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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 April 2013 (18.04.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/053899 A1

(51) International Patent Classification:
C07K 14/205 (2006.01)

(21) International Application Number:
PCT/EP2012/070282

(22) International Filing Date:
12 October 2012 (12.10.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 2011 00789 12 October 2011 (12.10.2011) DK
61/550,494 24 October 2011 (24.10.2011) US

(72) Inventors; and
(71) Applicants : **MØLLER, Niels Iversen** [DK/DK]; Ferlevej 100, DK-3250 Gilleleje (DK). **MATTSSON, Andreas** [DK/DK]; c/o Ole Maaløes Vej 3, DK-2200 København N (DK).

(74) Agents: **KOEFOED, Peter** et al.; Inspicos A/S, P.O. Box 45, Kogle Allé 2, DK-2970 Hørsholm (DK).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

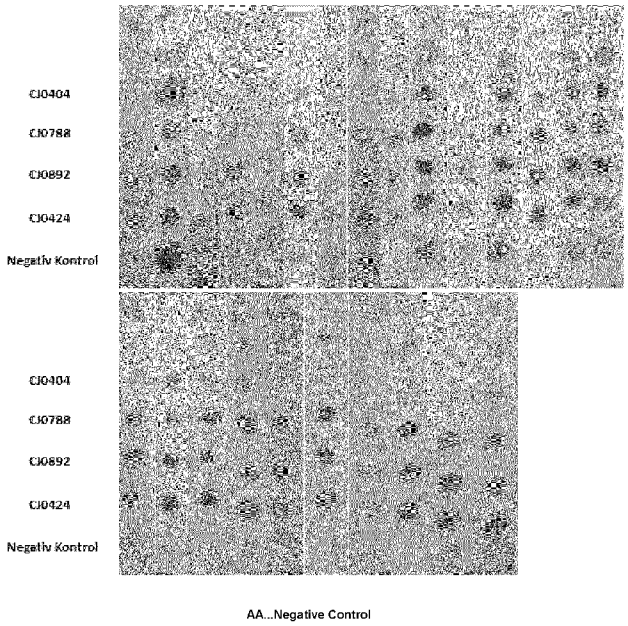
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

(54) **Title**: PEPTIDES DERIVED FROM CAMPYLOBACTER JEJUNI AND THEIR USE IN VACCINATION

(57) **Abstract**: Disclosed are polypeptides for Campylobacter jejuni that are useful as immungenic agents for vaccine use. Also dislcosed are nucleic acid fragments encoding the polypeptides as well as compositions, methods and molecular biology tools derived from or related to the proteins.

Fig. 2



WO 2013/053899 A1

PEPTIDES DERIVED FROM CAMPYLOBACTER JEJUNI AND THEIR USE IN VACCINATION

FIELD OF THE INVENTION

The present invention relates to the field of antimicrobial prophylaxis and therapy. In particular the present invention relates to novel proteins and polynucleotides derived from *Campylobacter jejuni*. The invention further relates to vectors comprising the polynucleotides, transformed host organisms expressing the polynucleotides, antibodies (mono- or polyclonal) specific for the polypeptides as well as diagnostic, prophylactic and therapeutic uses and methods. Finally, also methods of preparation are part of the invention.

BACKGROUND OF THE INVENTION

C. jejuni is a bacterium commonly associated with poultry, since it naturally colonises the digestive tract of many bird species. Contaminated drinking water and unpasteurized milk provide an efficient means for distribution in human populations. Contaminated food is a major source of isolated *C. jejuni* infections, with incorrectly prepared meat and poultry normally being the source of the bacteria.

Infection with *C. jejuni* usually results in enteritis, which is characterised by abdominal pain, diarrhea, fever, and malaise. The symptoms usually persist for between 24 hours and a week, but may be longer. Diarrhea can vary in severity from loose stools to bloody stools. The disease is usually self-limiting. However, it does respond to antibiotics. Severe (accompanying fevers, blood in stools) or prolonged cases may require ciprofloxacin, erythromycin, azithromycin or norfloxacin. The drug of choice is usually erythromycin. About 90% of cases respond to ciprofloxacin treatment. Fluid and electrolyte replacement may be required for serious cases.

The first full-genome sequence of *C. jejuni* was performed in 2000 (strain NCTC11168) with a circular chromosome of 1,641,481 base pairs

As mentioned, *C. jejuni* infections may successfully be treated by administration of antibiotics to patients in need thereof, but that would not prevent acute illness. Further, due to careless or thoughtless use of powerful antibiotics, many pathological germs, including *C. jejuni* become resistant against antibiotics over time. In particular in hospitals, treatment with antibiotics can prove inadequate: not only will a *C. jejuni* infection be life-threatining for patients that already suffer from other health problems meaning that treatment with antibiotics may simply be non-effective within the relevant time-span, but in addition

antibiotic-resistant *C. jejuni* strains will also withstand treatment with those antibiotics used as the initial choice in treatment. There is thus a need to provide alternatives to current treatment regimens. Also, infection with *C. jejuni* is associated with reactive arthritis and Guillain-Barré Syndrome.

Vaccination is considered to be a very effective method of preventing infectious diseases in human and veterinary health care. Vaccination is the administration of immunogenically effective amounts of antigenic material (the vaccine) to produce immunity to a disease/disease-causing pathogenic agent. Vaccines have contributed to the eradication of smallpox, the near eradication of polio, and the control of a variety of diseases, including rubella, measles, mumps, chickenpox, typhoid fever.

Before "the genomic era", vaccines were based on killed or live attenuated, microorganisms, or parts purified from them. Subunit vaccines are considered as a modern upgrade of these types of vaccine, as the subunit vaccines contain one or more protective antigens, which are more or less the weak spot of the pathogen. Hence, in order to develop subunit vaccines, it is critical to identify the proteins, which are important for inducing protection and to eliminate others.

An antigen is said to be protective if it is able to induce protection from subsequent challenge by a disease-causing infectious agent in an appropriate animal model following immunization.

The empirical approach to subunit vaccine development, which includes several steps, begins with pathogen cultivation, followed by purification into components, and then testing of antigens for protection. Apart from being time and labour consuming, this approach has several limitations that can lead to failure. It is not possible to develop vaccines using this approach for microorganisms, which cannot easily be cultured and only allows for the identification of the antigens, which can be obtained in sufficient quantities. The empirical approach has a tendency to focus on the most abundant proteins, which in some cases are not immuno-protective. In other cases, the antigen expressed during *in vivo* infection is not expressed during *in vitro* cultivation. Furthermore, antigen discovery by use of the empirical approach demands an extreme amount of proteins in order to discover the protective antigens, which are like finding needles in the haystack. This renders it a very expensive approach, and it limits the vaccine development around diseases, which is caused by pathogens with a large genome or disease areas, which perform badly in a cost-effective perspective.

OBJECT OF THE INVENTION

It is an object of embodiments of the invention to provide *C. jejuni* derived antigenic polypeptides that may serve as constituents in vaccines against *C. jejuni* infections and in diagnosis of *C. jejuni* infections. It is also an object to provide nucleic acids, vectors, transformed cells, vaccine compositions, and other useful means for molecular cloning as well as for therapy and diagnosis with relevance for *C. jejuni*.

SUMMARY OF THE INVENTION

It has been found by the present inventor(s) that *C. jejuni*, in particular drug resistant *C. jejuni*, expresses a number of hitherto unknown putatively surface exposed proteins which are candidates as vaccine targets as well as candidates as immunizing agents for preparation of antibodies that target *C. jejuni*. One of these putatively surface exposed antigens (cj0404; SEQ ID NO: 13) has now been tested for suitability as a vaccine agent and has as the only candidate among 25 randomly isolated *C. jejuni* proteins been found to be a capable of providing protection against challenge infection. The remaining 29 variants are currently being investigated in a similar setup.

So, in a first aspect the present invention relates to a polypeptide comprising
a) an amino acid sequence selected from the group consisting of any one of SEQ ID NOs: 1-30, or
b) an amino acid sequence consisting of at least 5 contiguous amino acid residues from any one of SEQ ID NOs: 1-30, or
c) an amino acid sequence having a sequence identity of at least 60% with the amino acid sequence of a),
d) an amino acid sequence having a sequence identity of at least 60% with the amino acid sequence of b), or
e) an assembly of amino acids derived from any one of SEQ ID NOs: 1-30 which has essentially the same 3D conformation as in the protein from whicht said assembly is derived so as to constitute a B-cell epitope,
said polypeptide being antigenic in a mammal.

In another aspect, the invention relates to an isolated nucleic acid fragment, which comprises
i) a nucleotide sequence encoding a polypeptide of the invention, or
ii) a nucleotide sequence consisting of any one of SEQ ID NOs: 31-90.
iii) a nucleotide sequence consisting of at least 10 consecutive nucleotides in any one of SEQ ID NOs: 31-90,

iv) a nucleotide sequence having a sequence identity of at least 60% with the nucleotide sequence in i) or ii),
v) a nucleotide sequence having a sequence identity of at least 60% with the nucleotide sequence in iii),
vi) a nucleotide sequence complementary to the nucleotide sequence in i)-v), or
vii) a nucleotide sequence which hybridizes under stringent conditions with the nucleotide sequence in i)-vi).

In a third aspect, the invention relates to a vector comprising the nucleic acid of the invention, such as a cloning vector or an expression vector.

In fourth aspect, the invention relates to a cell which is transformed so as to carry the vector of the invention.

In a fifth aspect, the invention relates to a pharmaceutical composition comprising a polypeptide of the invention, a nucleic acid fragment of the invention, a vector of the invention, or a transformed cell of the invention, and a pharmaceutically acceptable carrier, vehicle or diluent.

In a sixth aspect, the invention relates to a method for inducing immunity in an animal by administering at least once an immunogenically effective amount of a polypeptide of the invention, a nucleic acid fragment of the invention, a vector of the invention, a transformed cell of the invention, or a pharmaceutical composition of the fifth aspect of the invention so as to induce adaptive immunity against *C. jejuni* in the animal.

In a seventh and eighth aspect, the invention relatas to 1) a polyclonal antibody in which the antibodies specifically bind to at least one polypeptide of the invention, and which is essentially free from antibodies binding specifically to other *C. jejuni* polypeptides, and to 2) an isolated monoclonal antibody or antibody analogue which binds specifically to a polypeptide of the invention. In a related ninth aspect, the invention relates to a pharmaceutical composition comprising such a polyclonal or monoclona antibody and a pharmaceutically acceptable carrier, vehicle or diluent.

In a 10^{th} aspect, the invention relates to a method for prophylaxis, treatment or amelioration of infection with *C. jejuni*, in particular infection with multi-resistant *C. jejuni*, comprising administering a therapeutically effective amount of an antibody of the 7^{th} or 8^{th} aspect of the invention or a pharmaceutical composition of the eighth aspect to an individual in need thereof.

In an 11th aspect, the invention relates to a method for determining, quantitatively or qualitatively, the presence of *C. jejuni*, in particular the presence of multi-resistant *C. jejuni*, in a sample, the method comprising contacting the sample with an antibody of aspects 8 or 9 of the invention and detecting the presence of antibody bound to material in the sample.

In an 12th aspect of the invention is provided a method for determining, quantitatively or qualitatively, the presence of antibodies specific for *C. jejuni*, in particular the presence of antibodies specific for multi-resistant *C. jejuni*, in a sample, the method comprising contacting the sample with a polypeptide of the invention and detecting the presence of antibody that specifically bind said polypeptide.

In a 13th aspect, the invention relates to a method for determining, quantitatively or qualitatively, the presence of a nucleic acid characteristic of *C. jejuni*, in particular the presence of a nucleic acid characteristic of multi-resistant *C. jejuni*, in a sample, the method comprising contacting the sample with a nucleic acid fragment of the invention and detecting the presence of nucleic acid in the sample that hybridizes to said nucleic acid fragment.

In a 14th aspect, the invention relates to a method for the preparation of the polypeptide of the invention, comprising
- culturing a transformed cell of the present invention, which is capable of expressing the nucleic acid of the invention, under condiditions that facilitate that the transformed cell expresses the nucleic acid fragment of the invention, which encodes a polypeptide of the invention, and subsequently recovering said polypeptide, or
- preparing said polypeptide by means of solid or liquid phase peptide synthesis.

In a 15th aspect, the invention relates to a method for determining whether a substance, such as an antibody, is potentially useful for treating infection with *C. jejuni*, the method comprising contacting the polypeptide of the invention with the substance and subsequently establishing whether the substance has at least one of the following characteristics:
1) the ability to bind specifically to said polypeptide,
2) the ability to compeed with said polypeptide for specific binding to a ligand/receptor, and
3) the ability to specifically inactivate said polypeptide.

Finally, in a 16th aspect, the invention relates to a method for determining whether a substance, such as a nucleic acid, is potentially useful for treating infection with *C. jejuni*, the method comprising contacting the substance with the nucleic acid fragment of claim of the invention and subsequently establishing whether the substance has either the ability to
1) bind specifically to the nucleic acid fragment, or

2) bind specifically to a nucleic acid that hybridizes specifically with the nucleic acid fragment.

LEGENDS TO THE FIGURE

Fig. 1: Gels showing the the expression of 17 *C. jejuni* genes cloned in *E. coli* BL21. X: presence of expression product in BL21 after induction O: No induction of protein expression.

Fig. 2: Dot blots showing reactivity of 4 *C. jejuni* antigens against human sera.

Fig. 3: Dot blots showing reactivity of 17 *C. jejuni* antigens against human sera.

DETAILED DISCLOSURE OF THE INVENTION

Definitions

The term "polypeptide" is in the present context intended to mean both short peptides of from 2 to 10 amino acid residues, oligopeptides of from 11 to 100 amino acid residues, and polypeptides of more than 100 amino acid residues. Further-more, the term is also intended to include proteins, i.e. functional biomolecules comprising at least one polypeptide; when comprising at least two polypeptides, these may form complexes, be covalently linked, or may be non-covalently linked. The polypeptide (s) in a protein can be glycosylated and/or lipidated and/or comprise prosthetic groups.

The term "subsequence" means any consecutive stretch of at least 3 amino acids or, when relevant, of at least 3 nucleotides, derived directly from a naturally occurring amino acid sequence or nucleic acid sequence, respectively

The term “amino acid sequence” s the order in which amino acid residues, connected by peptide bonds, lie in the chain in peptides and proteins.

The term "adjuvant" has its usual meaning in the art of vaccine technology, i.e. a substance or a composition of matter which is 1) not in itself capable of mounting a specific immune response against the immunogen of the vaccine, but which is 2) nevertheless capable of enhancing the immune response against the immunogen. Or, in other words, vaccination with the adjuvant alone does not provide an immune response against the immunogen,

vaccination with the immunogen may or may not give rise to an immune response against the immunogen, but the combined vaccination with immunogen and adjuvant induces an immune response against the immunogen which is stronger than that induced by the immunogen alone.

"Sequence identity" is in the context of the present invention determined by comparing 2 optimally aligned sequences of equal length (e.g. DNA, RNA or amino acid)according to the following formula: $(N_{ref} - N_{dif})\cdot 100/N_{ref}$, wherein N_{ref} is the number of residues in one of the 2 sequences and N_{dif} is the number of residues which are non-identical in the two sequences when they are aligned over their entire lengths and in the same direction.So, two sequences 5'-ATTCGGAAC-3' and 5'- ATACGGGAC-3' will provide the sequence identity 77,78% (N_{ref}=9 and N_{dif}=2).

An "assembly of amino acids" means two or more amino acids bound together by physical or chemical means.

The "3D conformation" is the 3 dimensional structure of a biomolecule such as a protein. In monomeric polypeptides/proteins, the 3D conformation is also termed "the tertiary structure" and denotes the relative locations in 3 dimensional space of the amino acid residues forming the polypeptide.

"An immunogenic carrier" is a molecule or moiety to which an immunogen or a hapten can be coupled in order to enhance or enable the elicitation of an immune response against the immunogen/hapten. Immunogenic carriers are in classical cases relatively large molecules (such as tetanus toxoid, KLH, diphtheria toxoid etc.) which can be fused or conjugated to an immunogen/hapten, which is not sufficiently immunogenic in its own right – typically, the immunogenic carrier is capable of eliciting a strong T-helper lymphocyte response against the combined substance constituted by the immunogen and the immunogenic carrier, and this in turn provides for improved responses against the immungon by B-lymphocytes and cytotoxic lymphocytes. More recently, the large carrier molecules have to a certain extent been substituted by so-called promiscuous T-helper epitopes, *i.e.* shorter peptides that are recognized by a large fraction of HLA haplotypes in a population, and which elicit T-helper lymphocyte responses.

A "T-helper lymphocyte response" is an immune response elicited on the basis of a peptide, which is able to bind to an MHC class II molecule (e.g. an HLA class II molecule) in an antigen-presenting cell and which stimulates T-helper lymphocytes in an animal species as a consequence of T-cell receptor recognition of the complex between the peptide and the MHC Class II molecule prese

An "immunogen" is a substance of matter which is capable of inducing an adaptive immune response in a host, whose immune system is confronted with the immunogen. As such, immunogens are a subset of the larger genus "antigens", which are substances that can be recognized specifically by the immune system (e.g. when bound by antibodies or, alternatively, when fragments of the are antigens bound to MHC molecules are being recognized by T-cell receptors) but which are not necessarily capaple of inducing immunity - an antigen is, however, always capable of *eliciting* immunity, meaning that a host that has an established memory immunity against the antigen will mount a specific immune response against the antigen.

A "hapten" is a small molecule, which can neither induce or elicit an immune response, but if conjugated to an immunogenic carrier, antibodies or TCRs that recognize the hapten can be induced upon confrontation of the immune system with the hapten carrier conjugate.

An "adaptive immune response" is an immune response in response to confrontation with an antigen or immunogen, where the immune response is specific for antigenc determinants of the antigen/immunogen – examples of adaptive immune responses are induction of antigen specific antibody production or antigen specific induction/activation of T helper lymphocytes or cytotoxic lymphocytes.

A "protective, adaptive immune response" is an antigen-specific immune response induced in a subject as a reaction to immunization (artificial or natural) with an antigen, where the immune response is capable of protecting the subject against subsequent challenges with the antigen or a pathology-related agent that includes the antigen. Typically, prophylactic vaccination aims at establishing a protective adaptive immune response against one or several pathogens.

”Stimulation of the immune system" means that a substance or composition of matter exhibits a general, non-specific immunostimulatory effect. A number of adjuvants and putative adjuvants (such as certain cytokines) share the ability to stimulate the immune system. The result of using an immunostimulating agent is an increased "alertness" of the immune system meaning that simultaneous or subsequent immunization with an immunogen induces a significantly more effective immune response compared to isolated use of the immunogen.

Hybridization under "stringent conditions" is herein defined as hybridization performed under conditions by which a probe will hybridize to its target sequence, to a detectably greater degree than to other sequences. Stringent conditions are target-sequence-dependent and will differ depending on the structure of the polynucleotide. By controlling the stringency of the

hybridization and/or washing conditions, target sequences can be identified which are 100% complementary to a probe (homologous probing). Alternatively, stringency conditions can be adjusted to allow some mismatching in sequences so that lower degrees of similarity are detected (heterologous probing). Specificity is typically the function of post-hybridization washes, the critical factors being the ionic strength and temperature of the final wash solution. Generally, stringent wash temperature conditions are selected to be about 5°C to about 2°C lower than the melting point (Tm) for the specific sequence at a defined ionic strength and pH. The melting point, or denaturation, of DNA occurs over a narrow temperature range and represents the disruption of the double helix into its complementary single strands. The process is described by the temperature of the midpoint of transition, Tm, which is also called the melting temperature. Formulas are available in the art for the determination of melting temperatures.

The term "animal" is in the present context in general intended to denote an animal species (preferably mammalian), such as Homo sapiens, Canis domesticus, etc. and not just one single animal. However, the term also denotes a population of such an animal species, since it is important that the individuals immunized according to the method of the invention substantially all will mount an immune response against the immunogen of the present invention.

As used herein, the term "antibody"refers to a polypeptide or group of polypeptides composed of at least one antibody combining site. An "antibody combining site" is the three-dimensional binding space with an internal surface shape and charge distribution complementary to the features of an epitope of an antigen, which allows a binding of the antibody with the antigen. "Antibody"includes, for example, vertebrate antibodies, hybrid antibodies, chimeric antibodies, humanised antibodies, altered antibodies, univalent antibodies, Fab proteins, and single domain antibodies.

"Specific binding" denotes binding between two substances which goes beyond binding of either substance to randomly chosen substances and also goes beyond simple association between substances that tend to aggregate because they share the same overall hydrophobicity or hydrophilicity. As such, specific binding usually involves a combination of electrostatic and other interactions between two conformationally complementary areas on the two substances, meaning that the substances can "recognize" each other in a complex mixture.

The term "vector" is used to refer to a carrier nucleic acid molecule into which a heterologous nucleic acid sequence can be inserted for introduction into a cell where it can be replicated and expressed. The term further denotes certain biological vehicles useful for the same

purpose, e.g. viral vectors and phage – both these infectious agents are capable of introducing a heterelogous nucleic acid sequence

The term "expression vector" refers to a vector containing a nucleic acid sequence coding for at least part of a gene product capable of being transcribed. In some cases, when the transcription product is an mRNA molecule, this is in trun translated into a protein, polypeptide, or peptide.

Specific embodiments of the invention

The polypeptides of the invention

In some embodiments the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention constitute at least 6, such as at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27 at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34, at least 35, at least 36, at least 37, at least 38, at least 39, at least 40, at least 41, at least 42, at least 43, at least 44, at least 45, at least 46, at least 47, at least 48, at least 49, at least 50, and at least 51 contiguous amino acid residues.

The number may, where applicable, be higher, such as at least 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, at least 124, and at least 125 contiguous amino acid residues. Another way to phrase this is that for each of SEQ ID NOs: 1-30, the number of the contiguous amino acid residues is at least N-n, where N is the length of the sequence ID in question and n is any integer between 6 and N-1; that is, the at least 5 contiguous amino acids can be at least any number between 5 and the length of the reference sequence minus one, in increments of one.

In some embodiments, the polypeptide of the invention also has a sequence identity with the amino acid sequence of a) defined above of at least 65%, such as at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, and at least 99%. Similarly, the polypeptide of the invention in some embodiments also has a sequence identity with the amino acid sequence of b) defined above of at least 60%, such as at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least

92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, and at least 99%.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, and 47 in any one of SEQ ID NOs: 1-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, and 61 in any on of SEQ ID NOs: 2-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, and 112 in any one of SEQ ID NOs: 3-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, and 134 in any one of SEQ ID NOs: 4-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-

terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 135, 136, and 137 in any one of SEQ ID NOs: 5-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 138, 139, and 140 in any one of SEQ ID NOs: 6-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, and 170 in any one of SEQ ID NOs: 7-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, and 197 in any one of SEQ ID NOs: 8-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 198, 199, 200, 201, 202, 203, 204, 205, and 206 in any one of SEQ ID NOs: 9-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, and 240 in any one of SEQ ID NOs: 10-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, and 255 in any one of SEQ ID NOs: 11-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, and 269 in any one of SEQ ID NOs: 12-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has

its N-terminal amino acid residue corresponding to any one of amino acid residues 270, 271, 272, 273, and 274 in any one of SEQ ID NOs: 13-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, and 386 in any one of SEQ ID NOs: 14-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, and 538 in any one of SEQ ID NOs: 15-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, and 606 in any one of SEQ ID NOs: 16-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655 in any one of SEQ ID NOs: 17-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 656, 657, 658, 659, 660, 661 in any one of SEQ ID NOs: 18-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735,

736, 737, 738, 739, 740, 741, 742, 743, 744, 745, and 746 in any one of SEQ ID NOs: 19-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, and 861 in any one of SEQ ID NOs: 20-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 862, 863, 864, 865, 866, and 867 in any one of SEQ ID NOs: 21-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, and 942 in any one of SEQ ID NOs: 22-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first

residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000, 1001, 1002, 1003, 1004, 1005, 1006, 1007, 1008, 1009, 1010, 1011, 1012, 1013, 1014, 1015, 1016, 1017, 1018, 1019, 1020, 1021, 1022, 1023, 1024, 1025, 1026, 1027, 1028, 1029, 1030, 1031, 1032, 1033, 1034, 1035, 1036, and 1037 in any one of SEQ ID NOs: 23-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 1038, 1039, 1040, 1041, 1042, 1043, 1044, 1045, 1046, 1047, 1048, 1049, 1050, 1051, 1052, 1053, 1054, 1055, 1056, 1057, 1058, 1059, 1060, 1061, 1062, 1063, 1064, 1065, 1066, 1067, 1068, 1069, 1070, 1071, 1072, 1073, 1074, 1075, 1076, 1077, 1078, 1079, 1080, 1081, 1082, 1083, 1084, and 1085 in any one of SEQ ID NOs: 24-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 1086, 1087, 1088, 1089, 1090, 1091, 1092, 1093, 1094, 1095, 1096, 1097, 1098, 1099, 1100, 1101, 1102, 1103, 1104, 1105, 1106, 1107, 1108, 1109, 1110, 1111, 1112, 1113, 1114, 1115, and 1116 in any one of SEQ ID NOs: 25-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 1117, 1118, 1119, 1120, 1121, 1122, 1123, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, and 1140 in any one of SEQ ID NOs: 26-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1170, 1171, 1172, 1173, 1174, 1175, 1176, 1177, 1178, 1179, 1180, 1181, and 1182 in any one of SEQ ID NOs: 27-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 1183, 1184, 1185, 1186, 1187, 1188, 1189, 1190, 1191, 1192, 1193, 1194, 1195, 1196, 1197, 1198, 1199, 1200, 1201, 1202, 1203, 1204, 1205, 1206, 1207, 1208, 1209, 1210, 1211, 1212, 1213, 1214, 1215, 1216, 1217, 1218, 1219, 1220, 1221, 1222, 1223, 1224, 1225, 1226, 1227, 1228, 1229, 1230, 1231, 1232, 1233, 1234, 1235, 1236, 1237, 1238, 1239, 1240, 1241, 1242, 1243, 1244, 1245, 1246, 1247, 1248, 1249, 1250, 1251, 1252, 1253, 1254, 1255, 1256, 1257, 1258, 1259, 1260, 1261, 1262, 1263, 1264, 1265, 1266, 1267, 1268, 1269, 1270, 1271, 1272, 1273, 1274, 1275, 1276, 1277, 1278, 1279, 1280, 1281, 1282, 1283, 1284, 1285, 1286, 1287, 1288, 1289, 1290, 1291, 1292, 1293, 1294, 1295, 1296, 1297, 1298, 1299, 1300, 1301, 1302, 1303, 1304, 1305, 1306, 1307, 1308, 1309, 1310, 1311, 1312, 1313, 1314, 1315, 1316, 1317, 1318, 1319, 1320, 1321, 1322, 1323, 1324, 1325, 1326, 1327, 1328, 1329, 1330, 1331, 1332, 1333, 1334, 1335, 1336, 1337, 1338, 1339, 1340, 1341, 1342, 1343, 1344, 1345, 1346, 1347, 1348, 1349, 1350, 1351, 1352, 1353, 1354, 1355, 1356, 1357, 1358, 1359, 1360, 1361, 1362, 1363, 1364, 1365, 1366, 1367, 1368, 1369, 1370, 1371, 1372, 1373, and 1374 in any one of SEQ ID NOs: 28-30, if the length of the at least 5 amino acid residues so permit – if the length of the at least

5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 1375, 1376, 1377, 1378, 1379, 1380, 1381, 1382, 1383, 1384, 1385, 1386, 1387, 1388, 1389, 1390, 1391, 1392, 1393, 1394, 1395, 1396, 1397, 1398, 1399, 1400, 1401, 1402, 1403, 1404, 1405, 1406, 1407, 1408, 1409, 1410, 1411, 1412, 1413, 1414, 1415, 1416, 1417, 1418, 1419, 1420, 1421, 1422, 1423, 1424, 1425, 1426, 1427, 1428, 1429, 1430, 1431, 1432, 1433, 1434, 1435, 1436, 1437, 1438, 1439, 1440, 1441, 1442, 1443, 1444, 1445, 1446, 1447, 1448, 1449, 1450, 1451, 1452, 1453, 1454, 1455, 1456, 1457, 1458, 1459, 1460, 1461, 1462, 1463, 1464, 1465, 1466, 1467, 1468, 1469, 1470, 1471, 1472, 1473, 1474, 1475, 1476, 1477, 1478, 1479, 1480, 1481, 1482, 1483, 1484, 1485, 1486, 1487, 1488, 1489, 1490, 1491, and 1492 in SEQ ID NO: 29 or 30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

In the embodiments defined by option b) above, the polypeptide of the invention is also one that has at least 5 contiguous amino acid residues defined for option b) above and also has its N-terminal amino acid residue corresponding to any one of amino acid residues 1493, 1494, 1495, 1496, 1497, 1498, 1499, 1500, 1501, 1502, 1503, 1504, 1505, 1506, 1507, 1508, 1509, 1510, 1511, 1512, 1513 in SEQ ID NO: 30, if the length of the at least 5 amino acid residues so permit – if the length of the at least 5 amino acids are higher than 5, the N-terminal first residue will not be higher numbered than N-L+1, where N is the number of amino acid residues of the reference sequence and L is the number of amino acids defined for option b.

The polypeptide of the invention is in certain embodiments also fused or conjugated to an immunogenic carrier molecule; or, phrased otherwise, the polypeptide of the invention also includes such an immunogenic carrier molecule in addition to the material derived from SEQ ID NOs. 1-30. The immunogenic carrier molecule is a typically polypeptide that induces T-helper lymphocyte responses in a majority of humans, such as immunogenic carrier proteins selected from the group consisting of keyhole limpet hemocyanino or a fragment thereof, tetanus toxoid or a fragment thereof, dipththeria toxoid or a fragment thereof. Other suitable carrier molecules are discussed infra.

In preferred embodiments, the polypeptide of the invention detailed above is capable of inducing an adaptive immune response against the polypeptide in a mammal, in particular in a human being. Preferably, the adaptive immune response is a protective adaptive immune response against infection with *C. jejuni*, in particular multi-resistant *C. jejuni*. The polypeptide may in these cases induce a humeral and/or a cellular immune response.

Epitopes

SEQ ID NOs: 1-30 include antigenic determinants (epitopes) that are as such recognized by antibodies and/or when bound to MHC molecules by T-cell receptors. For the purposes of the present invention, B-cell epitopes (*i.e.* antibody binding epitopes) are of particular relevance.

It is relatively uncomplicated to identify linear B-cell epitopes – one very simple approach entails that antibodies raised agains *C. jejuni* or *C. jejuni* derived proteins disclosed herein are tested for binding to overlapping oligomeric peptides derived from any one of SEQ ID NO: 1-30. Thereby, the regions of the *C. jejuni* polypeptide which are responsible for or contribute to binding to the antibodies can be identified.

Alternatively, or additionally, one can produce mutated versions of the polypeptides of the invention, e.g. version where each single non-alanine residue in SEQ ID NOs.: 1-30 are point mutated to alanine – this method also assists in identifying complex assembled B-cell epitopes; this is the case when binding of the same antibody is modified by exchanging amino acids in different areas of the full-length polypeptide.

Also, in silico methods for B-cell epitope prediction can be employed: useful state-of-the-art systems for β-turn prediction is provided in Petersen B et al. (November 2010), Plos One **5**(11): e15079; prediction of linear B-cell epitopes, cf: Larsen J E P et al. (April 2006), Immunome Research, **2**:2; predictionof solvent exposed amino acids: Petersen B et al (July 2009), BMC Structural Biology, **9**:51.

The nucleic acid fragments of the invention

The nucleic acid fragment of the invention referred to above is preferably is a DNA fragment (such as SEQ ID NOs: 31-60) or an RNA fragment (such as SEQ ID NOs 61-90).

The nucleic acid fragment of the invention typically consists of at least 11, such as at least 12, at least 13, at least 14, at least 15, at least 16, at least 17 at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34, at least

35, at least 36, at least 37, at least 38, at least 39, at least 40, at least 41, at least 42, at least 43, at least 44, at least 45, at least 46, at least 47, at least 48, at least 49, at least 50, at least 51, at least 52, at least 53, at least 54, at least 55, at least 56, at least 57, at least 58, at least 59, at least 60, at least 61, at least 62, at least 63, at least 64, at least 65, at least 66, at least 67, at least 68, at least 69, at least 70, at least 71, at least 72, at least 73, at least 74, at least 75, at least 76, at least 77, at least 78, at least 79, at least 80, at least 81, at least 82, at least 83, at least 84, at least 85, at least 86, at least 87, at least 88, at least 89, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98, at least 99, at least 100, at least 101, at least 102, at least 103, at least 104, at least 105, at least 106, at least 107, at least 108, at least 109, at least 110, at least 111, at least 112, at least 113, at least 114, at least 115, at least 116, at least 117, at least 118, at least 119, at least 120, at least 121, at least 122, at least 123, at least 124, at least 125, at least 126, at least 127, at least 128, at least 129, at least 130, at least 131, at least 132, at least 133, at least 134, at least 135, at least 136, at least 137, at least 138, at least 139, at least 140, at least 141, at least 142, at least 143, at least 144, at least 145, at least 146, at least 147, at least 148, at least 149, at least 150, at least 151, at least 152, and at least 153 consecutive nucleotides in any one of SEQ ID NOs: 31-90. Longer fragments are contemplated, *i.e.* fragments having at least 200, at least 300 at least 400, at least 500, at least 600, at least 700, at least 800, at least 900, at least 1000, at least 1500, at least 2000, at least 2500, at least 3000, at least 3500, and at least 4000 nucleotides from those of SEQ ID NOs: 31-90 that encompass fragments of such lengths.

The nucleic acid fragment of the invention discussed above typically has a sequence identity with the nucleotide sequence defined for i) or ii) above, which is at least 65%, such as at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, and at least 99%.

The nucleic acid fragment of the invention discussed above may also have a sequence identity with the nucleotide sequence defined for iii) above, which is at least 65%, such as at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, and at least 99%.

The vectors of the invention

Vectors of the invention fall into several categories discussed *infra*. One preferred vector of the invention comprises in operable linkage and in the 5'-3' direction, an expression control region comprising an enhancer/promoter for driving expression of the nucleic acid fragment

defined for option i) above, optionally a signal peptide coding sequence, a nucleotide sequence defined for option i), and optionally a terminator. Hence, such a vector constitutes an expression vector useful for effecting production in cells of the polypeptide of the invention. Since the polypeptides of the invention are bacterial of orgin, recombinant production is conveniently effected in bacterial host cells, so here it is preferred that the expression control region drives expression in prokaryotic cell such as a bacterium, e.g. in E coli. However, if the vector is to drive expression in mammalian cell (as would be the case for a DNA vaccine vector), the expression control region should be adapted to this particular use.

At any rate, certain vectors of the invention are capable of autonomous replication.

Also, the vector of the invention may be one that is capable of being integrated into the genome of a host cell – this is particularly useful if the vector is use in the production of stably transformed cells, where the progeny will also include the genetic information introduced via the vector. Alternatively, vectors incapable of being integrated into the genome of a mammalian host cell are useful in e.g. DNA vaccination.

Typically, the vector of the invention is selected from the group consisting of a virus, such as a attenuated virus (which may in itself be useful as a vaccine agent), a bacteriophage, a plasmid, a minichromosome, and a cosmid.

A more detailed discussion of vectors of the invention is provided in the following:

Polypeptides of the invention may be encoded by a nucleic acid molecule comprised in a vector. A nucleic acid sequence can be "heterologous," which means that it is in a context foreign to the cell in which the vector is being introduced, which includes a sequence homologous to a sequence in the cell but in a position within the host cell where it is ordinarily not found. Vectors include naked DNAs, RNAs, plasmids, cosmids, viruses (bacteriophage, animal viruses, and plant viruses), and artificial chromosomes (e.g., YACs). One of skill in the art would be well equipped to construct a vector through standard recombinant techniques (for example Sambrook et al, 2001; Ausubel et al, 1996, both incorporated herein by reference). In addition to encoding the polypeptides of this invention, a vector of the present invention may encode polypeptide sequences such as a tag or immunogenicity enhancing peptide (e.g. an immunogenic carrier or a fusion partner that stimulates the immune system, such as a cytokine or active fragment thereof). Useful vectors encoding such fusion proteins include pIN vectors (Inouye et al, 1985), vectors encoding a stretch of histidines, and pGEX vectors, for use in generating glutathione S-transferase (GST) soluble fusion proteins for later purification and separation or cleavage.

Vectors of the invention may be used in a host cell to produce a polypeptide of the invention that may subsequently be purified for administration to a subject or the vector may be purified for direct administration to a subject for expression of the protein in the subject (as is the case when administering a nucleic acid vaccine).

Expression vectors can contain a variety of "control sequences," which refer to nucleic acid sequences necessary for the transcription and possibly translation of an operably linked coding sequence in a particular host organism. In addition to control sequences that govern transcription and translation, vectors and expression vectors may contain nucleic acid sequences that serve other functions as well and are described *infra*.

1. Promoters and Enhancers

A "promoter" is a control sequence. The promoter is typically a region of a nucleic acid sequence at which initiation and rate of transcription are controlled. It may contain genetic elements at which regulatory proteins and molecules may bind such as RNA polymerase and other transcription factors. The phrases "operatively positioned," "operatively linked," "under control," and "under transcriptional control" mean that a promoter is in a correct functional location and/or orientation in relation to a nucleic acid sequence to control transcriptional initiation and expression of that sequence. A promoter may or may not be used in conjunction with an "enhancer," which refers to a cis-acting regulatory sequence involved in the transcriptional activation of a nucleic acid sequence.

A promoter may be one naturally associated with a gene or sequence, as may be obtained by isolating the 5' non-coding sequences located upstream of the coding segment or exon. Such a promoter can be referred to as "endogenous." Similarly, an enhancer may be one naturally associated with a nucleic acid sequence, located either downstream or upstream of that sequence. Alternatively, certain advantages will be gained by positioning the coding nucleic acid segment under the control of a recombinant or heterologous promoter, which refers to a promoter that is not normally associated with a nucleic acid sequence in its natural environment. A recombinant or heterologous enhancer refers also to an enhancer not normally associated with a nucleic acid sequence in its natural state. Such promoters or enhancers may include promoters or enhancers of other genes, and promoters or enhancers isolated from any other prokaryotic, viral, or eukaryotic cell, and promoters or enhancers not "naturally occurring," i.e., containing different elements of different transcriptional regulatory regions, and/or mutations that alter expression. In addition to producing nucleic acid sequences of promoters and enhancers synthetically, sequences may be produced using recombinant cloning and/or nucleic acid amplification technology, including PCR™, in

connection with the compositions disclosed herein (see U.S. Patent 4,683,202, U.S. Patent 5,928,906, each incorporated herein by reference).

Naturally, it may be important to employ a promoter and/or enhancer that effectively direct(s) the expression of the DNA segment in the cell type or organism chosen for expression. Those of skill in the art of molecular biology generally know the use of promoters, enhancers, and cell type combinations for protein expression (see Sambrook et al, 2001, incorporated herein by reference). The promoters employed may be constitutive, tissue-specific, or inducible and in certain embodiments may direct high level expression of the introduced DNA segment under specified conditions, such as large-scale production of recombinant proteins or peptides.

Examples of inducible elements, which are regions of a nucleic acid sequence that can be activated in response to a specific stimulus, include but are not limited to Immunoglobulin Heavy Chain (Banerji et al, 1983; Gilles et al, 1983; Grosschedl et al, 1985; Atchinson et al, 1986, 1987; toiler et al, 1987; Weinberger et al, 1984; Kiledjian et al, 1988; Porton et al; 1990), Immunoglobulin Light Chain (Queen et al, 1983; Picard et al, 1984), T Cell Receptor (Luria et al, 1987; Winoto et al, 1989; Redondo et al; 1990), HLA DQα and/or DQβ (Sullivan et al, 1987), β-Interferon (Goodbourn et al, 1986; Fujita et al, 1987; Goodbourn et al, 1988), Interleukin-2 (Greene et al, 1989), Interleukin-2 Receptor (Greene et al, 1989; Lin et al, 1990), MHC Class II 5 (Koch et al, 1989), MHC Class II HLA-DRα (Sherman et al, 1989), β-Actin (Kawamoto et al, 1988; Ng et al; 1989), Muscle Creatine Kinase (MCK) (Jaynes et al, 1988; Horlick et al, 1989; Johnson et al, 1989), Prealbumin (Transthyretin) (Costa et al, 1988), Elastase I (Omitz et al, 1987), Metallothionein (MTII) (Karin et al, 1987; Culotta et al, 1989), Collagenase (Pinkert et al, 1987; Angel et al, 1987), Albumin (Pinkert et al, 1987; Tranche et al, 1989, 1990),α-Fetoprotein (Godbout et al, 1988; Campere et al, 1989), γ-Globin (Bodine et al, 1987; Perez-Stable et al, 1990),β- Globin (Trudel et al, 1987), c-fos (Cohen et al, 1987), c-HA-ras (Triesman, 1986; Deschamps et al, 1985), Insulin (Edlund et al, 1985), Neural Cell Adhesion Molecule (NCAM) (Hirsh et al, 1990),α1-Antitrypain (Larimer et al, 1990), H2B (TH2B) Histone (Hwang et al, 1990), Mouse and/or Type I Collagen (Ripe et al, 1989), Glucose-Regulated Proteins (GRP94 and GRP78) (Chang et al, 1989), Rat Growth Hormone (Larsen et al, 1986), Human Serum Amyloid A (SAA) (Edbrooke et al, 1989), Troponin I (TN I) (Yutzey et al, 1989), Platelet-Derived Growth Factor (PDGF) (Pech et al, 1989), Duchenne Muscular Dystrophy (Klamut et al, 1990), SV40 (Banerji et al, 1981; Moreau et al, 1981 ; Sleigh et al, 1985; Firak et al, 1986; Herr et al, 1986; Imbra et al, 1986; Kadesch et al, 1986; Wang et al, 1986; Ondek et al, 1987; Kuhl et al, 1987; Schaffner et al, 1988), Polyoma (Swartzendruber et al, 1975; Vasseur et al, 1980; Katinka et al, 1980, 1981; Tyndell et al, 1981 ; Dandolo et al, 1983; de Villiers et al, 1984; Hen et al, 1986; Satake et al, 1988; Campbell et al, 1988), Retroviruses (Kriegler et al, 1982, 1983; Levinson

et al, 1982; Kriegler et al, 1983, 1984a, b, 1988; Bosze et al, 1986; Miksicek et al, 1986; Celander et al, 1987; Thiesen et al, 1988; Celander et al, 1988; Choi et al, 1988; Reisman et al, 1989), Papilloma Virus (Campo et al, 1983; Lusky et al, 1983; Spandidos and Wilkie, 1983; Spalholz et al, 1985; Lusky et al, 1986; Cripe et al, 1987; Gloss et al, 1987; Hirochika et al, 1987; Stephens et al, 1987), Hepatitis B Virus (Bulla et al, 1986; Jameel et al, 1986; Shaul et al, 1987; Spandau et al, 1988; Vannice et al, 1988), Human Immunodeficiency Virus (Muesing et al, 1987; Hauber et al, 1988; Jakobovits et al, 1988; Feng et al, 1988; Takebe et al, 1988; Rosen et al, 1988; Berkhout et al, 1989; Laspia et al, 1989; Sharp et al, 1989; Braddock et al, 1989), Cytomegalovirus (CMV) IE (Weber et al, 1984; Boshart et al, 1985; Foecking et al, 1986), Gibbon Ape Leukemia Virus (Holbrook et al, 1987; Quinn et al, 1989).

Inducible Elements include, but are not limited to MT II - Phorbol Ester (TFA)/Heavy metals (Palmiter et al, 1982; Haslinger et al, 1985; Searle et al, 1985; Stuart et al, 1985; Imagawa et al, 1987, Karin et al, 1987; Angel et al, 1987b; McNeall et al, 1989); MMTV (mouse mammary tumor virus) - Glucocorticoids (Huang et al, 1981; Lee et al, 1981; Majors et al, 1983; Chandler et al, 1983; Lee et al, 1984; Ponta et al, 1985; Sakai et al, 1988);β-Interferon - poly(rl)x/poly(rc) (Tavernier et al, 1983); Adenovirus 5 E2 - ElA (Imperiale et al, 1984); Collagenase - Phorbol Ester (TPA) (Angel et al, 1987a); Stromelysin - Phorbol Ester (TPA) (Angel et al, 1987b); SV40 - Phorbol Ester (TPA) (Angel et al, 1987b); Murine MX Gene - Interferon, Newcastle Disease Virus (Hug et al, 1988); GRP78 Gene - A23187 (Resendez et al, 1988);α-2-Macroglobulin - IL-6 (Kunz et al, 1989); Vimentin - Serum (Rittling et al, 1989); MHC Class I Gene H-2κb - Interferon (Blanar et al, 1989); HSP70 - E1A/SV40 Large T Antigen (Taylor et al, 1989, 1990a, 1990b); Proliferin - Phorbol Ester/TPA (Mordacq et al, 1989); Tumor Necrosis Factor - PMA (Hensel et al, 1989); and Thyroid Stimulating Hormone α Gene - Thyroid Hormone (Chatterjee et al, 1989).

Also contemplated as useful in the present invention are the dectin-1 and dectin-2 promoters. Additionally any promoter/enhancer combination (as per the Eukaryotic Promoter Data Base EPDB) could also be used to drive expression of structural genes encoding oligosaccharide processing enzymes, protein folding accessory proteins, selectable marker proteins or a heterologous protein of interest.

The particular promoter that is employed to control the expression of peptide or protein encoding polynucleotide of the invention is not believed to be critical, so long as it is capable of expressing the polynucleotide in a targeted cell, preferably a bacterial cell. Where a human cell is targeted, it is preferable to position the polynucleotide coding region adjacent to and under the control of a promoter that is capable of being expressed in a human cell. Generally speaking, such a promoter might include either a bacterial, human or viral promoter.

In various embodiments, the human cytomegalovirus (CMV) immediate early gene promoter, the SV40 early promoter, and the Rous sarcoma virus long terminal repeat can be used to obtain high level expression of a related polynucleotide to this invention. The use of other viral or mammalian cellular or bacterial phage promoters, which are well known in the art, to achieve expression of polynucleotides is contemplated as well.

In embodiments in which a vector is administered to a subject for expression of the protein, it is contemplated that a desirable promoter for use with the vector is one that is not down-regulated by cytokines or one that is strong enough that even if down-regulated, it produces an effective amount of the protein/polypeptide of the current invention in a subject to elicit an immune response. Non-limiting examples of these are CMV IE and RSV LTR. In other embodiments, a promoter that is up-regulated in the presence of cytokines is employed. The MHC I promoter increases expression in the presence of IFN-γ.

Tissue specific promoters can be used, particularly if expression is in cells in which expression of an antigen is desirable, such as dendritic cells or macrophages. The mammalian MHC I and MHC II promoters are examples of such tissue-specific promoters. 2. Initiation Signals and Internal Ribosome Binding Sites (IRES)

A specific initiation signal also may be required for efficient translation of coding sequences. These signals include the ATG initiation codon or adjacent sequences. Exogenous translational control signals, including the ATG initiation codon, may need to be provided. One of ordinary skill in the art would readily be capable of determining this and providing the necessary signals. It is well known that the initiation codon must be "in-frame" with the reading frame of the desired coding sequence to ensure translation of the entire insert. The exogenous translational control signals and initiation codons can be either natural or synthetic and may be operable in bacteria or mammalian cells. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements.

In certain embodiments of the invention, the use of internal ribosome entry sites (IRES) elements are used to create multigene, or polycistronic, messages. IRES elements are able to bypass the ribosome scanning model of 5' methylated Cap dependent translation and begin translation at internal sites (Pelletier and Sonenberg, 1988). IRES elements from two members of the picornavirus family (polio and encephalomyocarditis) have been described (Pelletier and Sonenberg, 1988), as well an IRES from a mammalian message (Macejak and Sarnow, 1991). IRES elements can be linked to heterologous open reading frames. Multiple open reading frames can be transcribed together, each separated by an IRES, creating polycistronic messages. By virtue of the IRES element, each open reading frame is accessible to ribosomes for efficient translation. Multiple genes can be efficiently expressed using a

single promoter/enhancer to transcribe a single message (see U.S. Patents 5,925,565 and 5,935,819, herein incorporated by reference).

2. Multiple Cloning Sites

Vectors can include a multiple cloning site (MCS), which is a nucleic acid region that contains multiple restriction enzyme sites, any of which can be used in conjunction with standard recombinant technology to digest the vector. (See Carbonelli et al, 1999, Levenson et al, 1998, and Cocea, 1997, incorporated herein by reference.) Frequently, a vector is linearized or fragmented using a restriction enzyme that cuts within the MCS to enable exogenous sequences to be ligated to the vector. Techniques involving restriction enzymes and ligation reactions are well known to those of skill in the art of recombinant technology.

3. Splicing Sites

Most transcribed eukaryotic RNA molecules will undergo RNA splicing to remove introns from the primary transcripts. If relevant in the context of vectors of the present invention, vectors containing genomic eukaryotic sequences may require donor and/or acceptor splicing sites to ensure proper processing of the transcript for protein expression. (See Chandler et al, 1997, incorporated herein by reference.)

4. Termination Signals

The vectors or constructs of the present invention will generally comprise at least one termination signal. A "termination signal" or "terminator" is comprised of the DNA sequences involved in specific termination of an RNA transcript by an RNA polymerase. Thus, in certain embodiments a termination signal that ends the production of an RNA transcript is contemplated. A terminator may be necessary *in vivo* to achieve desirable message levels.

In eukaryotic systems, the terminator region may also comprise specific DNA sequences that permit site-specific cleavage of the new transcript so as to expose a polyadenylation site. This signals a specialized endogenous polymerase to add a stretch of about 200 A residues (poly A) to the 3' end of the transcript. RNA molecules modified with this polyA tail appear to more stable and are translated more efficiently. Thus, in other embodiments involving eukaryotes, it is preferred that that terminator comprises a signal for the cleavage of the RNA, and it is more preferred that the terminator signal promotes polyadenylation of the message.

Terminators contemplated for use in the invention include any known terminator of transcription described herein or known to one of ordinary skill in the art, including but not limited to, for example, the bovine growth hormone terminator or viral termination sequences, such as the SV40 terminator. In certain embodiments, the termination signal may be a lack of transcribable or translatable sequence, such as due to a sequence truncation.

5. Polyadenylation Signals

In expression, particularly eukaryotic expression (as is relevant in nucleic acid vaccination), one will typically include a polyadenylation signal to effect proper polyadenylation of the transcript. The nature of the polyadenylation signal is not believed to be crucial to the successful practice of the invention, and/or any such sequence may be employed. Preferred embodiments include the SV40 polyadenylation signal and/or the bovine growth hormone polyadenylation signal, convenient and/or known to function well in various target cells. Polyadenylation may increase the stability of the transcript or may facilitate cytoplasmic transport.

6. Origins of Replication

In order to propagate a vector in a host cell, it may contain one or more origins of replication sites (often termed "on"), which is a specific nucleic acid sequence at which replication is initiated. Alternatively an autonomously replicating sequence (ARS) can be employed if the host cell is yeast.

7. Selectable and Screenable Markers

In certain embodiments of the invention, cells containing a nucleic acid construct of the present invention may be identified *in vitro* or *in vivo* by encoding a screenable or selectable marker in the expression vector. When transcribed and translated, a marker confers an identifiable change to the cell permitting easy identification of cells containing the expression vector. Generally, a selectable marker is one that confers a property that allows for selection. A positive selectable marker is one in which the presence of the marker allows for its selection, while a negative selectable marker is one in which its presence prevents its selection. An example of a positive selectable marker is a drug resistance marker.

Usually the inclusion of a drug selection marker aids in the cloning and identification of transformants, for example, markers that confer resistance to neomycin, puromycin, hygromycin, DHFR, GPT, zeocin or histidinol are useful selectable markers. In addition to markers conferring a phenotype that allows for the discrimination of transformants based on

the implementation of conditions, other types of markers including screenable markers such as GFP for colorimetric analysis. Alternatively, screenable enzymes such as herpes simplex virus thymidine kinase (tk) or chloramphenicol acetyltransferase (CAT) may be utilized. One of skill in the art would also know how to employ immunologic markers that can be used in conjunction with FACS analysis. The marker used is not believed to be important, so long as it is capable of being expressed simultaneously with the nucleic acid encoding a protein of the invention. Further examples of selectable and screenable markers are well known to one of skill in the art.

The transformed cells of the invention

Transformed cells of the invention are useful as organisms for producing the polypeptide of the invention, but also as simple "containers" of nucleic acids and vectors of the invention.

Certain transformed cells of the invention are capable of replicating the nucleic acid fragment defined for option i) of the second aspect of the invention. Preferred transformed cells of the invention are capable of expressing the nucleic acid fragment defined for option i).

For recombinant production it is convenient, but not a prerequisite that the transformed cell according is prokaryotic, such as a bacterium, but generally both prokaryotic cells and eukaryotic cells may be used.

Suitable prokaryotic cells are bacterial cells selected from the group consisting of Escherichia (such as E. coli.), Bacillus [e.g. Bacillus subtilis], Salmonella, and Mycobacterium [preferably non-pathogenic, e.g. M. bovis BCG].

Eukaryotic cells can be in the form of yeasts (such as Saccharomyces cerevisiae) and protozoans. Alternatively, the transformed eukaryotic cells are derived from a multicellular organism such as a fungus, an insect cell, a plant cell, or a mammalian cell.

For production purposes, it is advantageous that the transformed cell of the invention is is stably transformed by having the nucleic acid defined above for option i) stably integrated into its genome, and in certain embodiments it is also preferred that the transformed cell secretes or carries on its surface the polypeptide of the invention, since this facilitates recovery of the polypeptides produced. A particular version of this embodiment is one where the transformed cell is a bacterium and secretion of the polypeptide of the invention is into the periplasmic space.

As noted above, stably transformed cells are preferred – these i.a. allows that cell lines comprised of transformed cells as defined herein may be established – such cell lines are partilucarly preferred aspects of the invention.

Further details on cells and cell lines are presented in the following:

Suitable cells for recombinant nucleic acid expression of the nucleic acid fragments of the present invention are prokaryotes and eukaryotes. Examples of prokaryotic cells include *E. coli*; members of the *Staphylococcus* genus, such as *S. epidermidis*; members of the *Lactobacillus* genus, such as *L. plantarum*; members of the *Lactococcus* genus, such as *L. lactis*; members of the *Bacillus* genus, such as *B. subtilis*; members of the *Corynebacterium* genus such as *C. glutamicum*; and members of the *Pseudomonas* genus such as *Ps. fluorescens*. Examples of eukaryotic cells include mammalian cells; insect cells; yeast cells such as members of the *Saccharomyces* genus (e.g. *S. cerevisiae*), members of the *Pichia* genus (e.g. *P. pastoris*), members of the *Hansenula* genus (e.g. *H. polymorpha*), members of the *Kluyveromyces* genus (e.g. *K. lactis* or *K. fragilis*) and members of the *Schizosaccharomyces* genus (e.g. *S. pombe*).

Techniques for recombinant gene production, introduction into a cell, and recombinant gene expression are well known in the art. Examples of such techniques are provided in references such as Ausubel, Current Protocols in Molecular Biology, John Wiley, 1987-2002, and Sambrook et al., Molecular Cloning, A Laboratory Manual, 2 nd Edition, Cold Spring Harbor Laboratory Press, 1989.

As used herein, the terms "cell," "cell line," and "cell culture" may be used interchangeably. All of these terms also include their progeny, which is any and all subsequent generations. It is understood that all progeny may not be identical due to deliberate or inadvertent mutations. In the context of expressing a heterologous nucleic acid sequence, "host cell" refers to a prokaryotic or eukaryotic cell, and it includes any transformable organism that is capable of replicating a vector or expressing a heterologous gene encoded by a vector. A host cell can, and has been, used as a recipient for vectors or viruses. A host cell may be "transfected" or "transformed," which refers to a process by which exogenous nucleic acid, such as a recombinant protein-encoding sequence, is transferred or introduced into the host cell. A transformed cell includes the primary subject cell and its progeny.

Host cells may be derived from prokaryotes or eukaryotes, including bacteria, yeast cells, insect cells, and mammalian cells for replication of the vector or expression of part or all of the nucleic acid sequence(s). Numerous cell lines and cultures are available for use as a host cell, and they can be obtained through the American Type Culture Collection (ATCC), which is

an organization that serves as an archive for living cultures and genetic materials (www.atcc.org) or from other depository institutions such as Deutsche Sammlung vor Micrroorganismen und Zellkulturen (DSM). An appropriate host can be determined by one of skill in the art based on the vector backbone and the desired result. A plasmid or cosmid, for example, can be introduced into a prokaryote host cell for replication of many vectors or expression of encoded proteins. Bacterial cells used as host cells for vector replication and/or expression include *Staphylococcus* strains, DH5α, JMl 09, and KC8, as well as a number of commercially available bacterial hosts such as SURE(R) Competent Cells and SOLOP ACK(TM) Gold Cells (STRATAGENE®, La Jolla, CA). Alternatively, bacterial cells such as E. coli LE392 could be used as host cells for phage viruses. Appropriate yeast cells include *Saccharomyces cerevisiae*, *Saccharomyces pombe*, and *Pichia pastoris*.

Examples of eukaryotic host cells for replication and/or expression of a vector include HeLa, NIH3T3, Jurkat, 293, Cos, CHO, Saos, and PC12. Many host cells from various cell types and organisms are available and would be known to one of skill in the art. Similarly, a viral vector may be used in conjunction with either a eukaryotic or prokaryotic host cell, particularly one that is permissive for replication or expression of the vector.

Some vectors may employ control sequences that allow it to be replicated and/or expressed in both prokaryotic and eukaryotic cells. One of skill in the art would further understand the conditions under which to incubate all of the above described host cells to maintain them and to permit replication of a vector. Also understood and known are techniques and conditions that would allow large-scale production of vectors, as well as production of the nucleic acids encoded by vectors and their cognate polypeptides, proteins, or peptides.

Expression Systems

Numerous expression systems exist that comprise at least a part or all of the compositions discussed above. Prokaryote- and/or eukaryote-based systems can be employed for use with the present invention to produce nucleic acid sequences, or their cognate polypeptides, proteins and peptides. Many such systems are commercially and widely available.

The insect cell/baculovirus system can produce a high level of protein expression of a heterologous nucleic acid segment, such as described in U.S. Patents 5,871,986, 4,879,236, both herein incorporated by reference, and which can be bought, for example, under the name MAXBAC® 2.0 from INVITROGEN® and BACPACK™ Baculovirus expression system from CLONTECH®

In addition to the disclosed expression systems of the invention, other examples of expression systems include STRATAGENE®'s COMPLETE CONTROL™ Inducible Mammalian Expression System, which involves a synthetic ecdysone-inducible receptor, or its pET Expression System, an E. coli expression system. Another example of an inducible expression system is available from INVITROGEN® , which carries the T-REX™ (tetracycline-regulated expression) System, an inducible mammalian expression system that uses the full-length CMV promoter. INVITROGEN® also provides a yeast expression system called the Pichia methanolica Expression System, which is designed for high-level production of recombinant proteins in the methylotrophic yeast Pichia methanolica. One of skill in the art would know how to express a vector, such as an expression construct, to produce a nucleic acid sequence or its cognate polypeptide, protein, or peptide.

Amplification of Nucleic Acids

Nucleic acids used as a template for amplification may be isolated from cells, tissues or other samples according to standard methodologies (Sambrook et al, 2001). In certain embodiments, analysis is performed on whole cell or tissue homogenates or biological fluid samples without substantial purification of the template nucleic acid. The nucleic acid may be genomic DNA or fractionated or whole cell RNA. Where RNA is used, it may be desired to first convert the RNA to a complementary DNA.

The term "primer," as used herein, is meant to encompass any nucleic acid that is capable of priming the synthesis of a nascent nucleic acid in a template-dependent process. Typically, primers are oligonucleotides from ten to twenty and/or thirty base pairs in length, but longer sequences can be employed. Primers may be provided in double-stranded and/or single-stranded form, although the single-stranded form is preferred.

Pairs of primers designed to selectively hybridize to nucleic acids corresponding to sequences of genes identified herein are contacted with the template nucleic acid under conditions that permit selective hybridization. Depending upon the desired application, high stringency hybridization conditions may be selected that will only allow hybridization to sequences that are completely complementary to the primers. In other embodiments, hybridization may occur under reduced stringency to allow for amplification of nucleic acids containing one or more mismatches with the primer sequences. Once hybridized, the template-primer complex is contacted with one or more enzymes that facilitate template-dependent nucleic acid synthesis. Multiple rounds of amplification, also referred to as "cycles," are conducted until a sufficient amount of amplification product is produced.

The amplification product may be detected or quantified. In certain applications, the detection may be performed by visual means. Alternatively, the detection may involve indirect identification of the product via chemiluminescence, radioactive scintigraphy of incorporated radiolabel or fluorescent label or even via a system using electrical and/or thermal impulse signals (Bellus, 1994).

A number of template dependent processes are available to amplify the oligonucleotide sequences present in a given template sample. One of the best known amplification methods is the polymerase chain reaction (referred to as PCR(TM)) which is described in detail in U.S. Patents 4,683,195, 4,683,202 and 4,800,159, and in Innis et al., 1988, each of which is incorporated herein by reference in their entirety.

Alternative methods for amplification of target nucleic acid sequences that may be used in the practice of the present invention are disclosed in U.S. Patents 5,843,650, 5,846,709, 5,846,783, 5,849,546, 5,849,497, 5,849,547, 5,858,652, 5,866,366, 5,916,776, 5,922,574, 5,928,905, 5,928,906, 5,932,451, 5,935,825, 5,939,291 and 5,942,391, GB Application No. 2 202 328, and in PCT Application No. PCT/US89/01025, each of which is incorporated herein by reference in its entirety.

Methods of Gene Transfer

Suitable methods for nucleic acid delivery to effect expression of compositions of the present invention are believed to include virtually any method by which a nucleic acid (e.g., DNA, including viral and nonviral vectors) can be introduced into a cell, a tissue or an organism, as described herein or as would be known to one of ordinary skill in the art. Such methods include, but are not limited to, direct delivery of DNA such as by injection (U.S. Patents 5,994,624, 5,981,274, 5,945,100, 5,780,448, 5,736,524, 5,702,932, 5,656,610, 5,589,466 and 5,580,859, each incorporated herein by reference), including microinjection (Harland and Weintraub, 1985; U.S. Patent 5,789,215, incorporated herein by reference); by electroporation (U.S. Patent No. 5,384,253, incorporated herein by reference); by calcium phosphate precipitation (Graham and Van Der Eb, 1973; Chen and Okayama, 1987; Rippe et al., 1990); by using DEAE dextran followed by polyethylene glycol (Gopal, 1985); by direct sonic loading (Fechheimer et al, 1987); by liposome mediated transfection (Nicolau and Sene, 1982; Fraley et al, 1979; Nicolau et al, 1987; Wong et al, 1980; Kaneda et al, 1989; Kato et al, 1991); by microprojectile bombardment (PCT Application Nos. WO 94/09699 and 95/06128; U.S. Patents 5,610,042; 5,322,783 5,563,055, 5,550,318, 5,538,877 and 5,538,880, and each incorporated herein by reference); by agitation with silicon carbide fibers (Kaeppler et al, 1990; U.S. Patents 5,302,523 and 5,464,765, each incorporated herein by reference); by Agrobacterium mediated transformation (U.S. Patents 5,591,616 and

5,563,055, each incorporated herein by reference); or by PEG mediated transformation of protoplasts (Omirulleh et al, 1993; U.S. Patents 4,684,611 and 4,952,500, each incorporated herein by reference); by desiccation/inhibition mediated DNA uptake (Potrykus et al, 1985). Through the application of techniques such as these, organelle(s), cell(s), tissue(s) or organism(s) may be stably or transiently transformed.

The antibodies of the invention – and their production/isolation

Antibodies directed against the proteins of the invention are useful for affinity chromatography, immunoassays, and for distinguishing/identifying staphylococcus proteins as well as for passive immunisation and therapy.

Antibodies to the proteins of the invention, both polyclonal and monoclonal, may be prepared by conventional methods. In general, the protein is first used to immunize a suitable animal, preferably a mouse, rat, rabbit or goat. Rabbits and goats are preferred for the preparation of polyclonal sera due to the volume of serum obtainable, and the availability of labeled anti-rabbit and anti-goat antibodies. Immunization is generally performed by mixing or emulsifying the protein in saline, preferably in an adjuvant such as Freund's complete adjuvant, and injecting the mixture or emulsion parenterally (generally subcutaneously or intramuscularly). A dose of 50-200 µg/injection is typically sufficient. Immunization is generally boosted 2-6 weeks later with one or more injections of the protein in saline, preferably using Freund's incomplete adjuvant. One may alternatively generate antibodies by *in vitro* immunization using methods known in the art, which for the purposes of this invention is considered equivalent to *in vivo* immunization. Polyclonal antiserum is obtained by bleeding the immunized animal into a glass or plastic container, incubating the blood at 25 C for one hour, followed by incubating at 4 C for 2-18 hours. The serum is recovered by centrifugation (eg. 1,000 g for 10 minutes). About 20-50 ml per bleed may be obtained from rabbits.

Monoclonal antibodies are prepared using the standard method of Kohler & Milstein [Nature (1975) 256 : 495-96], or a modification thereof. Typically, a mouse or rat is immunized as described above. However, rather than bleeding the animal to extract serum, the spleen (and optionally several large lymph nodes) is removed and dissociated into single cells. If desired, the spleen cells may be screened (after removal of nonspecifically adherent cells) by applying a cell suspension to a plate or well coated with the protein antigen. B-cells expressing membrane-bound immunoglobulin specific for the antigen bind to the plate, and are not rinsed away with the rest of the suspension. Resulting B-cells, or all dissociated spleen cells, are then induced to fuse with myeloma cells to form hybridomas, and are cultured in a selective l aedium (elg. hypexanthine, aminopterin, thymidine medium,"HAT"). The resulting

hybridomas are plated by limiting dilution, and are assayed for production of antibodies, which bind specifically to the immunizing antigen (and which do not bind to unrelated antigens). The selected MAb-secreting hybridomas are then cultured either *in vitro* (eg. in tissue culture bottles or hollow fiber reactors), or *in vivo* (as ascites in mice).

If desired, the antibodies (whether polyclonal or monoclonal) may be labeled using conventional techniques. Suitable labels include fluorophores, chromophores, radioactive atoms (particularly 32p and I25I), electron-dense reagents, enzymes, and ligands having specific binding partners. Enzymes are typically detected by their activity. For example, horseradish peroxidase is usually detected by its ability to convert 3,3', 5,5'-tetramethylbenzidine (TMB) to a blue pigment, quantifiable with a spectrophotometer. "Specific binding partner" refers to a protein capable of binding a ligand molecule with high specificity, as for example in the case of an antigen and a monoclonal antibody specific therefor. Other specific binding partners include biotin and avidin or streptavidin, IgG and protein A, and the numerous receptor-ligand couples known in the art. It should be understood that the above description is not meant to categorize the various labels into distinct classes, as the same label may serve in several different modes. For example, 1151 may serve as a radioactive label or as an electron-dense reagent. HRP may serve as enzyme or as antigen for a MAb. Further, one may combine various labels for desired effect. For example, MAbs and avidin also require labels in the practice of this invention: thus, one might label a MAb with biotin, and detect its presence with avidin labeled with, I25I, or with an anti-biotin MAb labeled with HRP. Other permutations and possibilities will be readily apparent to those of ordinary skill in the art, and are considered as equivalents within the scope of the instant invention.

According to the invention, the isolated monoclonal antibody or antibody analogue is preferably a monoclonal antibody selected from a multi-domain antibody such as a murine antibody, a chimeric antibody such as a humanized antibody, a fully human antibody, and single-domain antibody of a llama or a camel, or which is an antibody analogue selected from a fragment of an antibody such as an Fab or an $F(ab')_2$, an scFV; cf. also the definition of the term "antibody" presented above.

Compositions of the invention; vaccines

Pharmaceutical compositions, in particular vaccines, according to the invention may either be prophylactic (ie. to prevent infection) or therapeutic (ie, to treat disease after infection).

Such vaccines comprise immunising antigen(s), immunogen(s), polypeptide(s), protein(s) or nucleic acid(s), usually in combination with "pharmaceutically acceptable carriers", which

include any carrier that does not itself induce the production of antibodies harmful to the individual receiving the composition. Suitable carriers are typically large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, lipid aggregates (such as oil droplets or liposomes), and inactive virus particles.

Such carriers are well known to those of ordinary skill in the art. Additionally, these carriers may function as immunostimulating agents ("adjuvants"). Furthermore, the antigen or immunogen may be conjugated to a bacterial toxoid, such as a toxoid from diphtheria, tetanus, cholera, H. pylori, etc. pathogen, cf. the description of immunogenic carriers supra.

The pharmaceutical compositions of the invention thus typically contain an immunological adjuvant, which is commonly an aluminium based adjuvant or one of the other adjuvants described in the following:

Preferred adjuvants to enhance effectiveness of the composition include, but are not limited to : (1) aluminum salts (alum), such as aluminum hydroxide, aluminum phosphate, aluminum sulfate, etc; (2) oil-in-water emulsion formulations (with or without other specific immunostimulating agents such as muramyl peptides (see below) or bacterial cell wall components), such as for example (a) MF59 (WO 90/14837; Chapter 10 in Vaccine design: the subunit and adjuvant approach, eds. Powell & Newman, Plenum Press 1995), containing 5% Squalene, 0.5% Tween 80, and 0.5% Span 85 (optionally containing various amounts of MTP-PE (see below), although not required) formulated into submicron particles using a microfluidizer such as Model 110Y microfluidizer (Microfluidics, Newton, MA), (b) SAF, containing 10% Squalane, 0.4% Tween 80, 5% pluronic-blocked polymer L121, and thr-

MDP (see below) either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion, and (c) Ribi adjuvant system (RAS), (Ribi Immunochem, Hamilton, MT) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphoryl lipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (DetoxTM) ; (3) saponin adjuvants such as Stimulon™ (Cambridge Bioscience, Worcester, MA) may be used or particles generated therefrom such as ISCOMs (immunostimulating complexes); (4) Complete Freund's Adjuvant (CFA) and Incomplete Freund's Adjuvant (IFA); (5) cytokines, such as interleukins (eg. IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, etc.), interferons (eg. gamma interferon), macrophage colony stimulating factor (M-CSF), tumor necrosis factor (TNF), etc.; and (6) other substances that act as immunostimulating agents to enhance the effectiveness of the composition. Alum and MF59™ adjuvants are preferred.

As mentioned above, muramyl peptides include, but are not limited to, N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-normuramyl-L-alanyl-D-isoglutamine (nor-MDP), N-acetylmuramyl-L-alanyl-D-isoglutaminyl- L-alanine-2"-2'-dipalmitoyl-sn-glycero-3-hydroxyphosphoryloxy)-ethylamine (MTP-PE), etc.

The immunogenic compositions (eg. the immunising antigen or immunogen or polypeptide or protein or nucleic acid, pharmaceutically acceptable carrier, and adjuvant) typically will contain diluents, such as water, saline, glycerol, ethanol, etc. Additionally, auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, may be present in such vehicles.

Typically, the immunogenic compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection may also be prepared. The preparation also may be emulsified or encapsulated in liposomes for enhanced adjuvant effect, as discussed above under pharmaceutically acceptable carriers.

Immunogenic compositions used as vaccines comprise an immunologically effective amount of the antigenic or immunogenic polypeptides, as well as any other of the above-mentioned components, as needed. By "immunollogically effective amount", it is meant that the administration of that amount to an individual, either in a single dose or as part of a series, is effective for treatment or prevention. This amount varies depending upon the health and physical condition of the individual to be treated, the taxonomic group of individual to be treated (eg. nonhuma primate, primate, etc.), the capacity of the individual's immune system to synthesize antibodies or generally mount an immune response, the degree of protection desired, the formulation of the vaccine, the treating doctor's assessment of the medical situation, and other relevant factors. It is expected that the amount will fall in a relatively broad range that can be determined through routine trials. However, for the purposes of protein vaccination, the amount administered per immunization is typically in the range between 0.5 µg and 500 mg (however, oftn not higher than 5,000 µg), and very often in the range between 10 and 200 µg.

The immunogenic compositions are conventionally administered parenterally, eg, by injection, either subcutaneously, intramuscularly, or transdermally/transcutaneously (eg. W098/20734). Additional formulations suitable for other modes of administration include oral and pulmonary formulations, suppositories, and transdermal applications. In the case of nucleic acid vaccination, also the intravenous or intraarterial routes may be applicable.

Dosage treatment may be a single dose schedule or a multiple dose schedule. The vaccine may be administered in conjunction with other immunoregulatory agents.

As an alternative to protein-based vaccines, DNA vaccination (also termed nucleic acid vaccination or gene vaccination) may be used [eg. Robinson & Torres (1997) Seminars in Imlllunol 9: 271-283; Donnelly et al. (1997) Avnu Rev Innnunol 15 : 617-648; later herein].

Treatment methods of the invention

The method of the sixth aspect of the invention generally relates to induction of immunity and as such also entails method that relate to treatment, prophylaxis and amelioration of disease.

When immunization methods entail that a polypeptide of the invention or a composition comprising such a polypeptide is administered the animal (e.g. the human) typically receives between 0.5 and 5,000 µg of the polypeptide of the invention per administration.

In preferred embodiments of the sixth aspect, the immuniation scheme includes that the animal (e.g. the human) receives a priming administration and one or more booster administrations.

Preferred embodimentms of the 6th aspect of the invention comprise that the administration is for the purpose of inducing protective immunity against *C. jejuni*. In this embodiment it is particularly preferred that the protective immunity is effective in reducing the risk of attracting infection with *C. jejuni* or is effective in treating or ameliorating infection with *C. jejuni*.

As mentioned herein, the preferred vaccines of the invention induce humoral immunity, so it is preferred that the administration is for the purpose of inducing antibodies specific for *C. jejuni* and wherein said antibodies or B-lymphocytes producing said antibodies are subsequently recovered from the animal.

But, as also mentioned the method of the 6th aspect may also be useful in antibody production, so in other embodiments the administration is for the purpose of inducing antibodies specific for *C. jejuni* and wherrein B-lymphocytes producing said antibodies are subsequently recovered from the animal and used for preparation of monoclonal antibodies.

Pharmaceutical compositions can as mentioned above comprise polypeptides, antibodies, or nucleic acids of the invention. The pharmaceutical compositions will comprise a therapeutically effective amount thereof.

The term "therapeutically effective amount" or "prophylactically effective amount" as used herein refers to an amount of a therapeutic agent to treat, ameliorate, or prevent a desired disease or condition, or to exhibit a detectable therapeutic or preventative effect. The effect can be detected by, for example, chemical markers or antigen levels. Therapeutic effects also include reduction in physical symptoms, such as decreased body temperature. The precise effective amount for a subject will depend upon the subject's size and health, the nature and extent of the condition, and the therapeutics or combination of therapeutics selected for administration. Thus, it is not useful to specify an exact effective amount in advance. Reference is however made to the ranges for dosages of immunologically effective amounts of polypeptides, cf. above.

However, the effective amount for a given situation can be determined by routine experimentation and is within the judgement of the clinician.

For purposes of the present invention, an effective dose will be from about 0.01 mg/kg to 50 mg/kg or 0.05 mg/kg to about 10 mg/kg of the DNA constructs in the individual to which it is administered.

A pharmaceutical composition can also contain a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" refers to a carrier for administration of a therapeutic agent, such as antibodies or a polypeptide, genes, and other therapeutic agents. The term refers to any pharmaceutical carrier that does not itself induce the production of antibodies harmful to the individual receiving the composition, and which may be administered without undue toxicity. Suitable carriers may be large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, and inactive virus particles. Such carriers are well known to those of ordinary skill in the art.

Pharmaceutically acceptable salts can be used therein, for example, mineral acid salts such as hydrochlorides, hydrobromides, phosphates, sulfates, and the like; and the salts of organic acids such as acetates, propionates, malonates, benzoates, and the like. A thorough discussion of pharmaceutically acceptable excipients is available in Remington's Pharmaceutical Sciences (Mack Pub. Co., N. J. 1991).

Pharmaceutically acceptable carriers in therapeutic compositions may contain liquids such as water, saline, glycerol and ethanol. Additionally, auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, may be present in such vehicles. Typically, the therapeutic compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection may also be prepared. Liposomes are included within the definition of a pharmaceutically acceptable carrier.

As is apparent from the claim, the invention also relates to related embodiments to the treatment and prophylaxis disclosed herein: the invention also includes embodiments where

- the polypeptide of the invention is for use as a pharmaceutical, in particular for use as a pharmaceutical in the treatment, prophylaxis or amelioration of infection with *C. jejuni*;

- the nucleic acid fragment of the invention or the vector of the invention is for use as a pharmaceutical, in particular for use as a pharmaceutical in the treatment, prophylaxis or amelioration of infection with *C. jejuni*;

- the transformed cell of the invention is for use as a pharmaceutical, in particular for use as a pharmaceutical in the treatment, prophylaxis or amelioration of infection with *C. jejuni*.

- the antibody, antibody fragment or antibody analogue of the invention is for use as a pharmaceutical, in particular for use as a pharmaceutical in the treatment, prophylaxis or amelioration of infection with *C. jejuni*.

EXAMPLES

Material and methods

Bacterial strains and plasmid

The bacterial strains used in this study included *E. coli* SURE (Stratagene) and *E. coli* BL21 (DE3) (Stratagene) and the plasmid was pTLJ03. Strains and plasmid originates from a NCTC 11168 *C. jejuni* ORF library (Parrish et al., 2004) available from Geneservice. The expression clone set comprises >1,600 *C. jejuni* ORF's and the expression vector pTLJ03 generates N-terminal GST-His-tagged fusion proteins.

Strains were grown in LB media or the expression media MagicMedia (Invitrogen) at 37 ºC. pTLJ03 containing strains were grown in media containing 50 µg/mL ampicillin unless otherwise specified. *C. jejuni* 11168H is a stable motile variant of the reference strain *C. jejuni* NCTC 11168; its preparation is described *infra* in the section headed "recombinant DNA techniques". *C. jejuni* strains (NCTC 11168 and 11168H) were grown at 37 ºC microaerophilic on blood plates (BaseII and 5% blood) in BHI broth or biphasic (blood plates and BHI broth) with antibiotic when needed (30 µg/mL kanamycin or/and 50 µg/mL streptomycin).

Expression library

The library was originally created in *E. coli* SURE for optimal storage. This strain does not contain the T7 polymerase and for that reason the library was transformed to the *E. coli* BL21 (DE3) expression strain. The clones were grown separately overnight in microtiter plates in 200 µl LB media containing ampicillin and subsequently the plasmids were purified as a pool and transformed to the chemocompetent *E. coli* BL21 (DE3) strain. This revealed an expression library consisting of 2304 clones (24 microtiter plates).

Immunoblot assay

Individual clones were grown 16-20 hrs in microtiter plates in MagicMedia for optimal expression. 2 µl of the culture was spotted on nitrocellulose membranes. The membranes were blocked in blocking buffer 30 min., washed in PBS Tween and then incubated in primary antibody (1:1000) at 4°C for 16-20 hrs. The membranes were then washed in PBS Tween and incubated in secondary antibody (Polyclonal goat anti-rabbit immunoglobulins/HRP, Dako) for 1 hr. The reaction was visualised by chemoluminescence (chemoluminescent substrate, Invitrogen). The primary antibody was raised in rabbit immunised with a boiled-treated (100°C for 1 h) *C. jejuni* Penner serotype 2 originally isolated from a human patient. Rabbit serum from immunisations with the Penner serotype 2 was chosen since it corresponds to the serotype used for creating the commercial library (NCTC 11168). The serum was preincubated with *E. coli* BL21 (DE3) before use to minimise background reaction. To verify that the antigens also reacted against human serum, a dot blot with 10 selected clones expressing antigens and serum isolated from a patient infected with *C. jejuni* Penner serotype 2 (Strid MA et al. 2001, "Antibody responses to Campylobacter infections determined by an enzyme-linked immunosorbent assay: 2-year follow-up study of 210 patients", Clin. Diag. Lab. Immunol. 183:2553-9.) was carried out as described above.

Clone sequencing

Plasmid DNA was isolated from 100 ml *E. coli* BL21 (DE3) cultures using MidiPrep (Qiagen). Sequencing was conducted by Macrogen Inc. and the primer 5´GCT ATC CCA CAA ATT GAT AA 3´ (SEQ ID NO: 91).

Recombinant DNA techniques

C. jejuni 11168H knock-out mutants were kindly provided by Brendan Wren from the London School of Hygiene and Tropical Medicine, University of London. Mutants were constructed via insertion of the Km cassette into unique sites present in pUC18-based recombinant plasmids containing random 1-2 kb fragments from the *C. jejuni* NCTC 11168 genome library (Garénaux A et al. 2008, "Role of the Cj1371 periplasmic protein and the Cj0355c two-component regulator in the Campylobacter jejuni NCTC 11168 response to oxidative stress caused by paraquat", Res Microbiol. **159**: 718-26 and Parkhill J et al. 2000, "The genome sequence of the food-borne pathogen Campylobacter jejuni reveals hypervariable sequences", Nature 10;403(6770):665-8). The 11168H knock out mutant provided for this study is: Cj0034c. Subsequently the gene knock-outs were transferred from the *C. jejuni* 11168H strain to the *C. jejuni* 11168 strain to restore motility and spiral morfology. Natural transformation was performed as described previously (Wang Y and Taylor DE 1990, "Natural transformation in *Campylobacter* species", J Bacteriol. **172**: 949–55) with some modifications. *C. jejuni* cultures grown overnight on BHI agar plates were collected and resuspended in 12 ml BHI broth to OD_{600} of 0.001. Bacterial suspensions in three dilutions were transferred to sterilized Petri dishes, incubated at 37°C with no shaking under micro aerobic conditions over night. 200 µg cultures with OD_{600} 0.2-0.3 were transferred to sterilized tube with 1 ml BHI and incubated at 37°C with shaking under micro aerobic conditions 2 h. Then 10 ng of genomic DNA, purified with Qiagen blood and tissue kit, of the mutants, was added each tube. After additional incubation for 3 h, bacterial cultures were serially diluted and plated on BaseII agar plates with antibiotics (50 mg/l kanamycin). The agar plates were incubated at 37°C under microaerobic conditions 3 days. The mutants were checked for curved shape and motility before tested in assays.

INT407 adhesion assay

INT407 cells (representing intestinal cell line) were grown in MEM (+glutamax) media (Invitrogen) added 25 µg/ml gentamycin and 10% heat inactivated fetal bovine serum in 5% CO_2. Cells were seeded at 2.5 x 10^5pr well in 24 well plates, incubated overnight and checked for 100% confluent monolayer. The *E. coli* clones were grown overnight in MagicMedia broth at 37°C and *C. jejuni* on blood agar plates microaerophilic at 37°C. Immediately before

assay, the OD_{600} of the bacteria was adjusted to 1 in PBS and 1 ml bacteria culture was added the INT407 cells and cells were incubated with bacteria for 2 hours at 37°C, then resuspended and diluted in PBS and spotted on agar plates with appropriate antibiotics.

Electron microscopy

To investigate, whether the *C. jejuni* mutant strain differed morphologically from the wild type strain, a transmission electron microscopy analysis was conducted. Initially, the bacterial cultures were fixated in 1% glutaraldehyde (EMS, Hatfield, USA) for 30 minutes. To improve the adhesion of the bacteria, formvar coated 400-mesh copper grids were treated for 5 minutes with alcian blue (Sigma-Aldrich). The alcian blue treated grids were placed on top of cultures of *C. jejuni* NCTC11168 and *C. jejuni* NCTC11168Δ0034 (Cj0034c), respectively, and after 5 minutes of incubation, most of the suspensions were removed from the grids with filter paper and the grids were stained for 30 seconds with phosphotungstic acid (BDH Chemicals). The grids were allowed to air-dry, and then they were viewed in a Morgagni 268D transmission electron microscope, and pictures were taken using a Mega-view III digital camera.

Motility assay

A motility assay was carried out to ensure no altered motility for the 11168Δ0034 mutant. 0.25% soft agar plates were supplied with 1 µl bacterial culture (OD_{600} adjusted to 0.1) in the middle of the plate and diameter was measured over a time period.

Serum resistance assay

Serum sensitivity assays were performed by modification of the method of Blaser et al (Blaser MJ et al. 1985, "Susceptibility of *Campylobacter* isolates to the bactericidal activity of human serum", J Infect Dis.**151**: 227–235.) *C. jejuni* strains were grown overnight in Brucella biphasic cultures at 37°C, washed in PBS, pH 7.4, and adjusted to a concentration of 10^3 CFU/ml. *C. jejuni* cells (10-µl aliquots) were incubated in 240-µl pools of whole human blood (venous blood), human serum (whole blood incubated at 25°C 30 min, centrifuged 1000x*g* 10 min at 4°C and supernatant isolated) and heat inactivated human serum (56°C for 30 min) respectively for 30, 60, 90 and 120 min. Following the incubation period, CFU was enumerated on BHI agar.

Biofilm and autoagglutination

Cell-to-cell autoagglutination was assayed in PBS as described by Misawa and Blaser (Misawa N and Blaser MJ 2000, "Detection and characterization of autoagglutination activity by *Campylobacter jejuni*", Infect. Immun. **68:** 6168-6175.)

Biofilm assay was made in 50 ml centrifuge tubes containing 25 ml inoculated Brucella broth with NCTC 11168 and the knock out mutants in Cj0034c. A glass slide was added each tube and incubated micro aerobic for 48 h. Then the slides were stained with crystal violet and biofilm formation visualised.

Predictions of protein localization

Prediction of protein localization and amount of transmembrane helixes was made by TMHMM 2.0 server (Moller S et al. 2001, "Evaluation of methods for the prediction of membrane spanning regions", Bioinformatics, **17**: 646-653).

TheSignalP 3.0 server predicts the presence and location of signal peptide cleavage sites in amino acid sequences. The method incorporates a prediction of cleavage sites and a signal peptide/non-signal peptide prediction based on a combination of several artificial neural networks and hidden Markov models. The LipoP 1.0 server produces predictions of lipoproteins and discriminates between lipoprotein signal peptides, other signal peptides and N-terminal membrane helices in Gram-negative bacteria (Juncker AS et al. 2003, "Prediction of lipoprotein signal peptides in Gram-negative bacteria", Protein Sci. **12**:1652-62). All three servers are available at http://www.cbs.dtu.dk/services/.

Protein purification

His-tag purification was made with the already GST-His-tagged constructed vector from Geneservice. An overnight pre-culture of *E. coli* BL21(DE3) containing the vectors was 50-fold diluted to inoculate 1000 ml LB medium containing appropriate antibiotics. The cultures were incubated with shaking at 37°C to an OD_{600} of 0.5, then induced with 10 mM IPTG and incubated with shaking for 16 hours at 30°C. After induction, cells were lysed on ice in 20 ml lysis buffer (50 mM NaH_2PO_4, 300 mMNaCl, 10 mM imidazole 10% glycerol) by addition of 1 mg/ml lysozyme followed by sonication. Lysates were cleared by centrifugation at 15,000x*g* for 30 min. Proteins were purified by nickel affinity chromatography using the Ni-NTA resin (Qiagen) equilibrated with lysis buffer and eluted with 250 mM imidazole. Eluted proteins were concentrated and dialyzed against 25 mM HEPES pH 7.5, 50 mMNaCl, 10% glycerol.

Mouse vaccination and challenge studies

To study ability of the proteins to protection against infection, immunization of mice were carried out. Cj0404 (SEQ ID NO: 13) was tested together with other putative vaccine candidates for its ability to protect against *C. jejuni* infection. Mice (10 in each group) were immunized with 5 µg/dose, except one with 1.6 µg/dose (Cj1371c), along with adjuvant (GNE, Intervet, NL). Four weeks later, the mice (Balb/c for colonization and CH3/HeN for invasion) were treated for three days with streptomycin (5 g/l in drinking water) and challenged orally one day later with *C. jejuni* 81116 ($6x10^5$ CFU, colonization study) and 72Dz/92 ($5x10^7$ CFU, invasion study) respectively. Balb/c mice 6-8 weeks (female) were used in groups of three. One fresh faecal dropping was collected and weighted from each animal and dilutions were made in order to determine CFU/gram faeces. Faecal samples were collected from the Balb/c mice regularly in 23 days. Necropsy was prepared one week after challenge of the CH3/HeN mice, spleen and liver were collected and CFU/organ were detected.

Results

Identification of C. jejuni antigens

With the aim of identifying immuno-reactive *C. jejuni* proteins plasmid DNA was isolated from a pooled mixture of commercial library clones established by Parrish et al (Parrish JR et al. 2004, "High-throughput cloning of Campylobacter jejuni ORfs by *in vivo* recombination in Escherichia coli", J Proteome Res. **3**: 582-6.) with *C. jejuni* NCTC11168 ORFs in the plasmid pTLJ03 (Parrish JR et al. 2004). Plasmid DNA was transformed into *E. coli* BL21 to allow expression from the T7 promoter. The resulting transformants were individually spotted on a nitrocellulose membrane and reacted with serum isolated from a rabbit infected with a *C. jejuni* human clinical isolate (serotype 2). The screening revealed several immunogenic *E. coli* clones that selectively reacted with the serum. Inserts in plasmids isolated from the transformants that repeatedly proved as most immunogenic were selected for sequencing and from a total of 2304 clones, 52 inserts were sequenced representing 25 genes encoding potential antigens. The identified *C. jejuni* genes were classified according to their predicted function.

To confirm that the identified antigens also are functional in humans we reacted 10 of the 25 clones (Cj0034, Cj0203, Cj0404 (SEQ ID NO: 13), Cj0525c, Cj0645, Cj0917c, Cj1094c, Cj1371, Cj1382c, Cj1632c) with human antiserum obtained from a patient infected with a *C.*

jejuni Penner serotype 2 and found in all cases a positive reaction. This result supports that the antigens reacting with the mouse antiserum also are antigens in humans.

Prediction of protein localization

Prediction of localization of the proteins and amount of transmembrane helixes was made: 14 out of 25 proteins are predicted to contain one or more membrane helixes, two of them further with a signal peptide. Other ten of the proteins are predicted to be located externally, where three of them harbor a signal peptide. None of the proteins were predicted to contain a lipoprotein signal peptidase.

Several antigens support host cell adhesion

Adhesion of *C. jeuni* to host cells forms the first important step in the infection process. With the aim of addressing whether the identified antigens contribute to host cell invasion a selection of 10 *E. coli* clones expressing *C. jejuni* antigens were investigated for their ability to adhere to the intestinal epithelial cell line, INT407. Interestingly, expression of three of the *C. jejuni* antigens enhanced the ability of *E. coli* BL21 to adhere to INT407 cells, Cj0034c, Cj0404 (SEQ ID NO: 13) and Cj1371. Subsequently, gene-specific *C. jejuni* mutations were constructed in the corresponding genes, and the resulting mutants were examined in the same cell adhesion assay. While the absence of Cj0404 and Cj1371 did not affect the ability of *C. jejuni* to adhere to INT407 cells, inactivation of Cj0034 dramatically reduced adhesion suggesting that Cj0034 may contribute to establishment of *C. jejuni* in host organisms.

Further characterization of the Cj0034 mutant *C. jejuni* strain revealed, that the mutation does not result in major structural changes of the bacterial cell morphology as visualized by electron microscopy. Also, the inactivation of Cj0034 did not influence serum resistance, motility, auto-agglutination and biofilm formation, when compared to wild type strain.

Antigens as vaccine candidates

Five identified antigens were selected to test as vaccine candidates in two *Campylobacter* oral challenge mouse models; one in C3H/HeN mice in which invasion in liver and spleen was measured and the other in Balb/c mice in which shedding faecal was determined. The challenge study showed a reduced invasion into spleen and liver for at least two of the proteins; Cj0525c and Cj0404 (SEQ ID NO: 13). No decreased colonization for any of the proteins was observed.

FURTHER EXAMPLES

C. jejuni Antigen expression

30 genes encoding potentially antigenic *C. jejuni* proteins were identified and checked in NCBI and presence in the clone library. Of the 30 suggested gene sequences, 19 were commercially available and purchased from Life Sciences. All 19 were used for cloning in expression plasmid (with his-tag) and transformation into the expression strain *E. coli* BL21. Two of the constructs were not transferred to *E. coli* BL21 and after several attempts we did not proceed, which left 17 succesful transformants.

We also sepately PCR–cloned from *Campylobacter jejuni* 11168. Thus Cj0404, Cj0788, Cj0892 and Cj0424 were cloned into plasmid with his–tag and transformed into *E. coli* BL21. Previous work suggested that Cj0404 was antigenic (Clin Vaccine Immunol. 2012 Feb;19(2):113-9) whereas Cj0424 was identified by us.

Preliminary tests were performed with the 4 *C. jejuni* genes transformed in BL21.

Further, several inductions were made with the 17 *C. jejuni* genes transformed in *E. coli* BL21. Media and induction protocols were tested. "Magic media " was seen to induce relevant sized proteins as can be seen from the SDS gels shown in Fig. 1. It was demonstrated that 7 *C. jejuni* clones were induced (circle markings). Overnight cultures were run on the 12% SDS gel . All experiments were performed at least twice with essentially the same results.

Protein purification and verification of immunogenicity

The *C. jejuni* transformed clones were tested for antibody recognition in a dot blot assay.

The four selected clones produced from PCR cloning were tested for expression and antibody antigenicity in a dot blot assay against human sera (dot blot 1 shown in Fig. 2).

The 7 *E. coli* clones that could be induced to produce *C. jejuni* proteins were tested for reaction with antisera from rabbits immunised with five different Campylobacter strains of five different isolates. All clones reacted to all sera.

All experiments were performed at least twice with essentially the same results.

Since all antigens were recognised by rabbit antisera, they were subsequently tested with sera from patients that were shown to have antibodies against *Campylobacter jejuni* tested in the diagnostic test that runs at the Danish State Serum Institute (Strid et al. Clin Diagn Lab Immunol. 2001 Mar;8(2):314-9).

The sera were randomly picked but all exhibited antibodies against *Campylobacter jejuni*. Patients with no antibodies to *C. jejuni* by ELISA are not expected to react in the dot blot assay (data not shown). Examples of the dot blots are seen in Fig. 2.

From the dot blots it is seen that all patients found to have antibodies against *C. jejuni* by a diagnostic ELISA react also react with colonies of *E. coli* BL21 that express *C. jejuni* antigens. In many cases the negative control being an *E. coli* BL21 without a plasmid is seen to also react with the sera This is expected since humans have encountered *E. coli* infections and are colonised in the gut.

In Conclusion

We have identified 30 *C. jejuni* genes that are be potentially antigenic and recognised by antibodies against Campylobacter. We have been able to show that 7 of these are indeed able to be recognised by antibodies raised in humans after a natural infection with *Campylobacter jejuni* (diarrea).

SEQUENCES OF PROTEINS OF THE INVENTION:

The protein sequences of the invention mentioned in the above examples are related to the sequences in the sequence listing as follows:

Aa sequence	**Designation**	**Aa sequence**	**Designation**
SEQ ID NO: 1:	Cj0251c	SEQ ID NO: 16:	Cj1357c
SEQ ID NO: 2:	Cj1464	SEQ ID NO: 17:	Cj0144
SEQ ID NO: 3:	Cj1406c	SEQ ID NO: 18:	Cj0262c
SEQ ID NO: 4:	Cj0579c	SEQ ID NO: 19:	Cj0887c
SEQ ID NO: 5:	Cj0158c	SEQ ID NO: 20:	Cj1729c
SEQ ID NO: 6:	Cj0592c	SEQ ID NO: 21:	Cj0136
SEQ ID NO: 7:	Cj0783	SEQ ID NO: 22:	Cj0886c
SEQ ID NO: 8:	Cj0371	SEQ ID NO: 23:	Cj1365c
SEQ ID NO: 9:	Cj0424	SEQ ID NO: 24:	Cj0279
SEQ ID NO: 10:	Cj0944c	SEQ ID NO: 25:	Cj1677

Aa sequence	Designation	Aa sequence	Designation
SEQ ID NO: 11:	Cj0111	SEQ ID NO: 26:	Cj0628
SEQ ID NO: 12:	Cj0596	SEQ ID NO: 27:	Cj1476c
SEQ ID NO: 13:	Cj0404	SEQ ID NO: 28:	Cj0478
SEQ ID NO: 14:	Cj0606	SEQ ID NO: 29:	Cj0007
SEQ ID NO: 15:	Cj1178c	SEQ ID NO: 30:	Cj0479

For easy reference, the protein sequences of the invention are set forth in one-letter amino acid code in the following:

SEQ ID NO: 1
MAYEDEEDLN YDDYENEDEE YPQNHHKNYN YDDDDYEYDD DNNDDDFYEM D 51

SEQ ID NO: 2
MINPIQQSYV ANTALNTNRI DKETKTNDTQ KTENDKASKI AEQIKNGTYK IDTKATAAAI 60
ADSLI 65

SEQ ID NO: 3
MKKILILLTL CAFAFGASEC DRKIDRINKE ISFSKAHNDT ARTLSLELAL KQVQNDCAKD 60
PMFYDKKLEA KKLKEQEVEK IEKELDALKE QKDYMSKAEY KAKKEALKEQ KEKIKK 116

SEQ ID NO: 4
MSFGEIIVIL VVAILVLGPD KLPEAIVQIA KILKAVKRNI DDAKSSIEKE IRINDLKEEA 60
KKYKDEFSST NENIRKKLSF EEFDDLKRDI LDKTKVDLTF DSRDDKVKNN LSGQNLNTEE 120
KPNLSKLETQ DKNGKINV 138

SEQ ID NO: 5
MQKAKILIAL SFFLLVLSAC SNDEKNISKT QNTDQEVVQI EQNDEKTELS DSNLPLPVDD 60
EAQSSNDEHE VNPSIINSLY KQKCATCHGE KGELKPKNST AIKTLSNKIF IQKIKTIKDK 120
NHSFLSDEQI QNLADFINKG K 141

SEQ ID NO: 6
MRRLSILLAI LIVINITACD SKTENYYKNL PSEAKEKAKE CKESGTLSED CINALKVGVK 60
PTNEEGKYSP NTPKKSDNQI LEALKQNDLK KEKTTKDINQ SSENNESIII PPIAETPSEI 120
YPSKTTENNQ SSIFSDDVNM TQEK 144

SEQ ID NO: 7
MMKKKLVLLG SAAVVFFAAC AMNSGVSSEQ IGLRKASLEN ENKVNLVEAN FTTLQPGEST 60
RFERSYENAP PLIPHAIEDL LPITKDNNMC LSCHDKAIAA DAGATPLPAS HYYDFRHNKT 120
TGDMISDSRF NCTQCHVPQS DAKPLVGNSF KPEFKNEQLK SRSNLIDVIN EGVK 174

SEQ ID NO: 8
MKKIKKIIQI GMIGGLAAVA GGALAGCGSN NDNADTLNQA ANAQGAFVII EETAPGQYKI 60
KDQYPSDETR VVLKDLNGTE RILSKEEMDA LIKEEAAKID NGTSNLTKDN GQISSGGLSL 120
GETLLASAAG AILGSWIGSK LFNNQNFANQ QRGAFSNQSA YQRSVNSFNK AGTTSSASSA 180
KKSGFFGGGS KATSSSSSFG S 201

SEQ ID NO: 9
MTKFLSICSL IAMLLSGCGS DFPGQPSDVA RVQQNKYPNG NLKKEIPYNK DSRIHGLKRA 60
FYDNGQLRAE ENYKNGKKDG ISREYSRNGQ LLEEVHFKDN RGYGDFASYY ENGNMRAKGK 120
LLGYNEDGMP EFEGNYKEYY ENGTLMCDYN FDNKGKFDGV QKRYDENGAL EDEENYKNGL 180
KNGVFREYKK GEIVREEEYK NGILVAKPKN 210

SEQ ID NO: 10

MKKIFLSVFL VLSLNAQNLE IDKIRTDLYS KSGANVLKKV EISLEFDGNN LKENENKLID 60
AVNTVISGFF YEDIFTEIGK NNFKKTLEKF LDKKYKIKLD DIYIISLSGV EKFDLEEFKR 120
FLESTEAKEK GMGSEVKKAL ENLEVPKTQV PSVEKIPTPS VPNLEVKQVE QLFKDPDEEN 180
KNDNGEINID NLNTPKMTPD IEEKIKRDLI ANPPQIFKEN NASKPYHLPQ TGYDIKLDEN 240
STQN 244

SEQ ID NO: 11
MKNYGLSNLN SFLLALAIYI SIVILVFFRL VSEVEPAIQY TDIKDSFVDI ELAEPSKQVI 60
TQSNTPKEIQ KPTEQIDIEK LFAQTTNKTV KTEDIDQKAS NFNELFGNIK EIQEEKTTKI 120
QSSAKSGISS APKPQASELV KQLNDSLLQE ESSTQGESTK AQKIGIYDEF LGKVVRIITQ 180
RWTQYYPNSE KISVKVKIFI DENGKFGYTS VEKSGNPLYD AKVAEFLESQ KGKFITYPPQ 240
NKNISITMNL RDEVKVKND 259

SEQ ID NO: 12
MKKFSLVAAT LIAGVVLNVN AATVATVNGK SISDTEVSEF FAPMLRGQDF KTLPDNQKKA 60
LIQQYIMQDL ILQDAKKQNL EKDPLYTKEL DRAKDAILVN VYQEKILNTI KIDAAKVKAF 120
YDQNKDKYVK PARVQAKHIL VATEKEAKDI INELKGLKGK ELDAKFSELA KEKSIDPGSK 180
NQGGELGWFD QSTMVKPFTD AAFALKNGTI TTTPVKTNFG YHVILKENSQ AKGQIKFDEV 240
KQGIENGLKF EEFKKVINQK GQDLLNSAKV EYK 273

SEQ ID NO: 13
MENQKNEFDD IILEKSNKSE KVKKILLRVI ALVILFLAIM IVMKLINGSG DENTQNQSVL 60
PSEPIATQDN NNDTSFESMP ITDNTSAEDQ FEALRKQFQD EQNTTQNTTT SSSNNNDTTN 120
FAMPDQEVPA EPTATTSANT TPQASTPKQE VTQTAKSKEE AKKQTAVKKE KESAKQTPKK 180
EQNANDLFKN VDAKPVHPSG LASGIYVQIF SVSNLDQKSK ELASVKQKGY DYKLYKTTVG 240
SKEITKVLIG PFEKADIAAE LAKIRKDIAK DAFSFTLK 278

SEQ ID NO: 14
MKKKIVLIIL IAILGSVGAY FIFFNNDEKI SYLTQKIQKK DISQTIEAVG KVYAKDQVDV 60
GAQVSGQIIK LYVDVGTHVK QGDLIAQIDK DKQQNDLDIT KAQLESAKAN LESKKVALEI 120
ANKQYQREQK LYAAKASSLE NLETQKNNYY TLKANVAELN AQVVQLEITL KNAQKDLGYT 180
TITAPMDGVV INVAVDEGQT VNANQNTPTI VRIANLDEME VRMEIAEADV SKIKVGTELD 240
FSLLNDPQKT YHAKIASIDP ADTEVSDSST SSSSSSSSSS SSSSSNAIYY YAKFYVANKD 300
DFLRIGMSIQ NEIVVASAKA VLAVPTYAIK SDPKGYYVEI LENQKAVKKY VKLGIKDSIN 360
TQILEGVNED EELIVSSSAD GLAPKMKLRF 390

SEQ ID NO: 15
MKILLLNENP VVSRLVSLSA KKMSYDFEEL NAYSENLGNY DVIVVDSDTP APLKILKEKC 60
DRLIFLAPRN QNVEDIDAQI LQKPFLPTDF LNLLNNKDAN KHTSIDLPML SNDENPYADI 120
SLDLDNLNLD DLPDENSLDI NSEGMEDLSF DDDAQDDNAN KTLETQNLEH ETIKEQTQED 180
TQIDLDLTLE DGESEKEDLS QEHTALDTEP SLDELDDKND EDLEIKEDDK NEEIEKQELL 240
DDSKTNTLEM QEELSESQDD NSNKTLETQN LEHDNLEQET IKEQTQEDTQ IDLDLTLEDG 300
ESEKEDLSQE HTALDTEPSL DELDDKNDED LEDNKELQAN ISDFDDLPEV EEQEKEMDFD 360
DLPEDAEFLG QAKYNEESEE NLEEFAPVVE EDIQDEIDDF ASNLSTQDQI KEELAQLDEL 420
DYGIDSDNSS KVLEDFKDEP ILDDKELGTN EEEVVVPNLN ISDFDTLKES DIQEALGEEI 480
LEKNEEPIVS DVTKDDNSEE IVNELSQSIA GAITSSIKDD TLKAALKGMN MNININISFK 540
ED 542

SEQ ID NO: 16
MKKNILRLGI VVLVLLIAGV LWLNNDINQK KEDEANKNAI AANADFSLLS DDDPNFEKWG 60
KVFPEQLKMY LTVEKEEPKA TEFGGNLAYS KLIRFPQLTI LWAGYPFSLD FNEERGHFWV 120
QVDQMKTARN NKDFLNAHGL AAFKGQPAAC MNCHSGWTPW LIKNVAKGDF TAFNSTNYWT 180
MIKNIPAVDG IVENSPEHAG PHGGKRMGVT CADCHNPNDM SLRLTRPAAI NALVSRGYEK 240
DPVQGVKATR EEMRTLVCSQ CHVEYYFKPT GEKVKVMGET IVDDSSKKWW NGTQKNYDEY 300
EFWRDGNKVK EIETDGIVLT FPWSEWKKGQ PFRIEMLDDY YDKVRGVFGA DFTHKLTGAQ 360
IIKIQHPESE LYSGGVHAAN GVSCVDCHMP YVREGAKKVT QHNITSPLRD INSACKSCHK 420
QSEDYLKAQV LDIQNSVAHD QRTAEYAIVS LIMDTKKLRD ELGNMEKFQS DGKADAKKIS 480
EELKEVLELH RKAQMRADFV NAENSTGFHN PREASRMLLQ AVDMARMGQT KLVEIAAANG 540
IKDFKTSNLG FEDIQKFNPG ELYYKVDVNN HKAGERYYAD EKDVNGNPPK ELLEHDKELA 600

PYNYQVIDKK 610

SEQ ID NO: 17
MKSVKLKVSL IANLIAVVCL IILGVVTFIF VKQAIFHEVV NAEINYVKTA KNSIESFKAR 60
NSLALESLAK SILKHPIEQL DSQDALMHYV GKDLKNFRDA GRFLAVYIAQ PNGELVVSDP 120
DSDAKNLDFG TYGKADNYDA RTREYYIEAV KTNKLYITPS YIDVTTNLPC FTYSIPLYKD 180
GKFIGVLAVD ILAADLQAEF ENLPGRTFVF DEENKVFVST DKALLQKGYD ISAIANLAKT 240
KEDLEPFEYT RPKDGNERFA VCTKVSGIYT ACVGEPIEQI EAPVYKIAFI QTAIVIFTSI 300
ISVILLYFIV SKYLSPLAAI QTGLTSFFDF INYKTKNVST IEVKSNDEFG QISNAINENI 360
LATKRGLEQD NQAVKESVQT VSVVEGGNLT ARITANPRNP QLIELKNVLN KLLDVLQARV 420
GSDMNAIHKI FEEYKSLDFR NKLENASGSV ELTTNALGDE IVKMLKQSSD FANALANESG 480
KLQTAVQSLT TSSNSQAQSL EETAAALEEI TSSMQNVSVK TSDVITQSEE IKNVTGIIGD 540
IADQINLLAL NAAIEAARAG EHGRGFAVVA DEVRKLAERT QKSLSEIEAN TNLLVQSIND 600
MAESIKEQTA GITQINDSVA QIDQTTKDNV EIANESAIIS STVSDIANNI LEDVKKKRF 659

SEQ ID NO: 18
MQSINSGKSV GISAKLTLWV GILVVLILAI TSAISYFDSR NNTYELLKDT QLKTMQDVDA 60
FFKSYAMSKR NGIQILANEL TNRPDMSDEE LINLIKVIKK VNDYDLVYVG FDNTGKNYQS 120
DDQILDLSKG YDTKNRPWYK AAKEAKKLIV TEPYKSAASG EVGLTYAAPF YDRNGNFRGV 180
VGGDYDLANF STNVLTVGKS DNTFTEVLDS EGTILFNDEV AKILTKTELS INIANAIKAN 240
PALIDPRNQD TLFTAKDHQG VDYAIMCNSA FNPLFRICTI TENKVYTEAV NSILMKQVIV 300
GIIAIIIALI LIRFLISRSL SPLAAIQTGL TSFFDFINYK TKNVSTIEVK SNDEFGQISN 360
AINENILATK RGLEQDNQAV KESVQTVSVV EGGNLTARIT ANPRNPQLIE LKNVLNKLLD 420
VLQARVGSDM NAIHKIFEEY KSLDFRNKLE NASGSVELTT NALGDEIVKM LKQSSDFANA 480
LANESGKLQT AVQSLTTSSN SQAQSLEETA AALEEITSSM QNVSVKTSDV ITQSEEIKNV 540
TGIIGDIADQ INLLALNAAI EAARAGEHGR GFAVVADEVR KLAERTQKSL SEIEANTNLL 600
VQSINDMAES IKEQTAGITQ INDSVAQIDQ TTKDNVEIAN ESAIISSTVS DIANNILEDV 660
KKKRF 665

SEQ ID NO: 19
MRITNKLNFT NSVNNSMGGQ SALYQISQQL ASGLKIQNSY EDASTYIDNT RLEYEIKTLE 60
QVKESTSRAQ EMTQNSMKAL QDMVKLLEDF KVKVTQAASD SNSQTSREAI AKELERIKES 120
IVQLANTSVN GQYLFAGSQV ANKPFDSNGN YYGDKNNINV VTGAGTESPY NIPGWDLFFK 180
ADGDYKKQIS TNVSFTDNRW DLNKDPDKTK YLTGDSKWQQ LIGQSYVKDN SLDADKDFEY 240
DDSKLDFPPT TLYVQGTRPD GTSFKSAVLV KPEDTLEDVM ENIGALYGNT PNNKVVEVSM 300
NDSGQIQITD LKQGNNKLDF HAVAFTPQAD DKTELNNIIQ AAQDEGITME DVTNRVMTAA 360
LGNPNNGDIT NLNNPVTIQI NGQNFEIDLK QTDFIKSKMT DTDGNAANGA DYDNVYFEKN 420
GNTVYGNVSQ VIKGSNAYAT DSTKLSEVMA GDSLNGTTLN LKVNSKGGNS YDVTINLQTS 480
TVSYPDPNNP GQTISFPIMH TNPATGNSGV VTGSNDITYG QINDIIGMFA ADKIPTTTIQ 540
ANNGQINNAD YTQIQQLMKD SQATVDVSMD YKGRISVTDK LSSGTNIEIS LSDSQSGQFP 600
APPFTTTSTV QNGPNFSFSA NNSLTIDEPN VDIIKDLDSM IDAVLKGNMR ADSESENPRN 660
TGMQGALERL DHLADHVSKL NTTMGAYHNT IEGVNTRTSF LSVNVQSIKS NVIDVDYGEA 720
MMNLMQVQLA YQASLKASTT ISQLSLLNYM 750

SEQ ID NO: 20
MMRSLWSGVS GLQAHQVAMD VEGNNISNVN TTGFKYSRAD FGTMFSQTVK IATAPTDGRG 60
GSNPLQIGLG VSVSSTTRIH SQGSVQTTDK NTDVAINGDG FFMVSDDGGL TNYLTRSGDF 120
KLDAYGNFVN NAGFVVQGWN INWDDQTIDS SRTPQNIFID PGMHIPAAKS TEVAIKANLN 180
SGLNIGTSSR NLYALDSVHG WNTKTQRAED ENDTGTTQFY TTSKNSVEVT EKGVDAGSLF 240
NAKGQGLNLR DGQGIWVSYA DATYSTNKVG VNAFDPNLQQ NQTAAFWGTA NQKVNLDITL 300
NGVRIQNADI QSIDDAIAYI NTFTAPTDTR DGTGVKAVKN KDGSGIDFVN DNADGTTDNM 360
KNINLVVANT NTAGELWNAV WNNNNQTFTF NNNGNGQAGT PTINKNGSSL WTATNITFTP 420
QPPQAATNVQ LTGGLNAQII TAHKYIYSSN PVDIGPMYNP DGGPAFQPGA NATTRPTEPG 480
SAAYWDAVNG GLLNTNVRTF RTTEDLRELL QRDARYGVDY DGSGTFAAAD INQNIKVVVT 540
ADGHFAISNA NEQSTVPPNA INGVGNATTT DPKNMSFNIT AYSNKQGTVS TNDAFTAIFK 600
AFDGPLVIGN QIKESEQLKL SAFSAGLEIY DSLGSKHTLE VQFVKQSTTQ DGGNEWQMII 660
RVPEPAEINT TGEGPNNIIV GTARFNNDGS LASYTPRTIN FSPNNGAAPN QQIKLSFGTS 720
GSNDGLVSSN SASTLTGQAT DGYTSGNLKP DAIRVDDKGN ILGEFTNGKT FAVAKIAMAS 780
VANNSGLEEI GGNLFKVTAN SGNIVVGEAG TGGRGEMKTS ALEMSNVDLS RSLTELIIIQ 840

RGYQANSKTI STSDQMLQTL IQLKQ 865

SEQ ID NO: 21
MAKIRIHEIA KELGYDSKEI IEKANELGLG IKTASNAVEP EIAAAIYEYI QTREIPEAFK 60
KNIKTPTAKK PKKENIKEQE KLNESEKKEP KKEEKLKQEV KKEELKIEKE NAKEEEKQEI 120
IDAHKPQSLA SATLAKRRGL VIVKKKKDEE EIQVKKEEVK NSNDISINNE ERLSLKTMFS 180
NADESLKKKK KEKKSFVASK KESTEKMNFL DEHDFGDISL DDEDEVVLPD FSVKEQEKPQ 240
NINKKQPNFI RQAVGNSAGF GFEGGIQRRS RKKPSKKIEK KEVEEVGSVA ISKEIRVYEF 300
ADKIGKSTSE VISKLFMLGM MTTKNDFLDE DAIEILAAEF GIEINIINEA DEFDYVKDYE 360
EETDEKDLVT RAPVITIMGH VDHGKTSLLD YIRKSRVASG EAGGITQHVG AYMVEKNGRK 420
ITFIDTPGHE AFTAMRARGA SITDIVIIVV AADDGVKPQT KEAINHAKAA GVPIIIAINK 480
MDKEAANPDM VKTQLAEMEI MPVEWGGSYE FVGVSAKTGM GIEDLLEIVL LQADILELKA 540
NPKSFAKASI IESSVQKGRG AVATVIVQNG TLTVGSTVVA GEAYGKVRAM SDDQGKALKE 600
IKPGECGVIV GLSEVADAGE ILIAVKTDKE AREYANKRHE YNRQKELSKS TKVSIDELGA 660
KIKEGNLKAL PVILKADVQG SLEALKASLE KLRNDEIKVN IIHSGVGGIT QSDIELASAS 720
ENSIVLGFNI RPTGEVKERA KDKGVEIKTY NVIYNLLDDV KALLGGMMSP IISEEQLGQA 780
EIRQVINVPK IGQIAGCMVT EGVINRGAKI RLIRDGVVVY EGNVSSLKRF KDDAKEVAKG 840
YECGVGIEGC DDMRVGDYIE SYKEVEEQAS L 871

SEQ ID NO: 22
MLAPGMGEWV YKANLFLFGE FAYYYPFFLF ILNYVYYKRN YKLANFTRRE LFGIGFAFFS 60
SLLLFAVFYP NSGYILELAY AIFSTILGHT GSGIFALLLL LFSLVLLFPK FAKEILKIEL 120
DFTYLLKVEQ AFKSLLMRVF GGENEKEDVG KSEPIVPKLN ILQDSIYGNL QINKKGETNN 180
LEQIIKDSNI NASKNSITTA KENFEKLKNQ ILDETIEIDK QSLKESRSFV HEHSQQVRNF 240
AQKASKMSIS LDEDFNFISE EEVDMIPERF LKPKKLEDIK QIDTNKNLDE PSYKRKNIEI 300
PVSNQEVKPK IFTKELELRE NLIKKEKLEQ EYKAYQNEIL ENKVKQEIKK LEEYDAINSS 360
DIIEGNKYSF NSPKTIKTET EESDKINENK NLDKADNIFE FAPIVEELNH PYIEPTPIKN 420
INEIVIEEKN TLDFIQNTET KIDNEKTNDQ EIKLQKAVLA KEIAINQALL REIEQGEIEK 480
PKDFTLPPLD FLANPKEHKQ EINESEIDKK IYNLLEKLRR FKIGGDVIST YVGPVVTTFE 540
FRPSADVKVS RILNLQDDLT MALMAKSIRI QAPIPGKDVV GIEVPNDEIQ TIYLREILQS 600
EVFKNAKSPL TIALGKDIVG NAFVTDLKKL PHLLIAGTTG SGKSVGINSM LLSLLYRNSP 660
KTLRLMMIDP KMLEFSIYND IPHLLTPVIT DPKKAVNALS NMVAEMERRY RLMADAKTKN 720
IENYNEKMKE LGGEKLPFIV VIIDELADLM MTAGKDVEFY IGRLAQMARA SGIHLIVATQ 780
RPSVDVVTGL IKANLPSRIS YKVGQKIDSK VILDAMGAES LLGRGDCLFT PPGTSSIVRL 840
HAPFASEFEI EKIVDFLKDQ QSVEYDESFL KDQQSVGVTT NESFDGEADE LYEEAKRVIL 900
EDGKTSISYL QRRLKIGYNR SANIIEQLTQ NGILSEPDAK GQREIL 946

SEQ ID NO: 23
MKKFFCLTLV CKLFALSEFE LHHIDKVHKL GYSGDTIIIG VADDAFNQDH ISLKDKILKS 60
TYPTDTAGKQ LIPDLKKSTH GSHVAGIAVG AKIGDSKPYG VAYGAKFYGA GVFPNGSYTQ 120
IPDIYNFFKD VSIINNSWGI NFYPYFNLKA SNSGLVDCTQ TNQGTSYNIC NTPLEYVMKA 180
DKVANDMMRL SKDKGVLNVF AAGNEGILSP ALHAILPSYD ESLRAWLAVG ALDANEITLE 240
SDGTLIIKSQ GLADFSNGFK GATNFSLVAA GVNINNVDSS TNDKFTKKSG TSMAAPMVSG 300
TAALVKQNFP FLDGKQIADI LLSTANKNYK APKFTVKQVT DGTNQPKFLI VYISQDPPGI 360
EDEIKRDLKQ LYNGIQVQVN GQWIDYSDYI WDNRDSAQSQ KLNTSTISSI NGVVRVEKEE 420
LFGQGILDAQ KALKGLSILD ANRLSDQDVL KYEQEPNTAY YTINTAGYDA EFSNDISQRK 480
WDESTHLSSA INKPTHLANL NIGLSKEGEG ILIISGQNTY EGATLIKQGE LKLKGKVKNN 540
AYVEQKAILS GNGIVGQNLN NKGIVRPGNE DLNDLTVQGT YTQEGVDSKL QLDFGNYKNS 600
KLIAKTYDIK SGNLEYIPLP KYYILNKPVK INLGDLEKSL SSFNHVLIQN TYALNFDFVL 660
SDDLVSINKT LIKPNLKPNA YEIPNTSLGN ALRQLRSRAD LSQTYQEFFA SLDNGIDVKT 720
KLNRIEGSGY LSTFSNHNQS NLMQNNMLFT LHPLNINNFA QNNNILLAST YLPRIFSNEE 780
YFWHLTPSYK YYKDKDFSGQ KTGANISLGE NFSSGFLAYA LSLSSAKFNF NNGSDLKSYN 840
MDLLLNYNHD LDFIKILSGL GIGVGFNTLN RFVVEQPIEG KYKTLQTSAQ LGVTKDIILG 900
QDFIFNPLMY FTHSFFYQED FKENKSPFAK NYESLKHHSI NANLGFNLAK NIEQDDYQAS 960
FSTFVIFEKR IYGRTLENKA SFVDFPIAFI QKYKLKDNIL SQGFNSEFLY KNNVFWQFML 1020
MNRFSHNAYE LHLMSSVGKR F 1041

SEQ ID NO: 24
MPKRTDIKSI LLIGSGPIVI GQACEFDYSG TQAAKTLKEL GYRVVLINSN PATIMTDPEF 60

ADATYIEPIT KESILSIIKK EKIDAILPTM GGQVALNVAM EVYESGLLGD VKFLGANPEA 120
IKKGEDRQVF KECMKKIGMD LPKSMYAYNY DEALKAVDEI DFPLMIRASY TLGGAGSGVV 180
YNMDEFKELT NTALALSPIH EILIEESLLG WKEYEMEVIR DRADNCIIVC SIENIDPMGV 240
HTGDSITIAP ALTLTDKEYQ VMRNASFAIL REIGVDTGGS NVQFAINPKN GRMIVIEMNP 300
RVSRSSALAS KATGYPIAKV ATLLAVGFSL DEIKNDITGT PASFEPVIDY IVTKIPRFTF 360
EKFPGANTTL GTAMKSVGEV MAIGRTFKES IQKALCSLER SLSGFDRVKF EDRNDLVFKI 420
RNANEKRLLY VAQAFREGFS VEELYELCKI DPWFLTQIKE IVDFEEQIDM DILNNKALLR 480
KAKTMGFSDK MIALLVNLKD NLELSQNDIY YVRMKQKIIA EFSEVDTCAG EFEALTPYLY 540
SSINVSELTQ SKNDAKDKKE KKVMIIGGGP NRIGQGIEFD YACVHASFAL KDMGIKTIMY 600
NCNPETVSTD YDTSDILYFE PIDFEHLRAV IEREKPDGVI VHFGGQTPLK FAKRLSAFGA 660
KIIGTSARVI DMAEDRKKFA EFITKLGINQ PKNSTATSVE EAVLKASDIG YPVLVRPSYV 720
LGGRAMRVVN DEAELRLYMQ EAVDVSDKSP VLIDQFLDNA TEIDVDAICD GKDVYVAGIM 780
EHIEEAGIHS GDSACSLPPC NIDEKMQEFI AQKTADIALN LGVVGLLNIQ FALHNNELYM 840
IEVNPRASRT IPFVSKATGI PLAKVATRVM WQGNLKEALK FYDTFKVVNF DTKILRPKTP 900
KYMSVKEAVF PFAKLSGSDL ELGPEMRSTG EVMGISKDFA NSYAKSQIAS FNHLPEQGVV 960
FISLKDKDKK YTKKIAAEYV KLGFKLMATG GTCKEILESG FECELVHKIS EGRPNVEDKL 1020
KNGEIHLVIN TSDSHSFKGD TKKIRENIIR FKIPYFTNLR SALAGAKSIK AIQSKSCLDV 1080
KSLQEWLKS 1089

SEQ ID NO: 25
MKNITLTKIP IGEGKEPCLN SKKIVLSLAT ISFLASCANA KLNSEIKTYD EVNKNVKTRS 60
ASVYSPQAKI NTTINSLHNQ QVTITGNGTS NSLTIGSSGT LGSIGNTGKI IYAHANGSNT 120
LTLANLTNNR TINGKIGIEN NGNFTGTIAV NTFENTGQIN GQIYMGIWGN NSGTLNIDKF 180
DNSGTIIDNN KGVFEGKNTN IQTFNNSGFI SANKGVDIGN IGTIKNFNNN GTIQGSEVGV 240
AINTKIDTFT NNGFINSPGS GQWNNGIWIS SNATIEKLVN NGTIKGGHSA IMVTSQHIKT 300
VENTGIIHAE GEWGSSILLE YGGFIEHIIN TGTISNNNVG IGSAYGVFGT LTIKDGGMVY 360
GKYSAIGVGR SQTLGDLYID GRSNNGTVSG IYSEEHGILL ENNSRTQKIE LKNGGIIKGN 420
IDGIRLINSA SLSGEMILSG EGSRVEGGRG VGILNRSGKI EGSIKVEDGA TVTATSNRAI 480
ANSGSGSITG GITVSGKNTK LEGNIINTGN ASIGSDIKIE GGAKVEGGLV NQGNGSISGS 540
VQVSGGSSID SITNEGNGAI SGSITVYKDS KLDSITNTST SSTGISGSIT NNSDNKLEIS 600
NSGNIGGKIE STGSADMVIS NSNGGTISGG ISSSGSGSTS ISNSQGSTIN NGITVSGSAQ 660
VEISNQGSVG KDENGNTVTN NGSGSVGIKD WLVSTDKNTG KLNTVVIGGS RAFNVKVENI 720
TVDQSNVDLE ELNDINNIIS GVNQNNIGNI GTNGSGEISL SFDPITGKLT TDFNLNASIS 780
GATFRSLIST TSRRSTFIDN VMGNSMQSFA LASSSKSQSI AMSEKGNLYA DASDYIKSDL 840
NNGSYGSNKE HSLFILPYTS SQNVELSLNE ESKGHTKGTI IGYSTLKDSG IYGVYAGYED 900
TKMGSTYFDI NNRTYYAGLK YFNTLFTTEK GQEVYIKAQG KAALIKNDLT EKIGNNEAKA 960
EPNSYAYGVN TALGMNFISN KDIFSPEIGL AYEGGYTEAF SMKDTIGQAT VKGGERTYAN 1020
YLNLFSTKTS LTWFRDWLPN LKTSVELGAK FNINPKVEAE ARFGNIKVSD EFDLPRVQKF 1080
VSTSFIVPVN EAFYFSLNYN GMFDKDGNTH TGFAQFNYLW 1120

SEQ ID NO: 26
MNKTALTKTY TKDIQNSCLN SKKIVLSLAT ISFLASCTHA TLTPEIKTYE ETNRHAKARS 60
GLQSRNSNNE TINNLQTLTK TISDTGNTLV IESSGTITIS NDGQQAVNFQ PNSSTSTFLN 120
KGTLIGGNNT ASVQLGAANG NNGVSIETFN NQGIIGNGSS KFGVTVFGGG SKDNPKSIIN 180
NFSNSGTIHS NTGESIYFGN AKISSFVNSG TIKSKQGAGV NISQGTSIEN FNNTGTGIIE 240
GKRMGVNVRS TINTFVNDGL IAATNDGIQI NANVKTLINK GTIKGDAISI RSLGGTIETL 300
TNEGIMYGKS AGIYMNRSLV KTLTNSGTIN QNNSATWSAG IKLENGSIIE NIINTGSIRS 360
NAFGISVTGG KFGTLTIKDG GMVYGKYSAI GVGRSQTLGD LYIDGRSNNG TVSGIYSEEH 420
GILLENNSRT QKIELKNGGI IKGNIDGIRL INSASLSGEM ILSGEGSRVE GGRGVGILNR 480
SGKIEGSIKV EDGATVTATS NRAIANSGSG SITGGITVSG KNTKLEGNII NTGNASIGSD 540
IKIEGGAKVE GGLVNQGNGS ISGSVQVSGG SSIDSITNEG NGAISGSITV YKDSKLDSIT 600
NTSTSSTGIS GSITNNSDNK LEISNSGNIG GKIESTGSAD MVISNSNGGT ISGGISSSGS 660
GSTSISNSQG STINNGITVS GSAQVEISNQ GSVGKDENGN TVTNNGSGSV GIKDWLVSTD 720
KNTGKLNTVV IGGSRAFNVK VENITVDQSN VDLEELNDIN NIISGVNQNN IGNIGTNGSG 780
EISLSFDPIT GKLTTDFNLN ASISGATFRS LISTTSRRST FIDNVMGNSM QSFALASSSK 840
SQSIAMSEKG NLYADASDYI KSDLNNGSYG SNKEHSLFIL PYTSSQNVEL SLNEESKGHT 900
KGTIIGYSTL KDSGIYGVYA GYEDTKMGST YFDINNRTYY AGLKYFNTLF TTEKGQEVYI 960
KAQGKAALIK NDLTEKIGNN EAKAEPNSYA YGVNTALGMN FISNKDIFSP EIGLAYEGGY 1020
TEAFSMKDTI GQATVKGGER TYANYLNLFS TKTSLTWFRD WLPNLKTSVE LGAKFNINPK 1080

VEAEARFGNI KVSDEFDLPR VQKFVSTSFI VPVNEAFYFS LNYNGMFDKD GNTHTGFAQF 1140
NYLW 1144

SEQ ID NO: 27
MGKIMKTMDG NEAAAYAAYA FTEVAGIYPI TPSSPMADYT DMWAAAGKKN LFGVPVKIVE 60
MQSEAGAAGS VHGSLQAGAL TTTYTASQGL LLKIPNMYKI AGQLLPCVIH VAARSLAAQA 120
LSIFGDHQDI YAARQIGFAM LCSHSVQETM DLAGVAHLAA IKGRVPFLHF FDGFRTSHEI 180
QKVEVMDYAH FDRLLDREAL LEFRNNALNP ENPKTRGTAQ NDDIYFQTRE VSNRFYDALP 240
DVVNEYMQEI SKITGREYKP FTYYGHKEPE CVIVAMGSVT QALEEVVDYL NAKGEKVGIL 300
KVYLYRPFSL KYFFDVMPKS VKKIAVLDRT KEPGSLGEPL YLDVKSAFYG RENAPVIVGG 360
RYGLSSKDVD PAQMIAVFEN LKLDNPKDGF TVGIIDDVTH TSLSTGEKIS LGDESTIECL 420
FYGLGADGTV GANKNSIKII GDKTDFYAQA YFAYDSKKSG GYTRSHLRFS KKPIRSTYLV 480
STPHFIACSV AAYLEIYDVL AGIRKGGTFL LNSIWNAEET IRQLPDAVKK TLAEKEVNFY 540
IINATKLARD IGLGNRTNTI MQSAFFKLAK IIPYEDAQKY MKELAYKSYS KKGDAIVEMN 600
YKAIDVGADG LVKVEVDPNW KNLELKEKEQ TNAYKGTEFV EKIVKPMNAA KGDDLPVSAF 660
LGYEDGSFEH GTTEYEKRGV GVMVPRWIEA NCIQCNQCAS VCPHAVIRPF LINDEEMANA 720
PRGVKDHALE AKGTKGEKLS FKIQVSPLDC TGCELCVHEC PTKEKSLVMV PLQEEMDFGE 780
QENADYLFKE ITYKDDILNK ETTKGAQFAQ PLFEFHGACP GCGETPYITL ITRLFGERMI 840
VANATGCSSI YGGSAPSTPY RKSVKNGHGP AWGNSLFEDN AEFGLGMKIA TENTRHRIEH 900
IMNESMQEVP NALSALFKDW IANKDNGAMS VEIKDKMIPI LEQNKNIKAV QDILELKQYL 960
SKKSHWIFGG DGWAYDIGYG GLDHVLASGE NVNILVLDTE VYSNTGGQSS KSSRTGAVAQ 1020
FAAAGKPIQK KDLGQIAMTY GYIFVAQVNS TANYTHLIKA ITAAEAYDGP SLVICYSPCI 1080
AHGIKGGLGY SGEQGELATK CGYWPLYTFD PRLEEQGKNP LTLTGKEPDW DLYEQFLMNE 1140
VRYNSLKKAN PEHAAELFER NKKDAQRRYR QLKRIAMADY SNEVES 1186

SEQ ID NO: 28
MCDMLDNKLG NRLRVDFSNI SKQIEIPNLL QLQKKSFDYF LNLDNGESGI EKVFKSIFPI 60
HDPQNRLSLE YVSSEIGKPK YTIRECMERG LTYSVNLKMK IRLTLHEKDE KTGEKVGVKD 120
IKEQEIYIRE IPLMTDRVSF IINGVERVVV NQLHRSPGVI FKEEESSTVA NKLVYTAQII 180
PDRGSWLYFE YDAKDVLYVR INKRRKVPVT MLFRALGYKK QDIIKLFYPI QTIHVKKDKF 240
LTEFNPNDFM DRIEYDIKDE KGKIVHQAGK RLTKKKAEQL IKDGLKWIEY PVEILLNRYL 300
ANPIIDKESG EVLFDSLTLL DESKLAKIKE QKSFDIANDL ANGVDAAIIN SFAQDGETLK 360
LLKQSENIDD ENDLAAIRIY KVMRPGEPVV KDAAKAFVND LFFNPERYDL TKVGRMKMNH 420
KLGLEVPEYV TVLTNEDIIK TAKYLIKVKN GKGHIDDRDH LGNRRIRSIG ELLANELHLG 480
LAKMQKAIRD KFTSLNADLD KVMPYDLINP KMITTTIIEF FTGGQLSQFM DQTNPLSEVT 540
HKRRLSALGE GGLVKERAGF EVRDVHATHY GRICPVETPE GQNIGLINTL STYAKVNELG 600
FVEAPYRKVV NGKVTNEVVY LTATQEEGLF IAPASTKVDA KGNIVEEFVE ARQDGETILA 660
RREEVQLIDL CSGMVVGVAA SLIPFLEHDD ANRALMGSNM QRQAVPLLTA SAPIVGTGME 720
QIIARDAWEA VKAKRGGVVE KVDNKSIFIL GEDDKGPFID HYTMEKNLRT NQNTNYIQHP 780
IVKKGDIVKA GQIIADGPSM DQGELAIGKN ALIAFMPWNG YNYEDAIVVS ERIIREDTFT 840
SVHIYEKEIE ARELKDGIEE ITKDIPNVKE EDVAHLDESG IAKIGTHIKP GMILVGKVSP 900
KGEVKPTPEE RLLRAIFGEK AGHVVNKSLY ATASLEGVVV DVKIFTKKGY EKDDRAIKSY 960
DKEKMALEKE HHDRLLMMDR EEMLRVCALL SKASLNSDQK IGDKNYKKGQ TADISELEKI 1020
NRFTLTTLIK AYSKEIQKEY DDLKNHFQNE KKKLKAEHDE KLEILEKDDI LPSGVIKLVK 1080
VYIATKRKLK VGDKMAGRHG NKGIVSTIVP EVDMPYLPNG KSVDIALNPL GVPSRMNIGQ 1140
ILESHLGLVG LRLGDQIQEI FDRKQKDFLK ELRAKILEIC SIPRLANEKE FIKSLSDEEL 1200
LNYARDWSKG VKFSTPVFEG VNIEEFSKLF KMAKIDMDGK TELYDGRTGE KIAERVHVGC 1260
MYMLKLHHLV DEKVHARSTG PYSLVTQQPV GGKALFGGQR FGEMEVWALE AYGAAHTLRE 1320
MLTIKSDDVE GRFSAYKALT KGENVPATGI PETFFVLTNE LKSLALDVEI FDKDEDNE 1378

SEQ ID NO: 29
MDLENILENN QSIGLYHPKN EHDACGIAAV ANIRGIASYK VICDALEILM NLEHRGGTGA 60
EENSGDGAGI LIQIPHDFFK TQELGFELPK KGDYAVAQMF LSPNTDAKEE AKEIFLQGLK 120
DKKLEFLGFR EVPFNPSDIG ASALKAMPYF LQAFVKKPSK ISAGLEFERV LYSTRRLIEK 180
RAINVPKFYF SSFSSRTIVY KGMLLSTQLS DFYLDFKDVN MKSAIALVHS RFSTNTFPSW 240
ERAHPNRYMV HNGEINTIRG NVDSIRAREG LMQSEYFENL DEIFPIIAKL SSDSAMFDNT 300
LEFLALNGRT LEEAFMMMVP EPWHKNENME SKKRAFYEYH SLLMEPWDGP AAIVFTDGVI 360
MGASLDRNGF RPSRYYLTKD DMLILSSETG ALKLDEKNIK AKKRLEPGKL LLVDTARGRV 420
IADNEIKEHY ANAKPYKKWL KNLVELEKQK SGVYKHQFLK EDEVLKLQKA FGWSYDELKM 480

SVAAMAQNGK EAIAAMGVDT PLAILSKTYQ PLYNYFKQLF AQVTNPPLDA IREEIVTSTR 540
IYLGSEGNLL KPDENNAKRV KIALPVISNE ELFEVKALNK FQVKEFSILY DYSKKTLEKA 600
LDELCVKIED EVKKGVSIII LSDKGVDEKN AYIPALLAVS GVHNHLVRKN LRTHTSLIIE 660
SGEPREIHHF ACLLGYGATV INPYLVYESI QKLIANKDLN LSYEKAVENF IKASSSGIVK 720
IASKMGVSTL QSYNGSALFE CLGLSSKVID KYFTSTTSRI EGMDLEDFEK ELIALHKHAF 780
NDTHKALDSK GIHGFRSAKE EHLIDPLVIF NLQQACRNKD YKSFKKYSAL VDEKQVNLRS 840
LMEFDFSEAI SIDKVESVES IVKRFRTGAM SYGSISKEAH ECLAQAMNKI GAKSNSGEGG 900
EDEERYEIKE GVDKNSAIKQ VASGRFGVDL NYLSHAKEIQ IKVAQGAKPG EGGQLMGFKV 960
YPWIAKARHS TAGVTLISPP PHHDIYSIED LAQLIYDLKH ANKDAKISVK LVSENGIGTV 1020
AAGVAKAGAN LILVSGYDGG TGASPRTSIP HAGIPWELGL AETHQTLILN KLRDRVRLET 1080
DGKLMNGRDL AIAALLGAEE FGFATAPLIV LGCTMMRVCH LNTCPFGIAT QDTELRDRFK 1140
GKVDDVINFM YFIAEELREY MARLGFERLD DMIGRVDKLR QKSVQGKAGK LNLDKILKSL 1200
PTYNRTAVHF KDYKDNKLEK TIDYRILLPL CKNAVEKKEP IKLSLEVGNQ SRTFATMLSS 1260
EILKTYGKDA LDEDSIHIKA IGNAGNSFGA FLLKGIKLEI IGDSNDYLGK GLSGGKIIAK 1320
ISNEATFSPE ENIIAGNACL YGATKGEVYL DGIAGERFCV RNSGALAVVL GTGVHGCEYM 1380
TGGQVVVLGD VGANFAAGMS GGVVYIFGRH NEAHVNTELV DIKDLNAKDE KELKAVIEKH 1440
ITYTDSKKAK DILEKFDKKD FFKVMPRDYE KMLKMLDLCK NEKDPNLAAF LKITQK 1496

SEQ ID NO: 30
MSKFKVIEIK EDARPRDFEA FQLRLASPEK IKSWSYGEVK KPETINYRTL KPERDGLFCA 60
KIFGPIRDYE CLCGKYKKMR FKGVKCEKCG VEVANSKVRR SRMGHIELVT PVAHIWYVNS 120
LPSRIGTLLG VKMKDLERVL YYEAYIVENP GDAFYDNEST KKVEYCDVLN EEQYQNLMQR 180
YENSGFKARM GGEVVRDLLA NLDLVALLNQ LKEEMGATNS EAKKKTIIKR LKVVENFLNS 240
NLNANTDSDE AVPNRPEWMM ITNLPVLPPD LRPLVALDGG KFAVSDVNDL YRRVINRNTR 300
LKKLMELDAP EIIIRNEKRM LQEAVDALFD NGRRANAVKG ANKRPLKSLS EIIKGKQGRF 360
RQNLLGKRVD FSGRSVIVVG PKLRMDQCGL PKKMALELFK PHLLAKLEEK GYATTVKQAK 420
KMIENKTNEV WECLEEVVKG HPVMLNRAPT LHKLSIQAFH PVLVEGKAIQ LHPLVCAAFN 480
ADFDGDQMAV HVPLSQEAIA ECKVLMLSSM NILLPASGKS VTVPSQDMVL GIYYLSLEKA 540
GAKGSHKICT GIDEVMMALE SKCLDIHASI QTMVDGRKIT TTAGRLIVKS ILPDFVPENS 600
WNKVLKKKDI AALVDYVYKQ GGLEITASFL DRLKNLGFEY ATKAGISISI ADIIVPNDKQ 660
KAIDEAKKQV REIQNSYNLG LITSGERYNK IIDIWKSTNN VLSKEMMKLV EKDKEGFNSI 720
YMMADSGARG SAAQISQLAA MRGLMTKPDG SIIETPIISN FREGLNVLEY FISTHGARKG 780
LADTALKTAN AGYLTRKLID VAQNVKITIE DCGTHEGVEI NEITADSSII ETLEERILGR 840
VLAEDVIDPI TNSVLFAEGT LMDEEKAKIL GESGIKSVNI RTPITCKAKK GICAKCYGIN 900
LGEGKLVKPG EAVGIISAQS IGEPGTQLTL RTFHSGGTAS TDLQDRQVSA QKEGFIRFYN 960
LKTYKNKEGK NIVANRRNAA VLLVEPKIKT PFKGVINIEN IHEDVIVSIK DKKQEVKYIL 1020
RKYDLAKPNE LAGVSGSIDG KLYLPYQSGM QVEENESIVE VIKEGWNVPN RIPFASEILV 1080
EDGEPVVQNI KAGEKGTLKF YILKGDGLDR VKNVKKGDIV KEKGFFVVIA DENDREAKRH 1140
YIPRESKIEF NDSEKIDDAN TIIASAPKKE RKVIAEWDAY NNTIIAEIDG VVSFEDIEAG 1200
YSADEQIDEA TGKRSLVINE YLPSGVRPTL VIAGKGDKAV RYHLEPKTVI FVHDGDKIAQ 1260
ADILAKTPKA AAKSKDITGG LPRVSELFEA RKPKNAAVIA EIDGVVRFDK PLRSKERIII 1320
QAEDGTSAEY LIDKSKHIQV RDGEFIHAGE KLTDGVVSSH DVLKILGEKA LHYYLISEIQ 1380
QVYRGQGVVI SDKHIEVIVS QMLRQVKVVD SGHTKFIEGD LVSRRKFREE NERIIRMGGE 1440
PAIAEPVLLG VTRAAIGSDS VISAASFQET TKVLTEASIA GKFDYLEDLK ENVILGRMIP 1500
VGTGLYGEQN LKLKEQE 1517

CLAIMS

1. A polypeptide comprising
a) an amino acid sequence selected from the group consisting of any one of SEQ ID NOs: 13, 1-12 and 14-30, or
b) an amino acid sequence consisting of at least 5 contiguous amino acid residues from any one of SEQ ID NOs: 13, 1-12 and 14-30, or
c) an amino acid sequence having a sequence identity of at least 60% with the amino acid sequence of a),
d) an amino acid sequence having a sequence identity of at least 60% with the amino acid sequence of b), or
e) an assembly of amino acids derived from any one of SEQ ID NOs: SEQ ID NOs: 13, 1-12 and 14-30 which has essentially the same 3D conformation as in the protein from which said assembly is derived so as to constitute a B-cell epitope,
said polypeptide being antigenic in a mammal.

2. The polypeptide according to claim 1, wherein the at least 5 contiguous amino acids are at least 6, such as at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27 at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34, and at least 35 contiguous amino acid residues.

3. The polypeptide according to clam 1 or 2, wherein the sequence identity with the amino acid sequence of a) is at least 65%, such as at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, and at least 99%.

4. The polypeptide according to clam 1 or 2, wherein the sequence identity with the amino acid sequence of b) is at least 60%, such as at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, and at least 99%.

5. The polypeptide according to any one of the preceding claims, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, and 47 in any one of SEQ ID NOs: 1-30.

6. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, and 61 in any on of SEQ ID NOs: 2-30.

7. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, and 112 in any one of SEQ ID NOs: 3-30.

8. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, and 134 in any one of SEQ ID NOs: 4-30.

9. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 135, 136, and 137 in any one of SEQ ID NOs: 5-30.

10. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 138, 139, and 140 in any one of SEQ ID NOs: 6-30.

11. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, and 170 in any one of SEQ ID NOs: 7-30.

12. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, and 197 in any one of SEQ ID NOs: 8-30.

13. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino

acid residues 198, 199, 200, 201, 202, 203, 204, 205, and 206 in any one of SEQ ID NOs: 9-30.

14. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, and 240 in any one of SEQ ID NOs: 10-30.

15. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, and 255 in any one of SEQ ID NOs: 11-30.

16. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, and 269 in any one of SEQ ID NOs: 12-30.

17. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 270, 271, 272, 273, and 274 in any one of SEQ ID NOs: 13-30.

18. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, and 386 in any one of SEQ ID NOs: 14-30.

19. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455,

456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, and 538 in any one of SEQ ID NOs: 15-30.

20. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, and 606 in any one of SEQ ID NOs: 16-30.

21. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655 in any one of SEQ ID NOs: 17-30.

22. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 656, 657, 658, 659, 660, 661 in any one of SEQ ID NOs: 18-30.

23. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, and 746 in any one of SEQ ID NOs: 19-30.

24. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779,

780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, and 861 in any one of SEQ ID NOs: 20-30.

25. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 862, 863, 864, 865, 866, and 867 in any one of SEQ ID NOs: 21-30.

26. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, and 942 in any one of SEQ ID NOs: 22-30.

27. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000, 1001, 1002, 1003, 1004, 1005, 1006, 1007, 1008, 1009, 1010, 1011, 1012, 1013, 1014, 1015, 1016, 1017, 1018, 1019, 1020, 1021, 1022, 1023, 1024, 1025, 1026, 1027, 1028, 1029, 1030, 1031, 1032, 1033, 1034, 1035, 1036, and 1037 in any one of SEQ ID NOs: 23-30.

28. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 1038, 1039, 1040, 1041, 1042, 1043, 1044, 1045, 1046, 1047, 1048, 1049, 1050, 1051, 1052, 1053, 1054, 1055, 1056, 1057, 1058, 1059, 1060, 1061, 1062, 1063, 1064, 1065, 1066, 1067, 1068, 1069, 1070, 1071, 1072, 1073, 1074, 1075, 1076, 1077, 1078, 1079, 1080, 1081, 1082, 1083, 1084, and 1085 in any one of SEQ ID NOs: 24-30.

29. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 1086, 1087, 1088, 1089, 1090, 1091, 1092, 1093, 1094, 1095, 1096, 1097,

1098, 1099, 1100, 1101, 1102, 1103, 1104, 1105, 1106, 1107, 1108, 1109, 1110, 1111, 1112, 1113, 1114, 1115, and 1116 in any one of SEQ ID NOs: 25-30.

30. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 1117, 1118, 1119, 1120, 1121, 1122, 1123, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, and 1140 in any one of SEQ ID NOs: 26-30.

31. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1170, 1171, 1172, 1173, 1174, 1175, 1176, 1177, 1178, 1179, 1180, 1181, and 1182 in any one of SEQ ID NOs: 27-30.

32. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 1183, 1184, 1185, 1186, 1187, 1188, 1189, 1190, 1191, 1192, 1193, 1194, 1195, 1196, 1197, 1198, 1199, 1200, 1201, 1202, 1203, 1204, 1205, 1206, 1207, 1208, 1209, 1210, 1211, 1212, 1213, 1214, 1215, 1216, 1217, 1218, 1219, 1220, 1221, 1222, 1223, 1224, 1225, 1226, 1227, 1228, 1229, 1230, 1231, 1232, 1233, 1234, 1235, 1236, 1237, 1238, 1239, 1240, 1241, 1242, 1243, 1244, 1245, 1246, 1247, 1248, 1249, 1250, 1251, 1252, 1253, 1254, 1255, 1256, 1257, 1258, 1259, 1260, 1261, 1262, 1263, 1264, 1265, 1266, 1267, 1268, 1269, 1270, 1271, 1272, 1273, 1274, 1275, 1276, 1277, 1278, 1279, 1280, 1281, 1282, 1283, 1284, 1285, 1286, 1287, 1288, 1289, 1290, 1291, 1292, 1293, 1294, 1295, 1296, 1297, 1298, 1299, 1300, 1301, 1302, 1303, 1304, 1305, 1306, 1307, 1308, 1309, 1310, 1311, 1312, 1313, 1314, 1315, 1316, 1317, 1318, 1319, 1320, 1321, 1322, 1323, 1324, 1325, 1326, 1327, 1328, 1329, 1330, 1331, 1332, 1333, 1334, 1335, 1336, 1337, 1338, 1339, 1340, 1341, 1342, 1343, 1344, 1345, 1346, 1347, 1348, 1349, 1350, 1351, 1352, 1353, 1354, 1355, 1356, 1357, 1358, 1359, 1360, 1361, 1362, 1363, 1364, 1365, 1366, 1367, 1368, 1369, 1370, 1371, 1372, 1373, and 1374 in any one of SEQ ID NOs: 28-30.

33. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 1375, 1376, 1377, 1378, 1379, 1380, 1381, 1382, 1383, 1384, 1385, 1386, 1387, 1388, 1389, 1390, 1391, 1392, 1393, 1394, 1395, 1396, 1397, 1398, 1399, 1400, 1401, 1402, 1403, 1404, 1405, 1406, 1407, 1408, 1409, 1410, 1411, 1412, 1413, 1414,

1415, 1416, 1417, 1418, 1419, 1420, 1421, 1422, 1423, 1424, 1425, 1426, 1427, 1428, 1429, 1430, 1431, 1432, 1433, 1434, 1435, 1436, 1437, 1438, 1439, 1440, 1441, 1442, 1443, 1444, 1445, 1446, 1447, 1448, 1449, 1450, 1451, 1452, 1453, 1454, 1455, 1456, 1457, 1458, 1459, 1460, 1461, 1462, 1463, 1464, 1465, 1466, 1467, 1468, 1469, 1470, 1471, 1472, 1473, 1474, 1475, 1476, 1477, 1478, 1479, 1480, 1481, 1482, 1483, 1484, 1485, 1486, 1487, 1488, 1489, 1490, 1491, and 1492 in SEQ ID NO: 29 or 30.

34. The polypeptide according to any one of claims 1-4, wherein the at least 5 contiguous amino acid residues has an N-terminal amino acid residue corresponding to any one of amino acid residues 1493, 1494, 1495, 1496, 1497, 1498, 1499, 1500, 1501, 1502, 1503, 1504, 1505, 1506, 1507, 1508, 1509, 1510, 1511, 1512, 1513 in SEQ ID NO: 30.

35. A polypeptide comprising
a) the amino acid sequence SEQ ID NO: 13, or
b) an amino acid sequence consisting of at least 5 contiguous amino acid residues from one SEQ ID NO: 13, or
c) an amino acid sequence having a sequence identity of at least 60% with the amino acid sequence of a),
d) an amino acid sequence having a sequence identity of at least 60% with the amino acid sequence of b), or
e) an assembly of amino acids derived from SEQ ID NOs: 13 which has essentially the same 3D conformation as in the protein from which said assembly is derived so as to constitute a B-cell epitope,
said polypeptide being antigenic in a mammal.

36. The polypeptide according to claim 35, which is as defined in any one of claims 2-17.

37. The polypeptide according to any one of the preceding claims, which is fused or conjugated to an immunogenic carrier molecule.

38. The polypeptide according to claim 37, wherein the immunogenic carrier molecule is a polypeptide that induces T-helper lymphocyte responses in a majority of humans, such as immunogenic carrier proteins selected from the group consisting of keyhole limpet hemocyanin or a fragment thereof, tetanus toxoid or a fragment thereof, dipththeria toxoid or a fragment thereof.

39. The polypeptide according to any one of the preceding claims, which is capable of inducing an adaptive immune response against the polypeptide in a mammal, in particular in a human being.

40. The polypeptide according to claim 39, which is capable of inducing, in the mammal, a protective adaptive immune response against infection with *C. jejuni*.

41. The polypeptide according to claim 39 or 40, which induces a humoral and/or a cellular immune response.

42. An isolated nucleic acid fragment, which comprises
i) a nucleotide sequence encoding a polypeptide according to any one of the preceding claims, or
ii) a nucleotide sequence consisting of the amino acid encoding part of any one of SEQ ID NOs: 30-90.
iii) a nucleotide sequence consisting of at least 10 consecutive nucleotides in the amino acid encoding part of any one of SEQ ID NOs: 30-90,
iv) a nucleotide sequence having a sequence identity of at least 60% with the nucleotide sequence in i) or ii),
v) a nucleotide sequence having a sequence identity of at least 60% with the nucleotide sequence in iii),
vi) a nucleotide sequence complementary to the nucleotide sequence in i)-v), or
vii) a nucleotide sequence which hybridizes under stringent conditions with the nucleotide sequence in i)-vi).

43. The nucleic acid fragment according to claim 42, which is a DNA or an RNA fragment.

44. The nucleic acid fragment according to claim 42 or 43, wherein the nucleotide sequence consists of at least 11, such as at least 12, at least 13, at least 14, at least 15, at least 16, at least 17 at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34, at least 35, at least 36, at least 37, at least 38, at least 39, at least 40, at least 41, at least 42, at least 43, at least 44, at least 45, at least 46, at least 47, at least 48, at least 49, at least 50, at least 51, at least 52, at least 53, at least 54, at least 55, at least 56, at least 57, at least 58, at least 59, at least 60, at least 61, at least 62, at least 63, at least 64, at least 65, at least 66, at least 67, at least 68, at least 69, at least 70, at least 71, at least 72, at least 73, at least 74, at least 75, at least 76, at least 77, at least 78, at least 79, at least 80, at least 81, at least 82, at least 83, at least 84, at least 85, at least 86, at least 87, at least 88, at least 89, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98, at least 99, at least 100, at least 101, at least 102, at least 103, at least 104, at least 105, at least 106, at least 107, at least 108, at least 109, at least 110, at least 111, at least 112, at least 113, at least 114, at least 115, at least 116, at least 117, at least 118, at least 119, at least 120, at least

121, at least 122, at least 123, at least 124, at least 125, at least 126, at least 127, at least 128, at least 129, at least 130, at least 131, at least 132, at least 133, at least 134, at least 135, at least 136, at least 137, at least 138, at least 139, at least 140, at least 141, at least 142, at least 143, at least 144, at least 145, at least 146, at least 147, at least 148, at least 149, at least 150, at least 151, at least 152, and at least 153 consecutive nucleotides in the amino acid encoding part of any one of SEQ ID NOs: 31-90.

45. The nucleic acid fragment according to any one of claims 42-44, wherein the sequence identity with the nucleotide sequence in i) or ii) is at least 65%, such as at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, and at least 99%.

46. The nucleic acid fragment according to any one of claims 42-44, wherein the sequence identity with the nucleotide sequence in iii) is at least 65%, such as at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, and at least 99%.

47. A vector comprising the nucleic acid according to any one of claims 42-46, such as a cloning vector or an expression vector.

48. The vector according to claim 47, which comprises in operable linkage and in the 5'-3' direction, an expression control region comprising an enhancer/promoter for driving expression of the nucleic acid fragment defined in claim 42-i), optionally a signal peptide coding sequence, a nucleotide sequence defined in claim 42-i), and optionally a terminator.

49. The vector according to claim 47 or 48, wherein the expression control region drives expression in prokaryotic cell such as a bacterium, e.g. in E coli.

50. The vector according to claim any one of claims 47-49, which is capable of autonomous replication.

51. The vector according to any one of claims 47-50, which is capable of being integrated into the genome of a host cell.

52. The vector according to any one of claims 47-50, which is incapable of being integrated into the genome of a mammalian host cell.

53. The vector according to any one of claims 47-52, which is selected from the group consisting of a virus, such as a attenuated virus, a bacteriophage, a plasmid, a minichromosome, and a cosmid.

54. A cell which is transformed so as to carry the vector according to any one of claims 49-52.

55. The transformed cell according to claim 54, which is capable of replicating the nucleic acid fragment defined in claim 42-i).

56. The transformed cell according to claim 43, which is capable of expressing the nucleic acid fragment defined in claim 42-i).

57. The transformed cell according to any one of claims 54-56, which is selected from a prokaryotic cell and a eukaryotic cell.

58. The transformed cell according to any one of claims 54-56, which is a bacterial cell selected from the group consisting of Escherichia (such as E. coli.), Bacillus (e.g. Bacillus subtilis), Salmonella, and Mycobacterium, preferably non-pathogenic, e.g. M. bovis BCG.

59. The transformed cell according to any one of claims 54-58, which is stably transformed by having the nucleic acid defined in claim 42-i) stably integrated into its genome.

60. The transformed cell according to any one of claims 54-59, which secretes or carries on its surface the polypeptide according to any one of claims 1-39.

61. The transformed cell according to claim 60, wherein the cell is a bacterium and secretion is into the periplasmic space.

62. A cell line derived from a transformed cell according to any one of claims 54-61.

63. A pharmaceutical composition comprising a polypeptide according to any one of claims 1-41, a nucleic acid fragment according to any one of claims 42-46, a vector according to any one of claims 47-53, or a cell according to any one of claims 54-61, and a pharmaceutically acceptable carrier, vehicle or diluent.

64. The pharmaceutical composition according to claim 63, which further comprises an immunological adjuvant.

65. The pharmaceutical composition according to claim 64, wherein the adjuvant is an aluminium based adjuvant.

66. A method for inducing immunity in an animal by administering at least once an immunogenically effective amount of a polypeptide according to any one of claims 1-41, a nucleic acid fragment according to any one of claims 42-46, a vector according to any one of claims 47-53, a cell according to any one of claims 54-61, or a pharmaceutical composition according to any one of claims 62-65 so as to induce adaptive immunity against *C. jejuni* in the animal.

67. The method according to claim 66, wherein, when the polypeptide according to any one of claim 1-41 or a composition comprising said polypeptide is administered, the animal receives between 0.5 and 5,000 µg of the polypeptide according to any one of claims 1-41 per administration.

68. The method according to claim 66 or 67, wherein the animal receives a priming administration and one or more booster administrations.

69. The method according to any one of claims 66-68, wherein the animal is a human being.

70. The method according to any one of claims 66-69, wherein the administration is for the purpose of inducing protective immunity against *C. jejuni*.

71. The method according to claim 70, wherein the protective immunity is effective in reducing the risk of attracting infection with *C. jejuni* or is effective in treating or ameliorating infection with *C. jejuni*.

72. The method according to claim 66, wherein the administration is for the purpose of inducing antibodies specific for *C. jejuni* and wherein said antibodies or B-lymphocytes producing said antibodies are subsequently recovered from the animal.

73. The method according to claim 66, wherein the administration is for the purpose of inducing antibodies specific for *C. jejuni* and wherrein B-lymphocytes producing said

antibodies are subsequently recovered from the animal and used for preparation of monoclonal antibodies.

74. A polyclonal antibody in which the antibodies specifically bind to at least one polypeptide according to any one of claims 1-41, and which is essentially free from antibodies binding specifically to other *C. jejuni* polypeptides.

75. An isolated monoclonal antibody or antibody analogue which binds specifically to a polypeptide according to any one of claims 1-41.

76. The isolated monoclonal antibody or antibody analogue according to claim 75, which is a monoclonal antibody selected from a multi-domain antibody such as a murine antibody, a chimeric antibody such as a humanized antibody, a fully human antibody, and single-domain antibody of a llama or a camel, or which is an antibody analogue selected from a fragment of an antibody such as an Fab or an $F(ab')_2$, and an scFV.

77. A pharmaceutical composition comprising an antibody according to any one of claims 74-76 and a pharmaceutically acceptable carrier, vehicle or diluent.

78. A method for prophylaxis, treatment or amelioration of infection with *C. jejuni*, in particular infection with multi-resistant *C. jejuni*, comprising administering a therapeutically effective amount of an antibody according to any one of claims 74-76 or a pharmaceutical composition according to claim 77 to an individual in need thereof.

79. A method for determining, quantitatively or qualitatively, the presence of *C. jejuni*, in particular the presence of multi-resistant *C. jejuni*, in a sample, the method comprising contacting the sample with an antibody according to any one of claims 74-76 and detecting the presence of antibody bound to material in the sample.

80. A method for determining, quantitatively or qualitatively, the presence of antibodies specific for *C. jejuni*, in particular the presence of antibodies specific for multi-resistant *C. jejuni*, in a sample, the method comprising contacting the sample with a polypeptide according to any one of claims 1-41 and detecting the presence of antibody said polypeptide.

81. A method for determining, quantitatively or qualitatively, the presence of a nucleic acid characteristic of *C. jejuni*, in particular the presence of a nucleic acid characteristic of multi-resistant *C. jejuni*, in a sample, the method comprising contacting the sample with a nucleic acid fragment according to any one of claims 42-46 and detecting the presence of nucleic acid in the sample that hybridized to said nucleic acid fragment.

82. The method according to claim 80, which includes at least one step of molecular amplification of the nucleic acid which is to be detected in the sample, for instance a step of PCR amplification.

83. A method for the preparation of the polypeptide according to any one of claims 1-41, comprising
- culturing a transformed cell according to claim 45 and any one of claims 57-60, insofar as these depend on claim 56 under condiditions that facilitate that the transformed cell expresses the nucleic acid fragment according to claim 42-i) and any one of claims 43-46 insofar as these depend on claim 42-i) and subsequently recovering said polypeptide, or
- preparing said polypeptide by means of solid or liquid phase peptide synthesis.

84. A method for determining whether a substance, such as an antibody, is potentially useful for treating infection with *C. jejuni*, the method comprising contacting the polypeptide according to any one of claims 1-41 with the substance and subsequently establishing whether the substance has at least one of the following characteristics:
1) the ability to bind specifically to said polypeptide,
2) the ability to compeed with said polypeptide for specific binding to a ligand/receptor,
3) the ability to specifically inactivate said polypeptide.

85. A method for determining whether a substance, such as a nucleic acid, is potentially useful for treating infection with *C. jejuni*, the method comprising contacting the substance with the nucleic acid fragment of any one of claims 42-46 and subsequently establishing whether the substance has either the ability to
1) bind specifically to the nucleic acid fragment, or
2) bind specifically to a nucleic acid that hybridizes specifically with the nucleic acid fragment.

86. The polypeptide according to any one of claims 1-41 for use as a pharmaceutical.

87. The polypeptide according to any one of claims 1-41 for use as a pharmaceutical in the treatment, prophylaxis or amelioration of infection with *C. jejuni*.

88. The nucleic acid fragment according to any one of claims 42-46 or the vector according to any one of claims 47-53 for use as a pharmaceutical.

89. The nucleic acid fragment according to any one of claims 42-46 or the vector according to any one of claims 47-53 for use as a pharmaceutical in the treatment, prophylaxis or amelioration of infection with *C. jejuni*.

90. The cell according to any one of claims 54-61 for use as a pharmaceutical.

91. The cell according to any one of claims 54-61 for use as a pharmaceutical in the treatment, prophylaxis or amelioration of infection with *C. jejuni*.

92. The antibody, antibody fragment or antibody analogue according to any one of claims 74-76 for use as a pharmaceutical.

93. The antibody, antibody fragment or antibody analogue according to any one of claims 74-76 for use as a pharmaceutical in the treatment, prophylaxis or amelioration of infection with *C. jejuni*.

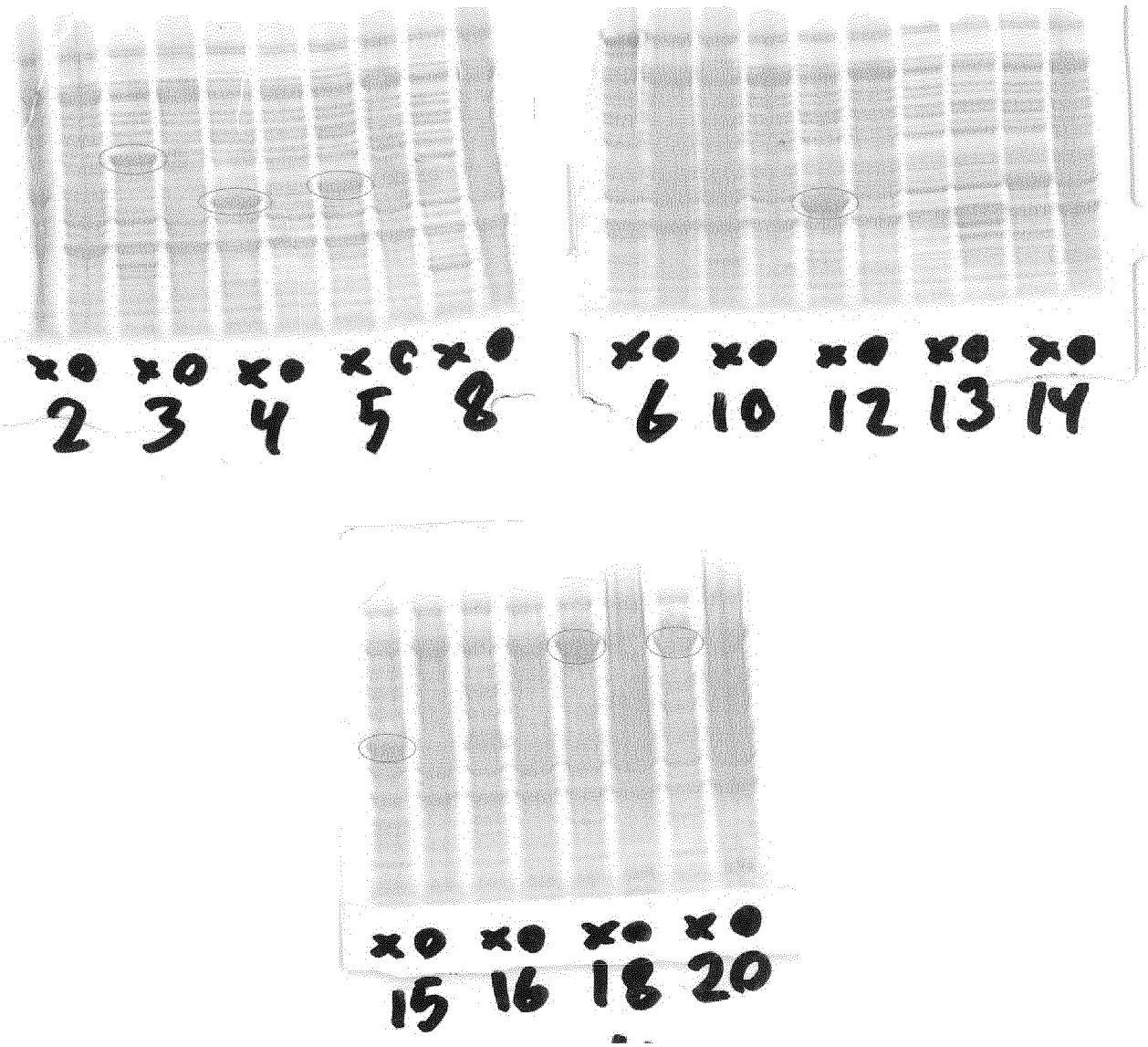


Fig. 1

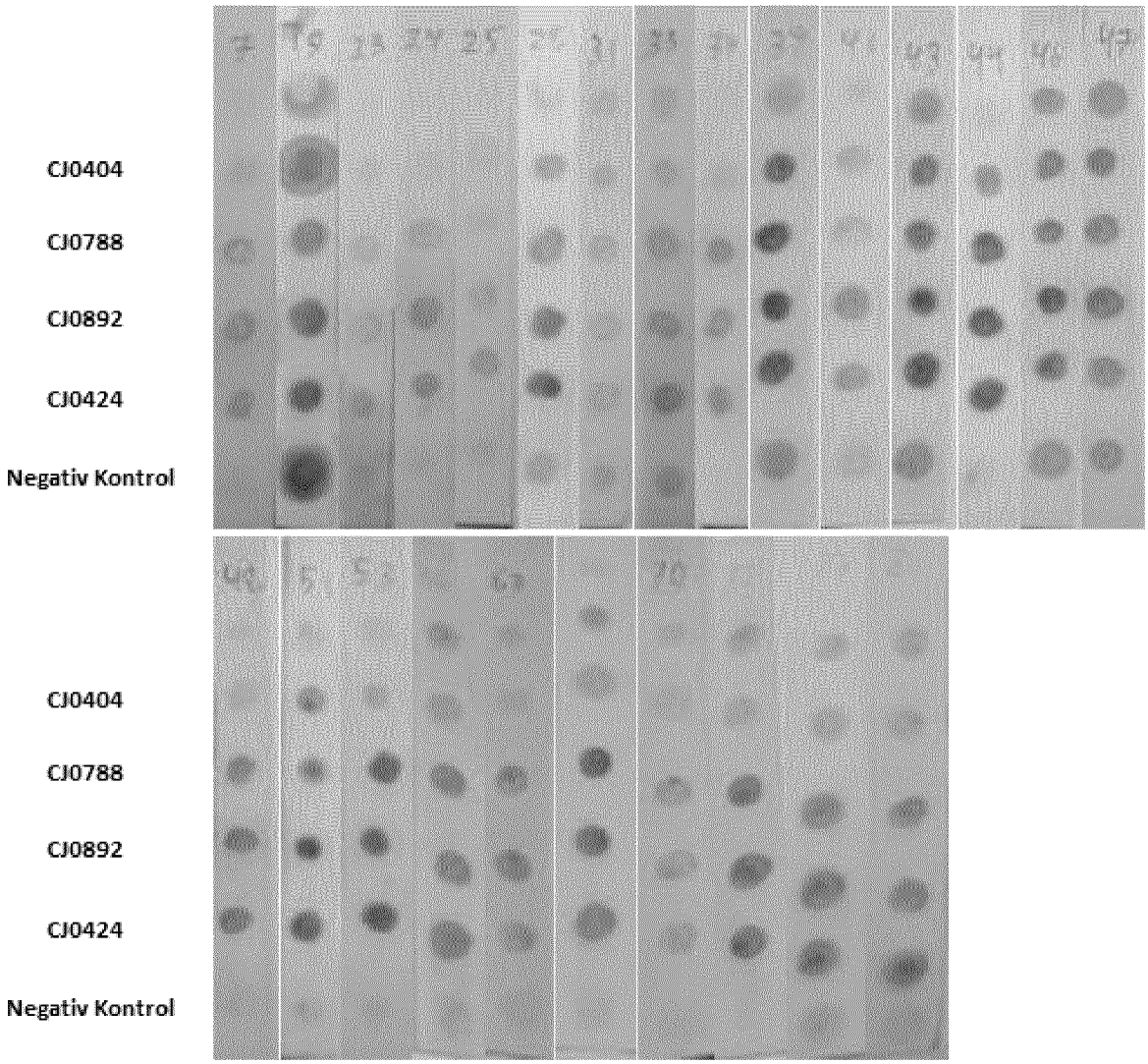

CJ0404
CJ0788
CJ0892
CJ0424
Negativ Kontrol
CJ0404
CJ0788
CJ0892
CJ0424
Negativ Kontrol

Fig. 2

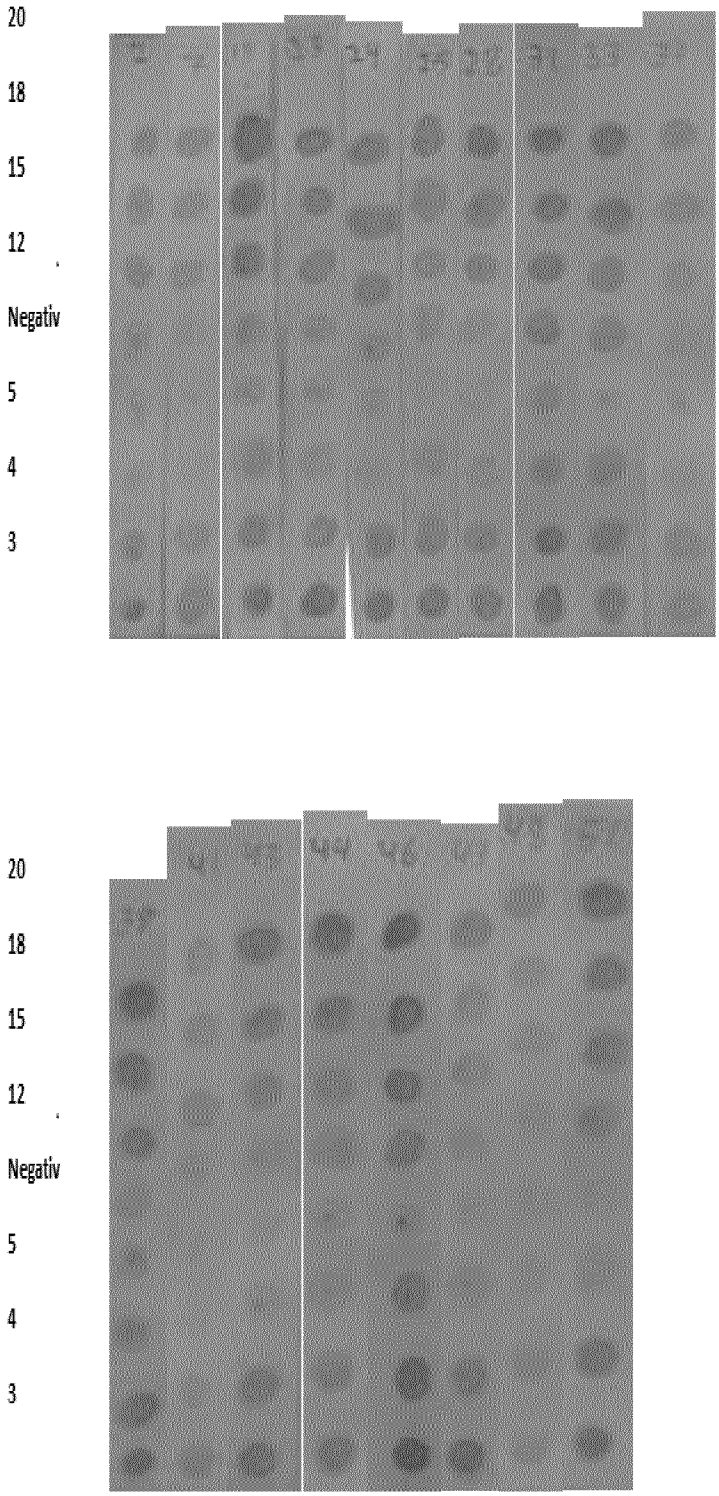


Fig. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2012/070282

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

35(completely); 1-34, 36-93(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

International application No
PCT/EP2012/070282

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K14/205
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBL, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/077183 A2 (ELITRA PHARMACEUTICALS INC [US]; WANG LIANGSU [US]; ZAMUDIO CARLOS [US) 3 October 2002 (2002-10-03)	1-36, 39-63, 66, 70-80, 83-93
Y	claim 28; sequence 54311 page 195, line 16 - line 26	37,38, 64,65, 67-69, 81,82

A	US 2003/039963 A1 (BRAHMACHARI SAMIR KUMAR [IN] ET AL) 27 February 2003 (2003-02-27) paragraph [0001]; claim 1; sequence 42	1-93

	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 December 2012	13/03/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Obel, Nicolai

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PARKHILL J ET AL: "THE GENOME SEQUENCE OF THE FOOD-BORNE PATHOGEN CAMPYLOBACTER JEJUNIREVEALS HYPERVARIABLE SEQUENCES", NATURE: INTERNATIONAL WEEKLY JOURNAL OF SCIENCE, NATURE PUBLISHING GROUP, UNITED KINGDOM, vol. 403, 10 February 2000 (2000-02-10), pages 665-668, XP000906767, ISSN: 0028-0836, DOI: 10.1038/35001088 sequence Q0PBA6	1,35, 42-46, 86,88
Y	WO 00/27205 A1 (US NAVY [US]; GUERRY PATRICIA [US]; TRUST TREVOR [US]; BURG EDWARD [US) 18 May 2000 (2000-05-18) claims 14,15; example 2	37,38, 64,65, 67-69, 81,82
A	MAOJUN ZHANG ET AL: "Genomic Characterization of the Guillain-Barre Syndrome-Associated Campylobacter jejuni ICDCCJ07001 Isolate", PLOS ONE, vol. 5, no. 11, 1 January 2010 (2010-01-01), page e15060, XP055047335, ISSN: 1932-6203, DOI: 10.1371/journal.pone.0015060 the whole document	1-93

1

Information on patent family members

International application No
PCT/EP2012/070282

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02077183 A2	03-10-2002	NONE	
US 2003039963 A1	27-02-2003	NONE	
WO 0027205 A1	18-05-2000	AU 1820800 A	29-05-2000
		EP 1156717 A1	28-11-2001
		US 6987176 B1	17-01-2006
		WO 0027205 A1	18-05-2000

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 35(completely); 1-34, 36-93(partially)

SEQ ID NO 13 for treatment of Campylobacter infections.

2-30. claims: 1-34, 36-93(all partially)

Each further protein for treatment of Campylobacter infections.
