and GBS 690, (6) GBS 80 and GBS 691 and (7) GBS 80 and GBS 147.

6. The immunogenic composition of claim 4, wherein said combination comprises GBS 80 and GBS 691.
7. The immunogenic composition of claim 1, wherein said composition comprises a combination of at least three GBS polypeptide antigens.
8. The immunogenic composition of claim 7, wherein said combination comprises GBS 80 and GBS 691.
9. The immunogenic composition of claim 7, wherein said combination comprises GBS 80.
10. The immunogenic composition of claim 1, wherein at least one GBS polypeptide antigen is covalently linked to the GBS saccharide antigen.
11. The immunogenic composition of claim 1, wherein said GBS saccharide antigen is covalently linked to a carrier protein.
12. The immunogenic composition of claim 11, wherein said carrier protein is selected from the group consisting of tetanus toxoid, diphtheria toxoid, *N. meningitides* outer membrane protein, heat shock protein, pertusis protein, protein D from *H. influenzae*, and toxin A or B from *C. difficile*.
13. The immunogenic composition of claim 12, wherein said carrier protein is selected from the group consisting of tetanus toxoid and diphtheria toxoid.
14. The immunogenic composition of claim 13, wherein said carrier protein is a diphtheria toxoid.
15. The immunogenic composition of claim 14, wherein said diphtheria toxoid is CRM197.

16. A method for the therapeutic or prophylactic treatment of GBS infection in an animal susceptible to GBS infection comprising administering to said animal a therapeutic or prophylactic amount of the immunogenic composition of claim 1.

17. A method for the manufacture of a medicament for raising an immune response against GBS comprising combining a GBS saccharide antigen and at least two GBS polypeptide antigens, wherein said GBS saccharide antigen comprises a saccharide selected from GBS serotype Ia, Ib, and III, and wherein said GBS polypeptide antigens comprise a combination of at least two polypeptide or fragments thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.

SEQUENCE LISTING

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SEQ ID NO. 9

ATGAAACGTAATACTTTATTTCTTAATACGGTGACGGTTTTAACGTTAGCTGCTGCAATGAATACTAGCAGTATCTATGCTAATAGTACTGAGACA
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CCTGTCTGTGAGAGTACTTCTACTAAGTTAACTGAAGAGACTTACAACAACAAAAGATGGTCAAGATTTAGCCAACTGGTGAGAAAGGTTCAAGTT
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GAAGAGGCTAGAAAACCTTAAAGATACCAATCAGCCGTTTTAGTGTTCCTTGTAGTCAAGGGGTTAGGGCAGATTTAAAGGTTGGTGAACC
AATAATGGCTTGATCTATGCAGATGGAAAAATTAGCACATTTGACAGTAGTATGTCAAAAATAAAGATTTAGGATTTATTTTAGGACAA
ACGAACTTTCCAGATFATGGGTGGCGTAATATAACAGATTTCTAAATTAACGTTTAAACGCTAATAGTGAACAACGTCACATTTCTTAAGAAAACAAGGATTCAAAGTAAACA
GAGATAGACTTACCAATTTGATGGTAGAGCATTAATGCGTGTATTTCAACCTTGGCTATTTGGCATGGGAGGAGCTTTTTCAACAATGAAAAAGAC
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AGTTTAAAGCTTCAATAACAGATCCATATGTAACAGAGGAAGATAAAGAGAGCAGTTTTATAATATGGAATAAAGCTTGGAGCAAGAAAGAAATTTGCT
CTCTTTAATCGCCAGTGGGAGCCTATGTTGCGTAGAACCTTTTACACAAATTTGCTAATATGACAGGACTCCAGCTATCAGTATCCGACTTAC
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TCATCATTAGTAAATTTAGAAGAAAATTCAGAAATTTACTCAAGTATCTATCTCTAAAAAATGGATGAATCGTCTGTTAAAAATAAACCATCCGTA
ATGGCATATCAAAAAGCACTTCCATAACAGGTTGATACAGAATCAAGCCTATCTCCAGTTTTAGTAGTAACCCTTTTATAGCTTGTTTAGCTTT
GTAACAAAAAAGAAATCAGAAAAGT

SEQ ID NO. 10

MKRKYFLLNTVTVLTLAAAMNTSSITYANSTETSASVVPNTNTIVQTNDSNPTAKFVSESGQSVIGQVKPDNSAALTVDTPHHISAPDALKTKTQSS
PVVESTSTKLTEETYKQKDGQDLANMVRSGQVTSEELVNMAFYDI IAKENPSLNAVITRRQEAIEEARKLKDNTQPFVGLVPLLVKGLGHSIKGGET
NNGLIYADGKISTFDSYVVKYKDLGFIILGQTNFPEYGNRNI TDSKLYGLTHNPWDLAHNAGSSGGSAAIASGMTPIASGSDAGGSIRIPSSW
TGLVGLKPTRGLVSNKPKDSYSTAVHFPLTKSSRDAETLLTYLKKSDQTLVSVNDLKLSPAIAYTLKSPMGTEVSQDAKNAIMDNVTLFRKQGFKVT
EIDLPI DGRALMRDYSTLAI GMGAFSTIEKDLKKGFTKEDVDPITWAVHVIYQNSDKAELKKSIMEAQKHMDYRKAMEKHLKQFPFI FLSPTTA
SLAPLNTDPYVTEEDKRAIYNMENLSQEERIALFNQWPEMLRRTPFTQIANMTGLPAISIPTYLSESLPIGTM LMAGANYDMVLIKFATPFKEH
HGFNVKQRIIDKEVKPSTGLIQPTNSL FKAHSSLVNLEENSQVTQVSI SKKWMKSSVKNKPSVMAYQKALPKTGDTESSLS PVLVVLLLLACFSF
VTKKNQKS

SEQ ID NO. 11

TTCGCTAAAAAACAACAACTACCAATTGATAAACTTGCCATTGCGCTTATATCTACGAGCATCTTGCTCAATGCACAATCAGACATTAAAGCAAAT
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ACCTCACAAACTCCTAGTGATGTAGGAGAAACAGTAGCAGATGACGCTAATGATCTAGCCCCTCAAGCTCCTGCTAAAACTGCTGATACACCGCA
ACCTCAAAGCGACTATTAGGGATTTGAACGACCCCTTCTCATGTCAAACCCCTGCAGGAAAAAGCAGGCAAGGGAGCTGGGACCGTTGTCAGTG
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CAAGACGATGATAGCCA TACTATATCCACCGTACGCTAATGAGCAACATATGCTGCGATCTCTCAAATGGGGACGGTAAACAGATTATGTC
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GTTGTTGCTAACGGAACCTACACCTATCGTTCGCTACACCGGATTAGCTCAGGTGCAAAGAACAACACACTGATTTTGTGATGTTGTTAGC
AATAACGACCTGAAGTCGCAACATCGGCAACATCTCAACAGAAAGATAGTCGTTTGAACCTGTCATCTAAACCAAAAACAGCCCAACCGGTTTAC
CGTGAGCGTATGCTTACCTTATATGGATGAGGATCTGCCAACACAGAGTATATTTCTCAAATGAAGATGGTACCTTTACTCTTCTGAAAGAG
GCTGAAACAATGGAAGGGCGTACTGTTCCATGAAAATGTCAGACTTTACTTATGTTGTTGAAGATAATGGTGGTAAACATCACTTATACACCAAGT
ACTAAGCTATTGGAGGGCCACTCTAATAAGCCAGAACAAGACGTTT CAGATCAAGCACAGACAAGAAACCAAGAGCTAAACCAAGAAACAAGCGGT
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CGTACTCTAGAGAAAGCATCTTCTAAGCGTCTTTAGCTACAAAAGCATCAACAAGAGATCAGTTACCAACGACTAATGACAAGGATACAAATCGT
TTACATCTCCTTAAGTTAGTTATGACCACCTTCTTCTTGGGA

SEQ ID NO. 12

MRKKQKLPFDKLAIALISTSI LLNAQSDIKANTVTEDETPATEQAVEPPQPIAVSEESRSSKETKTSQTPSDVGETVADDANDLAPQ
APAKTADTPATSKATIRDLNDPSHVKTLQEKAGKAGTVVAVIDAGFDKNHEAWRLTDKTKARYQSKENLEKAKKEHGI TYGEWVN
DKVAYYHDYSKDGKNAVDQEHGTHVSGILSGNAPSEMKEPYRLEGAMPEAQ LLLLMRVEIVNGLADYARNYAQAIRDVAVNLGAKVIN
MSFGNAALAYANLPDETKKAFDYAKSGVSI VTSAGNDS SFGGKPRPLADHPDYGVVGT PAAADSTLTVASYS PDKQLTETATVK
TDDHQDKEMPVISTNRFEPNKAYDYAYANRGTKEDDFKDVGEKIALIERGIDDFKDKIANAKKAGAVGVLIYDNQDKGFPIELPNV
DQMPAAFISRRDGLLLKDNPKPTITFNATPKVLPTASGTKLSRFSSWGLTADGNIKPDIAAPGQDILSSVANNKYAKLSGTSMSAP
LVAGTIMGLLQKQYETQYPDMTPSERLDLAKKVLMS SATALYDEDEKAYFSPRQQGAGAVDAKKAS AATMYVTDKNTSSKVHLN NV
SDKFEVTVTVHNKSDKPYELYQVTVQTDKVDGKH FALAPKALYETSWQKITIPANSSKQVTVPIDASRF SKDLLAQMKNGYFLEG
FVRFKQDPTKEELMSIPIYIGFRGDFGNLSALEKPIYDSKDGSSPYHEANSDAKDQLDGDGLQFYALKNNFTALTTESNPWTIYKAV
KEGVENIEDIESSEITETIFAGTFAKQDDSHYIHRHANGKPYAATSPNGDGNRDYVQFQGTFLRNAKNLVAEVL DKEGNVWVTS
EVTEQVVKYNNNDLASTLGS TRFEKTRWDGKDKDGKVVANGTYTYRVRYP I SSGAKEQHTDFDVI VDNTPPEVATSATFSTEDSR
LTLASKPKTSQPVYRERIA YTYMDEDLPTTEYISPNEGTF TLPEEAETMEGATVPLKMSDFTYVVEDMAGNIYTYTPVTKLLEGHS
NKPEQDGSQAPDKKPEAKPEQDGSQTPDKK KETKPEK DSSGQTPGKTPQKGQSSRTLEKRSSKRALATKASTRDQLPTTNDKDT
NRLHLLKLVMTTFFLG

SEQ ID NO. 13

ATGGGACGAGTAATGAAAAACAATAACAACATTTGAAAAATAAAAAAGTTTTAGTCTTGGTTTAGCACGATCTGGAGAAGCTGCTGC
ACGTTTGTAGTAAAGTTAGGAGCAATAGTGACAGTTAATGATGGCAAACCATTTGATGAAAAATCCAACAGCACAGTCTTTGTGG
AAGAGGGTATTAAGTGGTTTGTGGTAGTCATCCTTTAGAATTGTTAGATGAGGATTTTTGTACATGATTAATAAATCCAGGAATA
CCTTATAACAATCCTATGGTCAAAAAAGCATTAGAAAAACAATCCCTGTTTTGACTGAAGTGGAAATTAGCATACTTAGTTTCAGA
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CAAGACAAGCAACTTTCTATAAAGGGGAGAATATATGTGAGTAGATGACATTTGGTGTCCCAGGAAGCCATAACGTAGAGAATGC
TCTAGCAACTATTGCGGTTGCTAAACTGGCTGGTATCAGTAATCAAGTTATTAGAGAACTTTAAGCAATTTTGGAGGTGTTAAAC
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ATGCTTTAGATGTTAGAGATGCGGTACATAAAGCTTATGAGGTGGCAACAACAGGCGATGTTATCTTGTCTAAGTCTGCAAAATGCA
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SEQ ID NO. 14

MGRVMKTIITTFENKKVLVGLLARSGEAAARLLAKLGAIVTVNDGKPFDENPTAQSLEEGI KVVCGSHPLELLEDFCYMIKNPGI
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SSFQLMGVKEFRPHIAVINLMPHLDYHGSFEDYVAAKWNINQMSDDFLVLFNFGI SKELAKTTKATIVPFSTTEKVDGAYV
QDKQLFYKGENIMSVDIIVPGSHNVENALATIIVAKLAGISNOVIRETLNFGVVKHRLQSLGKVHGISFYNDSKSTNIIATQKA
LSGFDNTKVIILLAGGLDRGNEFDELIPIITGLKHMVVLGESASRVKRAAQKAGVTVSDALDVRDAVHKAYEVAQQGDVILLSPAN
SWDMYKNFEVRGDEFIDTFESLRGE

SEQ ID NO. 15

ATGAAACGTATTGCTGTTTTAACTAGTGGTGGTACGCCCTGGTATGAACGCTGCTATCCGTGCAGTTGTTGCTAAAGCAATTTGAAAGGTATG
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GGAAAGTTTTTACGTTTCAGCAGCTTATCCTGAATTTGCTGAACTTGAAGGTGAGTTAAAGGGATTGAACAGCTTAAAAACACGGTATTGAAGG
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SEQ ID NO. 16

MKRIAVLTSGGDAPGMNAAIRAVVRKAISEGMEVYGINQGYGMVTDIFPLDANSVGDITINRGGTFLRSARYPEFAELGQLKGI EQLKKHIEG
VVVIGDGSYHGAMRLTEHGFPVAVLPGTIDNDIVGTDYITIGFDTAVATAVENLDRDTSASHNRTFVVEVMGRNAGDIALWSGIAAGADQIIVP
EEEFNIDEVSVNVRAGYAAAGKHHQIIVLAEGVMSGDEFKTMKAAGDSDLRVTLNLGHLRGGSPFARDRVLASRMGAYAVQLLKEGRGLAVGVH
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SEQ ID NO. 17

ATGAATAAAAAGGTACTATTGACATCGACAATGGCAGCTTCGCTATTATCAGTCGCAAGTGTTCAGCACAGAAACAGATACGACGTTGGACAGCA
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CAGAAGAGTCACTGCCACTTCAATGAAAATAGAAACACCAGCAACAATGCTGCTGGTCAAACAACAGCTACTGTGGATTTGAAAACCAATCAA
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AGACTTTCAAGGTTCTTATATAATTTTTATTA



SEQ ID NO. 18

MNKKVLLTSTMAASLLSVASVQAQETDFTWTARTVSEVKADLVKQDNKSSYTVKYGDTLSVISEAMSIDMNVLAKINNIADINLIYPETTLTVTYD
QKSHATATSMKIEPATNAAGQTTATVDLKTNQVSVADQKVSINLTI SEGMPPEAATIVSPMKTYSSAPALKSKEVLAQEQAVSQAAANEQVSPAPV
KSTITSEVPAAKEEVKPTQTSVQSSTTVSPASVAAETPAPVAKVAPVRTVAAPRVASVKVTPKVTGASPEHVSAPAVPVTTTSPATDSKLQATEV
KSTVPAQKAPTATPVAQPASTTNAVAHPENAGLQPHVAAYKEKVASTYGVNEFSTYRAGDPGDHGKGLAVDFIVGTNQLGNKVAQYSTQNMAAN
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SEQ ID NO. 19

ATGAAAAAGAAAATATTTTGAAGTAGTGTCTTGGTTTGTGCTGGGACTTCTATTATGTTCTCAAGCGTTCGCGGACCAAGTCGGTGTC
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SEQ ID NO. 20

MKKKIILKSSVLLGLVAGTSMIFSSVFADQVGVQVIGVNDVHFGALDNTGTANMPDGKVANAGTAAQLDAYMDDAQKDFKQTNPNGESIRVQAGDMVG
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PVNNKSVNVGFIGIVTKDIPNLVLRKNYEQYEFLEAETIVKYAKELQAKNVKAIIVLHVLPATSKNDIAEAGEAAEMMKVNVQLFPENSVDIVFAG
HNHQYTNGLVKGTRIVQALSQKAYADVRLDQDFIETPSAKVIAVAPGKKTGSADIQAIQVQANTIVKQVTEAKIGTAEVSVMTIRSDVDQD
NVSPVGSLLITEAQLAIARKSWPIDFAMTNNGGIRADLLIKPDGTTTWGAAQAVQFPNGNIIQVVEITGRDLYKALNEQYDQKQNFLLQIAGLRITY
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ETITQNDGTHSIIKKLYLDRQNIVAQEIIVSDTLNQTKSKSTKINPVTTIHKKQLHQFTAIPNMRNYGKPSNSTTVKSKQLPKTNSEYQSFMSV
FGVGLIGIALNTRKKHKM

SEQ ID NO. 21

ATGAATAAACCGCTAAAATCGTTGCAACACTTGGTCTGCGGTTGAATCCGTTGGTGGTAAGAAGTTTGGTGAGTCTGGATACTGGGGTGAAGC
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CAAGGAGCTCGTATGGCTACTGTTTCGTAAAGCAGAGAGATGCAAGCAAAAAGTTGGCTTCCCTTGTATATAAAGGACCTGAAATTCGTACA
GAACTTTTGAAGATGTTGTCAGATTTCCATTATATACAAACAGGTACAAAATTAAGTGTGCTACTAAGCAAGGTATCAAACTCACTCCAGAAAGT
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TCTAAATCCGCTCCAGATGCAGACATTTGGCTGTTACATTTGATGAAAAAGTACAACCTTCAATGATGATTAAGTGGGTTTATCCCTGTCTT
GCAGACAAAACAGCATCTACAGATGATATGTTGAGGTTGCAAGCAGTGTAGCACTTGAAGCAGGATTTGTTGAATCAGGCGATAATATCGTTTATC
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SEQ ID NO. 22

MNKRVKIVATLGPVAFERGGKFGESGYWGESLDVEASAEDIAQLIKEGANVFRFNFSHGDHAEQGMATVRKAEETAGQKVGFLLDTKGPEIRT
ELFEDGADFHSYTTGTKLRVATKQGIKSTPEVIALNVAGGLDIFDDVEVGKQILVDDGKGLTVFAKDKDTRFEVTVVENDGLIGKQKGVNIPTK

IFPPALAEARNADIRFGLQGLNFIAISFVRTAKDVNEVRAICEETGXGHVVKLFAKIENQQGIDNIDEIIEAADGIMIARGDMGIEVPPFEMVPPVYO  
KMIITKVNAAGKAVITATNMLETMTDKPRATRSEVSDVFNVAVIDGTDATMLSGESANGKYPVESVRTMATIDKNAQTLLENYGRLLDSSAFPNNKT  
DVIIASAVKDATAHSMIDIKLVVITITETGNTARAI SKFRPDADILAVTFDEKVRQSLMINWGVIPVLADKPASTDDMFVAERVALEAGFVESGDNI VI  
VAGVPVGTGGTNTMRVRTVK

SEQ ID NO. 23

TTGTCTGCTATAATAGACAAAAAGGTGGTGTATTTATGTATTTAGCATTAATCGGTGATATCATTAAATTCAAAAAGATACCTTGA  
ACGTGAAACTTTTCCAAACAGTCTTTTTCAGCAACTAATGACCGAACTATCTGATGTATATGGTGAAGAGCTGATTTCTCCATTACACTA  
TTACAGCTGGTGTGAATTTCAAGCTTTTATGAAACCATCAAAAAAGGTATTTCAAATTTATGACCATATTCAACTAGCTCTAAAA  
CCTGTTAATGTAAGGTTCCGCTCGGTACAGGAAACATTATAACATCCATCAATTCAAATGAAAGTATCGGTGCTGATGGTCCCTGC  
CTACTGGCATGCTCGCTCAGCTATTAATCATATACATGATAAAAAATGATTTATGGAACAGTTCAAGTAGCTATTTGCCCTTGATGATG  
AAGACCAAACTTGAATTAACACTAAATAGTCTCATTTTCAGCTGGTGTATTTATCAAGTCAAAATGGACTACAAACCATTTTCAA  
ATGCTTGAGCACTTAATACTTCAAGATAATTTATCAAGAACAATTTCAACATCAAAAGTTAGCCCACTGGAAAAATATTGAACCTAG  
TGCGCTGACTAAACGCTTAAAGCAAGCGTCTGAAGATTTACTTAAAGAACGAGAACACAGGCAGCCGATCTATTAGTTAAAAGTT  
GCACCTCAAAC TAAAGGGGGAAGCTATGATTTTC

SEQ ID NO. 24

MSAIIIDKKVVI FMYLALIGDI INSKQILERETFQQSFQQLMTELSDVYGEELISPFITITAGDEFQALLKPSKVFQI IDHILQALKPVNVRFLGTT  
NIITSINSNESIGADGPAYWHARSA INHIHDKNYGTVQVAICLDEDEDQNLLELTLNLSI SAGDFIKSKWTTNHFQMLEHLI LQDNYQEQFQHOKLAQ  
LENI EPSALT KRKLKASGLKI YLRTRTQAADLLVKSCTQT KGGSYDF

SEQ ID NO. 25

ATGTTTTATACAATTGAAGAGCTGGTAGAGCAAGCTAATAGCCACATAAGGGTAAACATAGCAGAGCTCATGATCCAAACGGAAATGAAATGACT  
GGTAGAAGTCTGGAAGAAATTCGTTATATTTATGTCCCGAAATCTTGAAGTCATGAAAGCTTCTGTTATTTGATGGATTAAACCCCTAGTAAATCAATC  
AGTGGTTTAAACAGGCGGTGATGCTGTCAAGATGGATCAATATTTACAATCAGGAAAAACTATTTCAGATACCACAATCTTAGCTGCCGTTAGGAAT  
GCTATGGCTGTAAATGAGTTAAATGCTAAGATGGGACTGGTCTGTGCAACACCAACTGCAGGTAGTGCAGGATGTTTACCAGCTGTGATTTCTACA  
GCCATTGAAAAGCTTAATTTAACAGAGAAGAGCAACTTGATTTTCTATTACAGCCGGCGCATTTGGTCTCGTCATTGGTAATAATGCCTCTATC  
TCAGGTGCAGAAAGGAGGTTGCCAAGCTGAAGTTGGGTGCTAGTGTCTATGGCTGCGGCTGCTTTAGTTATGGCTGCTGGAGGTACTCCTTTCCAA  
GCTAGCCCAAGCTATAGCATTTGTTATTAATAAATAGCTTGGACTTATCTGTGACCCCTGTTGCAGGTTTGTGTTGAGGTTGAGGAGGAAAT  
GCTCTTGGATCAAGTTTGCCTTGTGCTGCTGATATGGCCTTGGCTGGTATTGAATCGCAAATCCAGTAGATGAAGTTATTTGATGCAATGTAT  
CAAGTTGGATCAAGTTTACCAGCTGCTTTTCTGTGAGACTGCAGAAAGGAGGACTTCTGCTCCACGCCGACAGGAAGACGTTATAGTAAAGAAATTTT  
GGGAA

SEQ ID NO. 26

MFYTIIEELVEQANSQHKGNIAELMIQTEIEMTGRSREEIRYIMSRNLEVMKASVIDGLTPSKSISGLTGGDAVKMDQYLQSGKTI SDTTILA AAVRN  
AMAVNELNAKMGVLVCAPTTAGSAGCLPAVISTAI EKLNLT EEEQLDFLFTAGAFGLVIGNNASISGAEGGCQAEVGSASAMAAAAALVMAAGTTPFQ  
ASQALAFVIKNMLGLICDPVAGLVEVPCVKRNALGSSFALVAADMALAGIESQIPVDEVIDAMYQVGSLSLPTAFRETAEGGLAATPTGRRYSKEIF  
GE

SEQ ID NO. 27

ATGAGCGTATATGTTAGTGGAAATAGGAATATTTCTTCTTTGGGAAAGAATTATAGCGAGCATAAACAGCATCTCTTCGACTTAAAAGAAGGAATTT  
CTAAACATTTATATAAAAATCAGACTCTATTTTGAATCTTATACAGGAAGCATAACTAGTGACCCAGAGGTTCTGAGCAATACAAAGATGAGAC  
ACGTAATTTTAAATTTGCTTTTACCCTTTTGAAGAGGCTCTGTCTTCTCAGGTGTTAATTTAAAAGCTTATCATAATATTGCTGTGTGTTAGGG  
ACCTCACTTGGGGGAAAGAGTGTCTGGTCAAAATGCCTTGTATCAATTTGAAGAAGGAGAGCGTCAAGTAGATGCTAGTTTATAGAAAAGCATCTG  
TTTACCATATTGCTGATGAATGATGGCTTATCATGATATTTGGGGAGCTTCTGATGTTATTTCAACCGCTGTTCTGCAAGTAATAATGCCGTAAT  
ATTAGGAACACAATTACTTCAAGATGGCGATTGTGATTTAGCTATTTGTGGTGGCTGTGATGAGTTAAGTGATATTTCTTTAGCAGGCTTCCATCA  
CTAGGAGCTATTAATACAGAAATGGCATGTCAGCCCTATTCTTCTGAAAAGGAATCAATTTGGGTGAGGGCGCTGGTTTGTGTTCTTGTCAAAG  
ATCAGTCTTAGCTAAATATGAAAAATTTACGGTGGCTTATTACTTCAGATGGTTATCATAAACAGCACCTAAGCCAACAGGTGAAGGGGCGGC  
ACAGATTGCAAAGCAGCTAGTGACTCAAGCAGGTTATTGACTACAGTGAAGTTGACTATATAACCGGTACCGGTACAGGTACTCAAGCTAATGATAAA  
ATGAAAAAAATATGTATGGTAAATTTTCCCGACAACGACATTGATCAGCAGTACCAAGGGGCAAACGGGTCTACTCTAGGGGCTGCAGGTATTA  
TCGAATTGATTAATGTTTAGCGGCAATAGAGGAACAGACTGTACCAGCAACTAAAAATGAGATTTGGGATAGAAGGTTTCCAGAAAATTTTGTCTA  
TCATCAAAAGAGAGAATACCCAATAAGAAATGCTTTAAATTTTTCGTTTGTCTTTGGTGGAAATAATAGTGGTGTCTTATTGTCTTTAGATTCA  
CCTCTAGAAAACATTACCTGTAGAGAAAATCTTAAATGGCTATCTTATCATCTGTTGCTTCCATTTCTAAGAAATGAATCACTTTCTATAACCTATG  
AAAAGTTGCTAGTAATTTCAACGACTTTGAAGCATTACGCTTTAAAGGGGCTAGACCACCCAAAACCTGTCAACCCAGCACAAATTTAGGAAAATGGA  
TGATTTTCTCAAAATGGTTGCCGTAACAACAGCTCAAGCACTAATAGAAAGCAATATTAATCTAAAAAACAAGATACTTCAAAAGTAGGAATTTGTA  
TTTACAACACTTCTGGACAGCTTGGTGTGAGGTTGTTGAAGGTTATGAAAAGCAAAATCAACAAGAAAGGATATGCAGATGTTTCTGCTCAGCATTCCCGT  
TTACAGTAAATGAATGACAGCAGCTGGTATGCTTTCTATCATTTTAAAAATAACAGGCTCCTTTATCTGTCTATTTCGACAAAATAGTGGAGCGCTTGTG  
TATACAATATGCCAAGGAAATGATGCGTAACGATAATCTAGACTATGTGATTTCTGTTTCTGCTAATCAGTGGACAGACATGAGTTTATGTTGGTGG  
CAACAAATFAAACTATGATAGTCAAAATGTTTGTGCGTTCTGATTTGTTTTCAGCAAGTCTCTCTCGTCAAGCATTGGATAATTTCTCTATAATAT  
TAGGTAGTAAACAAATFAAAATAGCCATAAAAACATTCACAGATGTGATGACTATTTTGGATGCTGCGCTTCAAAATTTATTTATCAGACTTAGGACT  
AACCATAAAAGATATCAAAGTTTTCGTTTGGAAATGAGCGGAAGAAGGCAAGTTAGTTTCAAGATTATGATTTCTTAGCGAACTTGTCTGAGTATTATAAT  
ATGCCAAACCTTGCTTCTGGTCAAGTTTGGATTTTTCATCTAATGGTGTGGTGAAGAACCTGGACTATACCTGTTAATGAAAGTATAGAAAAGGGCTATT  
ATTTAGTCCATCTTATTCGATCTTCGGTGGTATCTCTTTTGTCTATTATGAAAAAAGG

SEQ ID NO. 28

MSVYVSGIGI ISSLGKNYSEHKQHLFDLKEGISKHLYKNHDSILES YTGSI TSDPEVPEQYKDETRNFKFAFTA FEEALASSGVNLKAYHNI AVCLG
TSLGGKSAGQNALYQFEEGERQVDASLLEKASVYHIADELMA YHDI VGASYVI STAC SASNNAVILGTQLLQDGDCLAI CGGCDELSDI SLAGFTS
LGAINTEMACOPYSSGKGINLGEAGFVVLVKDQSLAKYKGI IGLLITSDGYHI TAPKPTGEGAAQIAKQLVTOAGIDYSEIDYINGHGTGTQANDK
MEKNMYGKFFPTTLLSSTKQGTGHTLGAAGI IELINCLAAIEBQTVPATKNEIGIEGFPENFVYHQKREYPI RNALNFSFAFGGNNSSGVLLSSSLDS
PLETL PARENLMKMAILSSVASISKNESLSITYEKVANSFNDFEALRFK GARPPKTVNPAQFRKMDDFSKMVAVTTAQALIESNINLKKQDTSKVGIV
FTTSLSGPVEVVEGIEKQITTEGYAHVSASRFPTVMNAAAGMLSIIFKITGPLSVISTNSGALDGIQYAKEMMRNDLDYVILV SANQWTDMSFMWW
QQLNYSQMFVGS DYCSAQVLSRQALDNSPI ILSGSKQLKYSHKTF TDVMTIFDAALQNL LSDLGLTIKDIKGFVWNERKKA VSSDYDFLANLSEYYN
MENLASGQGFSSNGAGEELDYTVNESIEKGYLVLSY SIFGGISFAIIEKR

SEQ ID NO. 29

ATGAAAATAGATGACCTAAGAAAAAGCGACAATGTTGAAGATCGTTCGCTCCAGTAGCGGAGGTTTCACTTCTTAGCGGAGGAAGTGGATTACCGATT
CTTCAACTTTTATTGCTGCGAGGGAGTTGGAAAACCAAGCTTGTGGTTTTAATCATCTTACTGCTACTTGGCCGAGGGGGACTAACCAGCATTTTT
AATGACTCATCCTCACCTTCTAGTTACCAATCTCAGAAATGCTCACGTTCTGTTGATAATAGCGCAACGAGAGAACAATCGATTTCTGTTAATAAA
GTCCCTTGGCTCAACTGAGGATTTCTGGTCAACAAGATTCCAAACCCAAGGTTTTGGAAAATTATAAGGAACCAAAAACCTTGTCTTTACACCAATTCA
ATTCAAACAGGTTGTGGTATAGGTGAATCTGCTT CAGGACCATTTATTGTT CAGCAGATAAAAAATCTATCTTGATATTTCTTTTACAATGAA
TTATCATAAATATGGTGCTACTGGTGATTTTGTCTATGGCCTACGTCATCGCCACGGAAGTTGGTCACCACATTTCAAACAGAGTTAGGCATTATG
GATAAGTATAATAGAATGCGACACGGACTTACTAAGAAAAGCAAAATGCTTTAAATGTTTCGGCTAGAACTTCAAGCAGATTATTATGCAGGGGTA
TGGGCTCACTACATCAGGGGAAAAAATCTCTTAGAACAGGAGACTTTGAAGAGGCCATGAATGCTGCCACGCCGTCGGAGACGATACCCCTT CAG
AAAGAAACCTACGGAATTAGTGCTGATAGCTTTACCATGGAACAGCTGAACAACGCCAAGCTTGGTTTAAACAAAGGCTTTCAATATGGTGAC
ATCCAACACGGTGATACTTTCTCCGTAGAACATCTA

SEQ ID NO. 30

MKIDDLRKS DNVEDRRSSSGGSFSSGSGLPILQLLLLLRGSWKTKLVVLI LLLLLGGGGLT SIFNDSSSPSSYQSQNVRSVDNSATREQIDFV NK
VLGSTEDFWSQEFQTOGFGNYKEPKLVLYTNSIQTCGIGESASGFFYCSADKKIYLDISFYNELSHKYGATGDFAMAYVIAHEVGHHIQTELGIM
DKYNRMRHGLTKKEANALNVRLELQADY YAGVWAHYIRGNLLEQGDFF EAMNAAHAVGDDTLQKETYGKLV PDSFTHGTABQRQRWFKGFPQYGD
IQHGDTFSVEHL

SEQ ID NO. 31

ATGAAAAGATTACATAAACTGTTTATAACCGTAATTGCTACATTAGGTATGTTGGGGTAATGACCTTTGGTCTTCCAACGCAGCCGCAAAAACGTA
ACGCCGATAGTACATGCTGATGTCAATTCATCTGTTGATACGAGCCAGGAATTTCAAATAATTTAAAAATGCTATTTGGTAACCTACCATTTCAA
TATGTTAATGTATTTATGAATTAATAATAATCAGACAAATTTAAATGCTGATGTCAATGTTAAAGCGTATGTTCAAATAACAATTGACAATCAA
CAAAGACTATCAACTGCTAATGCAATGCTTGATAGAACCATTGCTCAATATCAAATCGCAGAGATACCCTCTTCCCGATGCAAATTTGGAACCA
TTAGGTTGGCATCAAGTAGCTACTAATGACCATTATGGACATGACGTCGACGCAAGGGGCATTTAATTTGCCTATGCTTTAGCTGAAATTTCAAAGGT
TGGGATGCTCCGTTGCTCAAATCCTCAAATGTTGTCACACAACAGCTCATTCCAACCAATCAAATCAAAAAATCAATCGTGGACAAAATTTATTTAT
GAAAGCTTAGTTCCGTAAGCGGTTGACCAAAAACAACGTTTCCGTTACCGTGTAACTCCATTGTACCGTAATGATACCTGATTAGTTCCATTTGCA
ATGCACCTAGAAGCTAATAACAAGATGGCACATTAGAATTTAATGTTGCTATTTCAAACACACAAGCATCATACACTATGGATTATGCAACAGGA
GAAATAACACTAAAT

SEQ ID NO. 32

MKRLHLKLFITVIATLGLMLGVMTFGLPTQPQNVTPIVHADVNSSVDTSQEFQNNLNKNAIGNLPPQYVNGIYELNNQTNLNLADVNVAKYVQNTIDNQ
QRLSTANAMLDRTIRQYQNRDRTLLPDANWKPLGWHQVATNDHYGHAVDKGHLLIAYALAGNFKGWDA SVSNPQNVVTTAHSNQSNOKINRGQNY
ESLVRKAVDQNKRVRYRVTPLYRNDTDLVPFAMHLEAKSQDGTLEFNVAIPNTQASVTMDYATGEITLN

SEQ ID NO. 33

ATGAGTAAACGACAAAATTTAGGAATTAGTAAAAAGGAGCAATATATACGAGGCTCTCAGTGGCACTAATTGTAGTAAATAGGTGGCTTTTTATGG
GTACAATCTCAACCTAATAAGAGTGCAGTAAAACTAATACAAAGTTTTAATGTTAGAGAAGGAAGTGTTCGTCCTCAACTCTTTTGACAGGA
AAAGCTAAGGCTAATCAAGAACAGTATGTGATTTTGTGCTAATAAAGGTAATCGAGCAACTGTCAAGTTAAAGTGGGTGATAAATCACAGCT
GGTCAGCAGTTAGTTCAATATGATACAACAACCTGCACAAAGCAGCCTACGACACTGTAATCGTCAATTAATAAAGTAGCGCGTCAGATTAATAAT
CTAAAGACAACAGGAAGTCTTCCAGCTATGGAATCAAGTGATCAATCTTCTTCATCATCACAAGGACAAGGGACTCAATCGACTAGTGGTGCAGC
AATCGTCTACAGCAAAATTTCAAAGTCAAGCTAATGCTTCATACAACCAACAACCTTCAAGATTGAATGATGCTTATGCGAGATGCACAGGCAGAA
GTAATAAAGCAAAAAGCATTTGAATGATACTGTTATTACAAGTGACGTTATCAGGGACAGTTGTTGAAGTTAATAGTGATTTGATCCAGCTTCA
AAACTAGTCAAGTACTTGTCCATGTAGCAACTGAAGGTAACCTCAAGTACAAGGAAACGATGAGTGAGTATGATTTGGCTAATGTTAAAAAAGAC
CAGGCTGTAAAAATAAAATCTAAGGTTCTATCCTGCAAGGAATGGGAAGGTAATAATTTCATATATCTCAAATTTCCAGAAGCAGAAGCAACAAC
AATGACTCTAATAACGGCTCTAGTGTGTAATTTAATAATAAAGTAGATATTACTAGCCCTCTCGATGCATTAATAACAAGTTTTTACCGTATCA
GTTGAAGTAGTTAATGGAGATAAGCACCTTATTGTTCCCTACAAGTTCTGTGATAAAACAAGATAATAAACACTTTGTTTGGGTATACAATGATTTCT
AATCGTAAAATTTCAAAGTTGAAGTCAAAATTTGGTAAAGCTGATGCTAAGACAACAAGAAATTTTTCAGGTTTGAAGCAGGACAAATCGTGGTT
ACTAATCCAAGTAAAACCTTCAAGGATGGGCAAAAATTTGATAATATTGAATCAATCGATCTTAACTCTAATAAGAAATCAGAGGTGAA

SEQ ID NO. 34

MSKRQNLGI SKKGAI ISGLSVALI VVIGGFLWVQS QPNKSAVKTNKVFNVREGSVSSSTLLTGKAKANQEYVYFDANKGNRATVTVKVGDKITAG  
QQLVQYDTTTTAQAAAYDTANRQLNKVARQINLNKTTGSLPAMESSDQSSSSSQGGTQSTSGATNRLQNNYQSQANASYNQQLQDLNDAYADAQAEVN  
KAQKALNDTVITSDVSGTVVEVNSDIDPASKTSQVLVHVATEGKLVQVQTMSEYDLANVKKDQAVKI KSKVYDPKWEWGKISYI SNYPEAEANNDNS  
NNGSSAVNYKYKVDITSPDLALKQGFVTVSEVVNGDKHLIVPTSSVINKDNKHFVWVYNDNRKISKVEVKIGKADAKTQEILSGLKAGQIVVTPNS  
KTFKDGQKIDNIESIDLNSNKKSEVK

**SEQ ID NO. 35**

ATGAAAAAATGGAAATTATGTCTCACACTACTGACCTTCTTTTGGTATCTTGGGACAACTAAACAAGAAAGCACTAAAACACTATT  
TCTAAAATGCCTAAAATTGAAGGCTTCACTTATTATGAAAAATTCCTGAAAAATCCGAAAAAGTAATTAATTTTACATATTCTTACACTGGGTAT  
TTATTTAACTAGGTGTTAATGTTTCAAGTTACAGTTAGACTTAGAAAAAGATAGCCCGTTTGGTAAACAACCTGAAAGAAGCTAAAAATTA  
ACTGCTGATGATACAGAAGCTATTGCCGCACAAAACCTGATTTAATCATGGTTTTCGATCAAGATCCAAACATCAATACTCTGAAAAAATGCA  
CCAACTTAGTTATTAATATGGTGCACAAAATTTTAGATATGATGCCAGCCTTGGGAAAGTATTCGGTAAAGAAAAAGAGCTAATCAGTGG  
GTTAGCCAATGAAAACTAAAACCTCTCGCTGTCAAAAAGATTTACCCATATCTTAAAGCCTAACACTACTTTTACTATTATGGATTTTATGAT  
AAAAATATCTATTATATGGTAATAATTTTGGACGCGGTGGAGAACTAATCTATGATCACTAGGTTATGCTGCCCGAAAAAGTCAAAAAGAT  
GTCTTTAAAAAAGGGTGGTTTACCGTTTCGCAAGAAGCAATCGGTGATTACGTTGGAGATTATGCCCTTGTTAATATAAACAAAAAGACTAAAAA  
GCAGCTTCACTAAAGAAAGTGTCTGGAAGAATTTACAGCTGTCAAAAAGGGCACATCATAGAAAGTAACTACGACGTGTTTTATTCT  
TCTGACCTCTATCTTTAGAGCTCAATTAATCATTACAAAAGGCTATCAAGAAAAATACAAAT

**SEQ ID NO. 36**

MKKIGIIVLTLTLFFLVSCGQQTQKQESTKTTISKMPKIEGFTTYGKI PENPKVINFTYSYTG YLLKLG VNVSSYSLDLEKDS PVF  
GKQLKEAKKLTADDTEAIAAQKPDLMVFDQDPNINLTKKIAPT LVI KYGAQNYLDMMPALGKVF GKEKEANQVWSQWKT KTLAVK  
KDLHHI LKPN TTF T I M D F Y D K N I Y L Y G N N F R G G E L I Y D S L G Y A A P E K V K D V F K K G W F T V S Q E A I G D Y V G D Y A L V N I N K T T K K A A  
SSLKESDVWKNLPAVKKGHI IESNYDV F Y F S D P L S L E A Q L K S F T K A I K E N T N

**SEQ ID NO. 37**

ATGAAAGTAAAAATAAGATTTTAAACGATGGTAGCACTTACTGTCTTAAACATGTGCTACTTATTCATCAATCGGTTATGCTGATACAGTGATAAGA  
ATACTGACACGAGTGTCTGACTACGACCTTATCTGAGGAGAAAAGATCAGATGAACCTAGACCAGTCTAGTACTGGTTCTTCTTCTGAAAAATGAATC  
GAGTTTCACTCAAGTGAACAGAAAATAAGGATATTTCTAGTGAACAAAAGTATTAATTTTCAAGATAGTATTAAGAATTTTAGTAAAGCAAGTA  
AGAACCAGACAGAAATTTGGCAATAATAAGGATATTTCTAGTGAACAAAAGTATTAATTTTCAAGATAGTATTAAGAATTTTAGTAAAGCAAGTA  
GTGATCAAGAAGAAGTGGATCGCGATGAATCATCATCTTCAAAAGCAATGATGGGAAAAAGGCCACAGTAAGCCTAAAAAGGAACCTTCTAAAAC  
AGGAGATAGCCACTCAGATACTGTAATAGCATCTACGGGAGGGATTTATCTGTATCATTAAGTTTTTACAATAAGAAAAATGAAACCTTAT

**SEQ ID NO. 38**

MKVKNKILFMVALTVLTCATYSSIGYADTSDKNNTDTSVVTTLSBEKRSDDELQDSSTGSSSENESSSSSEPETNPSTNPPTTEPSQSPSEENKPDG  
RTKTEIGNNKDISSGTKVLISEDSIKNFASKASSDQEVDRDESSSKANDGKKGHSKPKKELPKTGDSDTVIASTGGI ILLSLSFYNNKMKLY

**SEQ ID NO. 39**

ATGAAAAGGATACGGAAAAGCCTTATTTTGTCTCGGAGTAGTTACCCTAATTTGCTTATGTGCTTGTACTAAACAAAAGCCAGCAAAAAATGGCT  
TGTCAGTAGTGACTAGCTTTTATCCAGTATATCCATTACAAAAGCAGTTCTGGTGAATTTGAATGATTTAAAATGATTCGATCACAGTCAGGTAT  
TCATGTTTTGAAACCTCATCAAGTGATGTTGCTGCCATTTATGATGCTGATCTATTTCTTTATCATTCGCACACACTAGAAGCTTGGGCGAGACGT  
TTGGAACCTAGTTGTCATCACTCTAAAGTATCTGTAATTGAAGCTTCAAAGGATGATGATTTGGATAAAGTTTATGCTTAGAAGATGTAGAGGCAG  
AAAAAGGAGTAGATGAGTCAACCTTGTATGACCCCTCACATGGAATGACCCCTGAAAAGTATCTGAGGAAGCAACTCATCGCTACACAATTAGC  
TAAAAGGATCCTAAAAACGCTAAGGTTTATCAAAAATGCTGATCAATTTAGTGACAAAGCAATGGCTATTCAGAGAAGTATAAGCCAAAATTT  
AAAGCTGCAAAGTCTAAATACTTTGTGACTTACATACAGCATTCTCATACTTAGCTAAGCGATACGGATTGACTCAGTTAGGTATTCAGGTTGCT  
CAACCGAGCAAGAACCTAGTGCTAAAAAATAGCCGAAATTCAGGAGTTTGTGAAAACATATAAGGTTAAGACTATTTTGTGAAAGAGGAGTCTC  
ACCTAAATTAGCTCAAGCAGTAGCTTCACTACTCGAGTTAAAATGCAAGTTTAAAGTCTTTARAAGCAGTTCCCAAAAACAATAAGATTACTTA  
GAAAATTTGAAAACCTAATCTTAAGGTAAGTCTTGTCAAATCGTTAAATCAATAG

**SEQ ID NO. 40**

MKRIRKSLIFVLGVVTLICLCACTKQSQKNGLSVVTFSFYPVYSITKAVSGDLNDIKMIRSQSGIHGFEPSSSDVAIYDADLFLYHSHTLEAWARR  
LEPSLHHSKVSVIEASKGMTLDKVHGLEDEAEKGVDESTLYDPHTWNPVKVSEEAQLIATQLAKKDPKNAKVYQKNADQFSDKAMAI AEKYKPKF  
KAAKSKYFVTSHTAFSYLAKRYGLTQLGIAGVSTEQEPSAKKLAEIQEFVKTYKVKTIIFVEEGVSPKLAQAVASATRVKIASLSPLXAVPKNNKDYL  
ENLETNLKVLVKS LNQ

**SEQ ID NO. 41**

ATGCCTAAGAAGAAATCAGATACCCAGAAAAAGAAAGTGTCTTAAACGGAATGGCAAAAGCGTAACCTTGAATTTTAAAAAAGCAGAAAGAG  
ATGAAGAAGAACAAAACGTTATTAACGAAAAATTAGCCTTAGATAAAAAGAAAGTAAATTAATATTTCTTCTCTGAAAGAACCTCAAAATACTACTAA  
AATTAAGAAGCTTCAATTTTCCAAAGATTTCAAGACCTAAGATTGAAAAGAAACGAAAAAGAAAAATAGTCAACAGCTTAGCCAAAACCTAATCGC  
ATTAGAACTGCACCTATATTTGTAGTAGCATTCCTAGTCATTTTAGTTTCCGTTTTCTACTAECTCTTTTAGTAAGCAAAAACAATAACAGTTA  
GTGGAATCAGCATACACCTGATGATATTTGATAGAGAAAACGAATATTCAAAAAAGCATTATTTCTTTCTTAAATTTTAAACATAAAGCTAT  
TGAACAACGTTTAGCTGCAGAAGATGATGGGTAAAAACAGCTCAGATGACTTATCAATTTCCCAATTAAGTTTCATATTCAGTTCAAGAAAAATAAG

ATTATTGCATATGCACATACAAAGCAAGGATATCAACCTGTCTTGAAACTGGAAAAAGGCTGATCCTGTAAATAGTTCAGAGCTACCAAAGCACT  
TCTTAACAATTAACCTTGATAAGGAAGATAGTATTAAGCTATTAATTAAGATTAAAGGCTTTAGACCCCTGATTTAATAAGTGAGATTCAGGTGAT  
AAGTTTAGCTGATTCTAAAACGACACCTGACCTCCTGCTGTTAGATATGCACGATGGAAATAGTATTAGAATACCATTATCTAAATTTAAAGAAAGA  
CTTCCTTTTACAACAATAAAGAAGAACCTTAAGGAACCTTCTATTGTTGATATGGAAGTGGGAGTTTACACAACAACAATAACCATTTGAATCAA  
CCCCTGTAAAGCAGAAGATACAAAAATAAATCAACTGATAAAACACAACAACAATAAGGTTCAGGTTGCGGAAAATAGTCAAGGACAAACAATAA  
CTCAAAATACTAATCAACAAGGACAACAGATAGCAACAGAGCAGGCACCTAACCCCTCAAAATGTTAAT

**SEQ ID NO. 42**

MPKKKSDTPEKEEVVLTEWQKRNLEFLKRRKEDDEEQKRINEKLRLDKRSKLNISPEEPQNTTKIKKLHFPKISRPKIEKKQKKEKIVNSLAKTNR  
IRTAPIFVVAFLVILVSVFLLTPFSKQKTIITVSGNQHTPDDILIEKTNIQKNDYFFSLIFKHKAIEQRLAAEDVWVKTAQMTYQFPNKFHIQVQENK  
IIAYAHTKQGYQPVLETGKKADPVNSSELPKHFLTINLDKEDSIIKLLIKDLKALDPDLISEIQVISLADSKTTPDLLLLDMHDGNSIRIPLSKFKER  
LPFYKQIKKNLKEPSIVDMEVGVYTTNTNIESTPVKAEDTKNKSTDKTQTQNGQVAENSGQTNNSENTNQGGQIATEQAPNPQNVN