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#### (54) PROTEINS AND NUCLEIC ACIDS USEFUL IN VACCINES TARGETING PSEUDOMONAS **AERUGINOSA**

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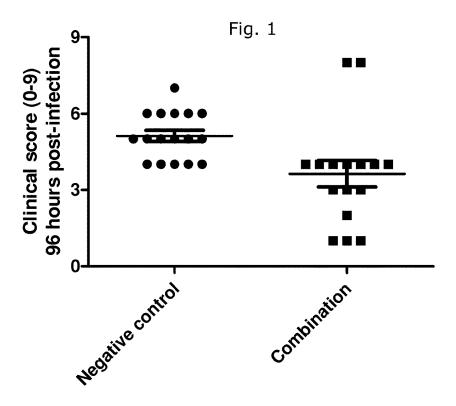
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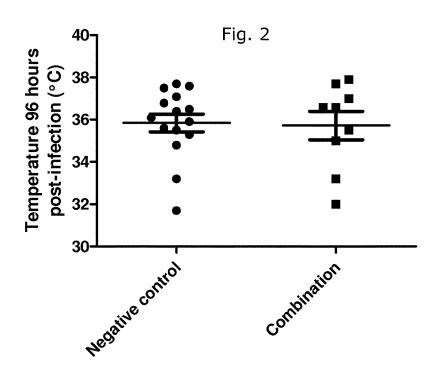
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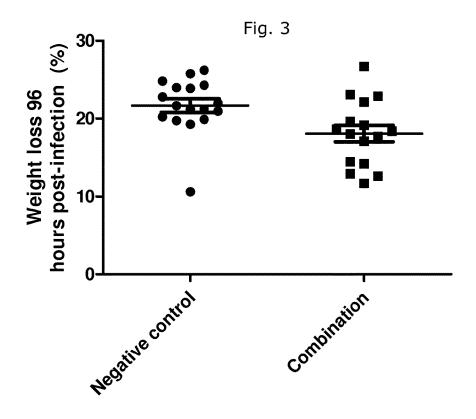
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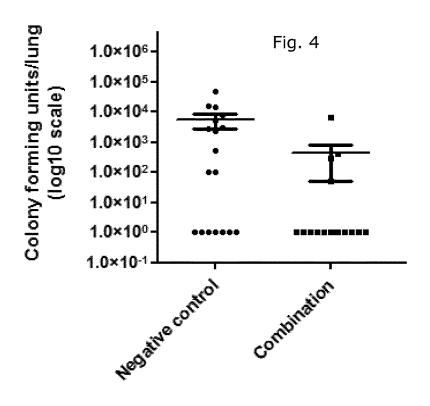
#### ABSTRACT (57)

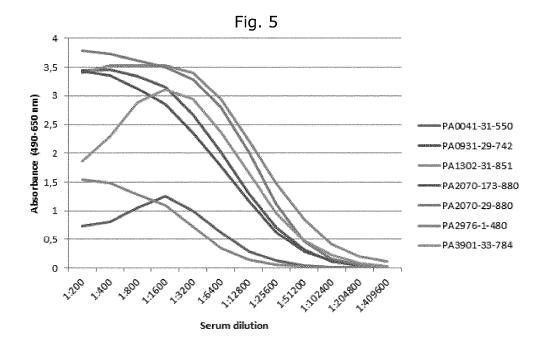
Disclosed are immunogenic proteins from Pseudomonas aeruginosa as well as nucleic acids, vectors and transformed cells useful for expression of the proteins. Also disclosed are methods for prophylaxis of infection with Pseudomonas aeruginosa using the proteins, nucleic acids, vectors or transformed cells.

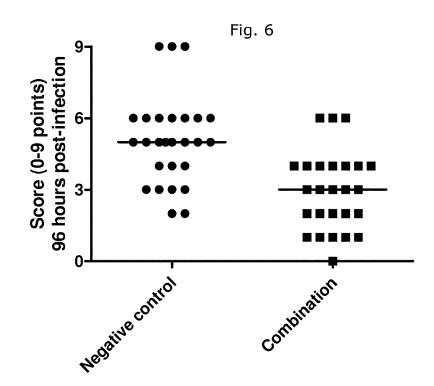


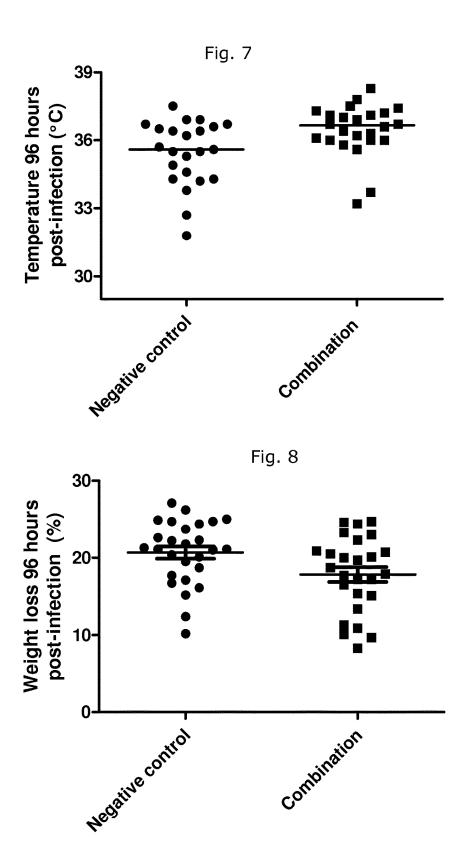


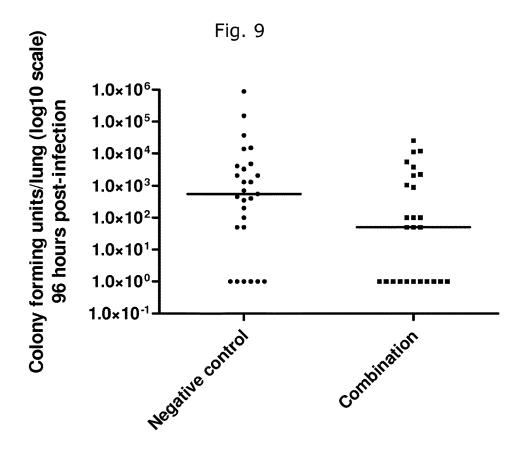


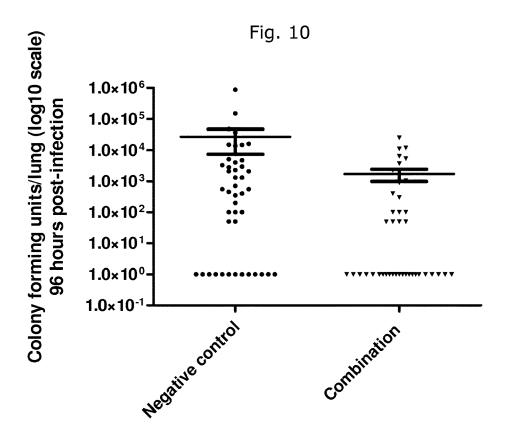


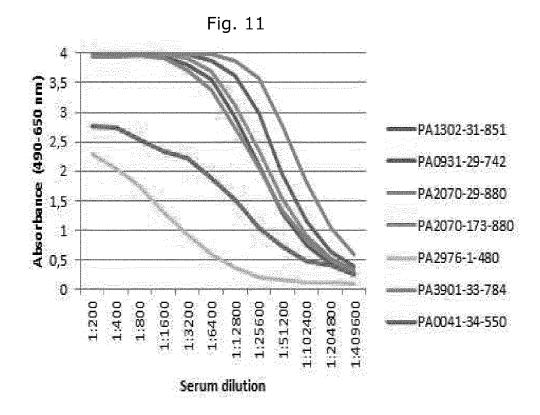












# PROTEINS AND NUCLEIC ACIDS USEFUL IN VACCINES TARGETING PSEUDOMONAS AERUGINOSA

#### FIELD OF THE INVENTION

[0001] 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 *Pseudomonoas aeruginosa*. 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

[0002] Pseudomonas aeruginosa is an opportunistic gramnegative pathogen. It represents a major course of hospital-aquired infections, especially in burnt and other immunocompromised patients, including transplant or cancer patients. Therefore, it is regarded as a "problem microbe" in human medicine.

[0003] Many efforts have been made so far in order to develop a vaccine against *Pseudomonas aeruginosa*. For example, in the EP-0 297 291 the complete amino acid-sequence of the outer membrane protein F, as well as the nucleotide sequence coding for OprF is disclosed. In the EP-0 357 024 the complete amino acid sequence of the outer membrane protein I and, additionally, the nucleotide sequence coding for OprI is shown. Furthermore, with both proteins it was shown that they may be useful for conferring immunoprotection against *Pseudomonas aeruginosa* to an animal or human proband. However, improvement of procedures of vaccination against and treatment of a lethal *Pseudomonas aeruginosa* infection is still an object.

[0004] Vaccination is considered to be a very effective method of preventing infectious diseases in human and veterinary health care. Vaccination is the administration of immungenically 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.

[0005] 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.

[0006] 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.

[0007] 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 immunoprotective. 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

[0008] It is an object of embodiments of the invention to provide *Pseudomonas aeruginosa* derived antigenic polypeptides that may serve as constituents in vaccines against *Pseudomonas aeruginosa* infections and in diagnosis of *Pseudomonas aeruginosa* 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 *Pseudomonas aeruginosa*.

#### SUMMARY OF THE INVENTION

**[0009]** It has been found by the present inventor(s) that *Pseudomonas aeruginosa* 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 *Pseudomonas aeruginosa*.

[0010] 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.

[0011] 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).

[0012] 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.

[0013] In fourth aspect, the invention relates to a cell which is transformed so as to carry the vector of the invention.

[0014] 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.

[0015] 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 *Pseudomonas aeruginosa* in the animal.

[0016] 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 *Pseudomonas aeruginosa* 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.

[0017] In a  $10^{th}$  aspect, the invention relates to a method for prophylaxis, treatment or amelioration of infection with *Pseudomonas aeruginosa*, 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.

[0018] In an 11<sup>th</sup> aspect, the invention relates to a method for determining, quantitatively or qualitatively, the presence of *Pseudomonas aeruginosa*, 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.

[0019] In an 12<sup>th</sup> aspect of the invention is provided a method for determining, quantitatively or qualitatively, the presence of antibodies specific for *Pseudomonas aeruginosa* 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.

[0020] In a 13<sup>th</sup> aspect, the invention relates to a method for determining, quantitatively or qualitatively, the presence of a nucleic acid characteristic of *Pseudomonas aeruginosa*, in particular the presence of a nucleic acid characteristic of *Pseudomonas aeruginosa*, 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.

[0021] In a  $14^{th}$  aspect, the invention relates to a method for the preparation of the polypeptide of the invention, comprising

[0022] 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

[0023] preparing said polypeptide by means of solid or liquid phase peptide synthesis.

[0024] In a 15<sup>th</sup> aspect, the invention relates to a method for determining whether a substance, such as an antibody, is potentially useful for treating infection with *Pseudomonas aeruginosa*, 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.

[0025] Finally, in a 16<sup>th</sup> aspect, the invention relates to a method for determining whether a substance, such as a nucleic acid, is potentially useful for treating infection with *Pseudomonas aeruginosa*, 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

[0026] FIG. 1. Graph of clinical score four days post-infection, Example 1.

[0027] Mice immunized with the 7-valent combination vaccine had a significantly lower clinical score 96 hours post-infection compared to the control group immunized with adjuvant. The data were analysed using Student's t-test, P=0.0109.

[0028] FIG. 2. Graph of body temperature four days post-infection, Example 1.

[0029] Comparison of body temperature, measured in the two groups of mice four days post-infection, showed that there was no significant difference in body temperature. The data were analyzed using the Mann Whitney test, P=0.8814. [0030] FIG. 3. Weight loss 96 hours post-infection, Example 1.

[0031] The group of mice immunized with the 7-valent combination vaccine had a significantly smaller weight loss than the control group. The data were analyzed using the Mann Whitney test,  $P\!=\!0.0081.$ 

[0032] FIG. 4. Lung bacteriology, Example 1.

[0033] The number of colony forming units was significantly smaller in lung homogenates from mice immunized with the 7-valent combination vaccine compared to the control group. Note that in this figure the CFU values equaled 0 are altered to 1, this is purely for illustrative purposes as a value of 0 cannot be shown on a logarithmic scale. The CFU data are given in appendix 4. The data were analyzed using the Mann Whitney test, P=0.0176.

[0034] FIG. 5. Mean antibody responses to the seven antigens tested in Example 1.

[0035] The Y-axis represents the absorbance measured at 490 nm-650 nm (reference), and the X-axis shows the serum

dilution. In general, the antibody response to five of the seven antigens was high, while the antibody response to PA2976-1-480 and PA0041-34-550 was quite low.

[0036] FIG. 6. Clinical score four days post-infection, Example 2.

[0037] The mice immunized with the 7-valent combination vaccine had a significantly lower clinical score 96 hours post-infection compared to the control group immunized with adjuvant. The data were analysed using a two-tailed t-test. P<0.0001.

[0038] FIG. 7. Body temperature four days post-infection, Example 2.

[0039] Comparison of body temperature, measured in the two groups of mice four days post-infection, showed that mice immunized with the 7-valent combination vaccine had a significantly higher body temperature compared to controls. The data were analyzed using the Mann Whitney test, P=0.0085.

[0040] FIG. 8. Weight loss 96 hours post-infection, Example 2.

[0041] The group of mice immunized with the 7-valent combination vaccine had a significantly smaller weight loss than the control group. The data were analyzed using a two-tailed t-test, P=0.0262.

[0042] FIG. 4. Lung bacteriology, Example 2.

[0043] There was no significant difference when comparing CFU in lung homogenates from mice immunized with the 7-valent combination vaccine and the control group. Note that in this figure the CFU values equaled 0 are altered to 1, this is purely for illustrative purposes as a value of 0 cannot be shown on a logarithmic scale. The CFU data are given in appendix 4. The data were analyzed using the Mann Whitney test, P=0.0888. In relation to this note that the high number of animals having complete clearance complicates statistical test of bacterial load, hence no significant p-value<0.05. However, a higher number of animals in the vaccinated group (11/26) experienced total clearance of bacteria in the kidneys compared to control (6/27).

[0044] FIG. 10. Lung bacteriology—combined results from Examples 1 and 2.

[0045] When pooling the CFU results obtained in ER\_0039 and ER\_0040, two completely identical experiments, the mice immunized with the 7-valent vaccine exhibit a significantly lower lung CFU compared to controls. Note that in this figure, the CFU values equaled 0 are altered to 1, this is purely for illustrative purposes as a value of 0 cannot be shown on a logarithmic scale. The data were analyzed using the Mann Whitney test, P=0.0044.

[0046] FIG. 11. Mean antibody responses to the seven antigens. The Y-axis represents the absorbance measured at 490 nm-650 nm (reference), and the X-axis shows the serum dilution. In general, the antibody responses to five of the seven antigens were high, while the antibody responses to PA2976-1-480 and PA0041-34-550 were quite low.

## DETAILED DISCLOSURE OF THE INVENTION

#### **Definitions**

[0047] 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.

[0048] 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 [0049] 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.

[0050] 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.

[0051] "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 77.8%  $(N_{ref}-9)$  and  $N_{dif}-2$ ). It will be understood that such a sequence identity determination requires that the two aligned sequences are aligned so that there are no overhangs between the two sequences: each amino acid in each sequence will have to be matched with a counterpart in the other sequence.

[0052] An "assembly of amino acids" means two or more amino acids bound together by physical or chemical means. [0053] 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.

[0054] "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.

[0055] 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

[0056] 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 capable 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.

[0057] 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.

[0058] 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.

[0059] 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.

[0060] "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.

[0061] 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. [0062] 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.

[0063] 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. [0064] "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.

[0065] 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 [0066] 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

**[0067]** 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 or exactly or at most 6, such as at least or exactly or at most 7, at least or exactly or at most 9, at least

or exactly or at most 10, at least or exactly or at most 11, at least or exactly or at most 12, at least or exactly or at most 13, at least or exactly or at most 14, at least or exactly or at most 15, at least or exactly or at most 16, at least or exactly or at most 17, at least or exactly or at most 18, at least or exactly or at most 19, at least or exactly or at most 20, at least or exactly or at most 21, at least or exactly or at most 22, at least or exactly or at most 23, at least or exactly or at most 24, at least or exactly or at most 25, at least or exactly or at most 26, at least or exactly or at most 27 at least or exactly or at most 28, at least or exactly or at most 29, at least or exactly or at most 30, at least or exactly or at most 31, at least or exactly or at most 32, at least or exactly or at most 33, at least or exactly or at most 34, at least or exactly or at most 35, at least or exactly or at most 36, at least or exactly or at most 37, at least or exactly or at most 38, at least or exactly or at most 39, at least or exactly or at most 40, at least or exactly or at most 41, at least or exactly or at most 42, at least or exactly or at most 43, at least or exactly or at most 44, at least or exactly or at most 45, at least or exactly or at most 46, at least or exactly or at most 47, at least or exactly or at most 48, at least or exactly or at most 49, at least or exactly or at most 50, at least or exactly or at most 51, at least or exactly or at most 52, at least or exactly or at most 53, at least or exactly or at most 54, at least or exactly or at most 55, at least or exactly or at most 56, at least or exactly or at most 57, at least or exactly or at most 58, at least or exactly or at most 59, at least or exactly or at most 60, at least or exactly or at most 61, at least or exactly or at most 62, at least or exactly or at most 63, at least or exactly or at most 64 and at least or exactly or at most 65 contiguous amino acid residues.

[0068] The number of contiguous amino acids in option b) can be higher, for all of SEQ ID NOs. 2-30. 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 or exactly or at most N-n, where N is the length of the sequence ID in question and n is any integer between 1 and N-5; that is, the at least or exactly 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.

[0069] Insofar as embodiment b relates to SEQ ID NOs: 2-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 66, at least or exactly or at most 67, at least or exactly or at most 68, at least or exactly or at most 69, at least or exactly or at most 70, at least or exactly or at most 71, at least or exactly or at most 72, at least or exactly or at most 73, at least or exactly or at most 74, at least or exactly or at most 75, at least or exactly or at most 76, or at least or exactly or at most 77 contiguous amino acid residues.

[0070] Insofar as embodiment b relates to SEQ ID NOs: 3-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 78, at least or exactly or at most 80, at least or exactly or at most 81, at least or exactly or at most 82, at least or exactly or at most 83, at least or exactly or at most 84, at least or exactly or at most 85, at least or exactly or at most 86, at least or exactly or at most 87, at least or exactly or at most 88, at least or exactly or at most 89, at least or exactly or at most 89, at least or exactly or at most 90, at least or exactly or at most 91, at least or exactly or at most 92, at least or exactly or at

most 93, at least or exactly or at most 94, at least or exactly or at most 95, at least or exactly or at most 96, at least or exactly or at most 97, at least or exactly or at most 98, at least or exactly or at most 99, at least or exactly or at most 100, at least or exactly or at most 101, at least or exactly or at most 102, or at least or exactly or at most 103 contiguous amino acid residues.

[0071] Insofar as embodiment b relates to SEQ ID NOs: 4-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 104, at least or exactly or at most 105, at least or exactly or at most 106, at least or exactly or at most 107, at least or exactly or at most 108, at least or exactly or at most 109, at least or exactly or at most 110, at least or exactly or at most 111, at least or exactly or at most 112, at least or exactly or at most 113, at least or exactly or at most 114, at least or exactly or at most 115, at least or exactly or at most 116, at least or exactly or at most 117, at least or exactly or at most 118, at least or exactly or at most 119, at least or exactly or at most 120, at least or exactly or at most 121, at least or exactly or at most 122, at least or exactly or at most 123, at least or exactly or at most 124, at least or exactly or at most 125, at least or exactly or at most 126, at least or exactly or at most 127, at least or exactly or at most 128, at least or exactly or at most 129, at least or exactly or at most 130, at least or exactly or at most 131, at least or exactly or at most 132, at least or exactly or at most 133, at least or exactly or at most 134, at least or exactly or at most 135, at least or exactly or at most 136, at least or exactly or at most 137, at least or exactly or at most 138, at least or exactly or at most 139, at least or exactly or at most 140, at least or exactly or at most 141, at least or exactly or at most 142, at least or exactly or at most 143, at least or exactly or at most 144, at least or exactly or at most 145, at least or exactly or at most 146, at least or exactly or at most 147, at least or exactly or at most 148, at least or exactly or at most 149, at least or exactly or at most 150, at least or exactly or at most 151, at least or exactly or at most 152, at least or exactly or at most 153, or at least or exactly or at most 154 contiguous amino acid residues.

[0072] Insofar as embodiment b relates to SEQ ID NOs: 5-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 155, at least or exactly or at most 156, at least or exactly or at most 157, at least or exactly or at most 158, at least or exactly or at most 159, at least or exactly or at most 160, at least or exactly or at most 161, at least or exactly or at most 162, at least or exactly or at most 163, at least or exactly or at most 164, at least or exactly or at most 165, at least or exactly or at most 166, at least or exactly or at most 167, at least or exactly or at most 168, at least or exactly or at most 169, at least or exactly or at most 170, at least or exactly or at most 171, at least or exactly or at most 172, at least or exactly or at most 173, at least or exactly or at most 174, at least or exactly or at most 175, at least or exactly or at most 176, at least or exactly or at most 177, or at least or exactly or at most 178 contiguous amino acid residues.

[0073] Insofar as embodiment b relates to SEQ ID NOs: 6-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 179, at least or exactly or at most 180, at least or exactly or at most 181,

at least or exactly or at most 182, at least or exactly or at most 183, at least or exactly or at most 184, at least or exactly or at most 185, at least or exactly or at most 186, at least or exactly or at most 187, at least or exactly or at most 188, at least or exactly or at most 189, at least or exactly or at most 190, at least or exactly or at most 191, at least or exactly or at most 192, at least or exactly or at most 193, at least or exactly or at most 194, at least or exactly or at most 195, at least or exactly or at most 196, at least or exactly or at most 197, at least or exactly or at most 198, at least or exactly or at most 199, at least or exactly or at most 200, at least or exactly or at most 201, at least or exactly or at most 202, at least or exactly or at most 203, at least or exactly or at most 204, at least or exactly or at most 205, at least or exactly or at most 206, at least or exactly or at most 207, at least or exactly or at most 208, at least or exactly or at most 209, at least or exactly or at most 210, at least or exactly or at most 211, at least or exactly or at most 212, at least or exactly or at most 213, at least or exactly or at most 214, at least or exactly or at most 215, at least or exactly or at most 216, at least or exactly or at most 217, at least or exactly or at most 218, at least or exactly or at most 219, at least or exactly or at most 220, at least or exactly or at most 221, at least or exactly or at most 222, at least or exactly or at most 223, at least or exactly or at most 224, at least or exactly or at most 225, at least or exactly or at most 226, at least or exactly or at most 227, at least or exactly or at most 228, at least or exactly or at most 229, at least or exactly or at most 230, at least or exactly or at most 231, at least or exactly or at most 232, at least or exactly or at most 233, at least or exactly or at most 234, at least or exactly or at most 235, at least or exactly or at most 236, at least or exactly or at most 237, at least or exactly or at most 238, at least or exactly or at most 239, at least or exactly or at most 240, at least or exactly or at most 241, at least or exactly or at most 242, at least or exactly or at most 243, at least or exactly or at most 244, at least or exactly or at most 245, at least or exactly or at most 246, at least or exactly or at most 247, at least or exactly or at most 248, at least or exactly or at most 249, at least or exactly or at most 250, at least or exactly or at most 251, at least or exactly or at most 252, at least or exactly or at most 253, at least or exactly or at most 254, at least or exactly or at most 255, at least or exactly or at most 256, at least or exactly or at most 257, at least or exactly or at most 258, at least or exactly or at most 259, at least or exactly or at most 260, at least or exactly or at most 261, at least or exactly or at most 262, at least or exactly or at most 263, at least or exactly or at most 264, at least or exactly or at most 265, at least or exactly or at most 266, at least or exactly or at most 267, at least or exactly or at most 268, at least or exactly or at most 269, at least or exactly or at most 270, at least or exactly or at most 271, at least or exactly or at most 272, at least or exactly or at most 273, at least or exactly or at most 274, at least or exactly or at most 275, at least or exactly or at most 276, at least or exactly or at most 277, at least or exactly or at most 278, at least or exactly or at most 279, at least or exactly or at most 280, at least or exactly or at most 281, at least or exactly or at most 282, at least or exactly or at most 283, at least or exactly or at most 284, at least or exactly or at most 285, at least or exactly or at most 286, at least or exactly or at most 287, at least or exactly or at most 288, at least or exactly or at most 289, at least or exactly or at most 290, at least or exactly or at most 291, at least or exactly or at most 292, at least or exactly or at most

293, at least or exactly or at most 294, at least or exactly or at most 295, at least or exactly or at most 296, at least or exactly or at most 297, at least or exactly or at most 298, at least or exactly or at most 299, at least or exactly or at most 300, at least or exactly or at most 301, at least or exactly or at most 302, or at least or exactly or at most 303 contiguous amino acid residues.

[0074] Insofar as embodiment b relates to SEQ ID NOs: 7-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 304, at least or exactly or at most 305, at least or exactly or at most 306, at least or exactly or at most 307, or at least or exactly or at most 308 contiguous amino acid residues.

[0075] Insofar as embodiment b relates to SEQ ID NOs: 8-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 309, at least or exactly or at most 310, at least or exactly or at most 311, at least or exactly or at most 312, at least or exactly or at most 313, at least or exactly or at most 314, at least or exactly or at most 315, at least or exactly or at most 316, at least or exactly or at most 317, at least or exactly or at most 318, at least or exactly or at most 319, at least or exactly or at most 320, at least or exactly or at most 321, at least or exactly or at most 322, at least or exactly or at most 323, at least or exactly or at most 324, at least or exactly or at most 325, at least or exactly or at most 326, at least or exactly or at most 327, at least or exactly or at most 328, at least or exactly or at most 329, at least or exactly or at most 330, at least or exactly or at most 331, at least or exactly or at most 332, at least or exactly or at most 333, at least or exactly or at most 334, at least or exactly or at most 335, at least or exactly or at most 336, at least or exactly or at most 337, at least or exactly or at most 338, or at least or exactly or at most 339 contiguous amino acid residues.

[0076] Insofar as embodiment b relates to SEQ ID NOs: 9-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 340, at least or exactly or at most 341, at least or exactly or at most 342, at least or exactly or at most 343, at least or exactly or at most 344, at least or exactly or at most 345, or at least or exactly or at most 346 contiguous amino acid residues.

[0077] Insofar as embodiment b relates to SEQ ID NOs: 10-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 347, at least or exactly or at most 348, at least or exactly or at most 349, at least or exactly or at most 350, or at least or exactly or at most 351 contiguous amino acid residues.

[0078] Insofar as embodiment b relates to SEQ ID NOs: 11-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 352, at least or exactly or at most 354, at least or exactly or at most 354, at least or exactly or at most 356, at least or exactly or at most 357, at least or exactly or at most 359, at least or exactly or at most 359, at least or exactly or at most 360, at least or exactly or at most 361, at least or exactly or at most 362, at least or exactly or at most 363, at least or exactly or at most 364, at least or exactly or at most 365, at least or exactly or at most 366, at least or exactly or at most 366, at least or exactly or at most 367, at least or exactly or at most 366, at least or exactly or at most 367, at least or exactly or at most

368, at least or exactly or at most 369, at least or exactly or at most 370, at least or exactly or at most 371, at least or exactly or at most 372, at least or exactly or at most 373, at least or exactly or at most 374, at least or exactly or at most 375, at least or exactly or at most 376, at least or exactly or at most 377, at least or exactly or at most 378, at least or exactly or at most 379, at least or exactly or at most 380, at least or exactly or at most 381, at least or exactly or at most 382, at least or exactly or at most 383, at least or exactly or at most 384, at least or exactly or at most 385, at least or exactly or at most 386, at least or exactly or at most 387, at least or exactly or at most 388, at least or exactly or at most 389, at least or exactly or at most 390, at least or exactly or at most 391, at least or exactly or at most 392, at least or exactly or at most 393, at least or exactly or at most 394, at least or exactly or at most 395, at least or exactly or at most 396, at least or exactly or at most 397, at least or exactly or at most 398, at least or exactly or at most 399, at least or exactly or at most 400, at least or exactly or at most 401, at least or exactly or at most 402, at least or exactly or at most 403, at least or exactly or at most 404, at least or exactly or at most 405, at least or exactly or at most 406, at least or exactly or at most 407, at least or exactly or at most 408, at least or exactly or at most 409, at least or exactly or at most 410, at least or exactly or at most 411, at least or exactly or at most 412, at least or exactly or at most 413, at least or exactly or at most 414, at least or exactly or at most 415, at least or exactly or at most 416, at least or exactly or at most 417, at least or exactly or at most 418, or at least or exactly or at most 419 contiguous amino acid residues.

[0079] Insofar as embodiment b relates to SEQ ID NOs: 12-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 420, at least or exactly or at most 421, at least or exactly or at most 422, at least or exactly or at most 424, at least or exactly or at most 425, or at least or exactly or at most 426 contiguous amino acid residues.

[0080] Insofar as embodiment b relates to SEQ ID NOs: 13-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 427 contiguous amino acid residues.

[0081] Insofar as embodiment b relates to SEO ID NOs: 14-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 428, at least or exactly or at most 429, at least or exactly or at most 430, at least or exactly or at most 431, at least or exactly or at most 432, at least or exactly or at most 433, at least or exactly or at most 434, at least or exactly or at most 435, at least or exactly or at most 436, at least or exactly or at most 437, at least or exactly or at most 438, at least or exactly or at most 439, at least or exactly or at most 440, at least or exactly or at most 441, at least or exactly or at most 442, at least or exactly or at most 443, at least or exactly or at most 444, at least or exactly or at most 445, at least or exactly or at most 446, at least or exactly or at most 447, at least or exactly or at most 448, at least or exactly or at most 449, at least or exactly or at most 450, at least or exactly or at most 451, at least or exactly or at most 452, at least or exactly or at most 453, at least or exactly or at most 454, at least or exactly or at most 455, at least or exactly or at most 456, at least or exactly or at most 457, at least or exactly or at most

458, at least or exactly or at most 459, at least or exactly or at most 460, at least or exactly or at most 461, at least or exactly or at most 462, at least or exactly or at most 463, at least or exactly or at most 464, at least or exactly or at most 465, at least or exactly or at most 466, at least or exactly or at most 467, at least or exactly or at most 468, at least or exactly or at most 469, at least or exactly or at most 470, at least or exactly or at most 471, at least or exactly or at most 472, at least or exactly or at most 473, at least or exactly or at most 474, at least or exactly or at most 475, at least or exactly or at most 476, at least or exactly or at most 477, at least or exactly or at most 478, at least or exactly or at most 479, at least or exactly or at most 480, at least or exactly or at most 481, at least or exactly or at most 482, at least or exactly or at most 483, at least or exactly or at most 484, at least or exactly or at most 485, at least or exactly or at most 486, at least or exactly or at most 487, at least or exactly or at most 488, at least or exactly or at most 489, at least or exactly or at most 490, at least or exactly or at most 491, at least or exactly or at most 492, at least or exactly or at most 493, at least or exactly or at most 494, at least or exactly or at most 495, at least or exactly or at most 496, at least or exactly or at most 497, at least or exactly or at most 498, at least or exactly or at most 499, at least or exactly or at most 500, at least or exactly or at most 501, at least or exactly or at most 502, at least or exactly or at most 503, at least or exactly or at most 504, at least or exactly or at most 505, at least or exactly or at most 506, at least or exactly or at most 507, at least or exactly or at most 508, at least or exactly or at most 509, at least or exactly or at most 510, at least or exactly or at most 511, at least or exactly or at most 512, at least or exactly or at most 513, at least or exactly or at most 514, at least or exactly or at most 515, at least or exactly or at most 516, at least or exactly or at most 517, at least or exactly or at most 518, at least or exactly or at most 519, at least or exactly or at most 520, at least or exactly or at most 521, at least or exactly or at most 522, at least or exactly or at most 523, at least or exactly or at most 524, at least or exactly or at most 525, at least or exactly or at most 526, at least or exactly or at most 527, at least or exactly or at most 528, at least or exactly or at most 529, at least or exactly or at most 530, at least or exactly or at most 531, at least or exactly or at most 532, at least or exactly or at most 533, at least or exactly or at most 534, at least or exactly or at most 535, at least or exactly or at most 536, at least or exactly or at most 537, at least or exactly or at most 538, at least or exactly or at most 539, at least or exactly or at most 540, at least or exactly or at most 541, at least or exactly or at most 542, at least or exactly or at most 543, at least or exactly or at most 544, at least or exactly or at most 545, at least or exactly or at most 546, at least or exactly or at most 547, at least or exactly or at most 548, at least or exactly or at most 549, at least or exactly or at most 550, at least or exactly or at most 551, at least or exactly or at most 552, at least or exactly or at most 553, at least or exactly or at most 554, at least or exactly or at most 555, at least or exactly or at most 556, at least or exactly or at most 557, at least or exactly or at most 558, at least or exactly or at most 559, at least or exactly or at most 560, at least or exactly or at most 561, at least or exactly or at most 562, at least or exactly or at most 563, at least or exactly or at most 564, at least or exactly or at most 565, at least or exactly or at most 566, or at least or exactly or at most 567 contiguous amino acid residues.

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[0082] Insofar as embodiment b relates to SEQ ID NOs: 15-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 568, at least or exactly or at most 569, at least or exactly or at most 570, at least or exactly or at most 571, at least or exactly or at most 572, at least or exactly or at most 573, at least or exactly or at most 574, at least or exactly or at most 575, at least or exactly or at most 576, at least or exactly or at most 577, or at least or exactly or at most 578 contiguous amino acid residues.

[0083] Insofar as embodiment b relates to SEQ ID NOs: 16-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 579, at least or exactly or at most 580, at least or exactly or at most 581, at least or exactly or at most 582, at least or exactly or at most 583, at least or exactly or at most 584, at least or exactly or at most 585, at least or exactly or at most 586, at least or exactly or at most 587, at least or exactly or at most 588, at least or exactly or at most 589, at least or exactly or at most 590, at least or exactly or at most 591, at least or exactly or at most 592, at least or exactly or at most 593, at least or exactly or at most 594, at least or exactly or at most 595, at least or exactly or at most 596, at least or exactly or at most 597, at least or exactly or at most 598, at least or exactly or at most 599, at least or exactly or at most 600, at least or exactly or at most 601, at least or exactly or at most 602, at least or exactly or at most 603, at least or exactly or at most 604, at least or exactly or at most 605, at least or exactly or at most 606, at least or exactly or at most 607, at least or exactly or at most 608, at least or exactly or at most 609, at least or exactly or at most 610, at least or exactly or at most 611, at least or exactly or at most 612, at least or exactly or at most 613, at least or exactly or at most 614, at least or exactly or at most 615, at least or exactly or at most 616, at least or exactly or at most 617, at least or exactly or at most 618, at least or exactly or at most 619, or at least or exactly or at most 620 contiguous amino acid residues.

[0084] Insofar as embodiment b relates to SEQ ID NOs: 17-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 621, at least or exactly or at most 622, at least or exactly or at most 623, at least or exactly or at most 624, at least or exactly or at most 625, at least or exactly or at most 626, at least or exactly or at most 627, at least or exactly or at most 628, at least or exactly or at most 629, at least or exactly or at most 630, at least or exactly or at most 631, at least or exactly or at most 632, at least or exactly or at most 633, at least or exactly or at most 634, at least or exactly or at most 635, at least or exactly or at most 636, at least or exactly or at most 637, at least or exactly or at most 638, at least or exactly or at most 639, at least or exactly or at most 640, at least or exactly or at most 641, at least or exactly or at most 642, at least or exactly or at most 643, at least or exactly or at most 644, at least or exactly or at most 645, at least or exactly or at most 646, at least or exactly or at most 647, at least or exactly or at most 648, at least or exactly or at most 649, at least or exactly or at most 650, at least or exactly or at most 651, at least or exactly or at most 652, at least or exactly or at most 653, at least or exactly or at most 654, at least or exactly or at most 655, at least or exactly or at most 656, at least or exactly or at most 657, at least or exactly or at most 658, at least or exactly or at most 659, at least or exactly or at most 660, at least or exactly or at most 661, at least or exactly or at most 662, at least or exactly or at most 663, at least or exactly or at most 664, at least or exactly or at most 665, at least or exactly or at most 666, at least or exactly or at most 667, at least or exactly or at most 668, at least or exactly or at most 669, at least or exactly or at most 670, at least or exactly or at most 671, at least or exactly or at most 672, at least or exactly or at most 673, at least or exactly or at most 674, at least or exactly or at most 675, at least or exactly or at most 676, at least or exactly or at most 677, at least or exactly or at most 678, at least or exactly or at most 679, at least or exactly or at most 680, at least or exactly or at most 681, at least or exactly or at most 682, at least or exactly or at most 683, at least or exactly or at most 684, at least or exactly or at most 685, at least or exactly or at most 686, or at least or exactly or at most 687 contiguous amino acid residues.

[0085] Insofar as embodiment b relates to SEQ ID NOs: 18-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 688, at least or exactly or at most 689, at least or exactly or at most 690, at least or exactly or at most 691, at least or exactly or at most 692, at least or exactly or at most 693, at least or exactly or at most 694, at least or exactly or at most 695, at least or exactly or at most 696, at least or exactly or at most 697, at least or exactly or at most 698, at least or exactly or at most 699, at least or exactly or at most 700, at least or exactly or at most 701, at least or exactly or at most 702, at least or exactly or at most 703, at least or exactly or at most 704, at least or exactly or at most 705, at least or exactly or at most 706, at least or exactly or at most 707, at least or exactly or at most 708, at least or exactly or at most 709, at least or exactly or at most 710, at least or exactly or at most 711, at least or exactly or at most 712, at least or exactly or at most 713, at least or exactly or at most 714, at least or exactly or at most 715, at least or exactly or at most 716, at least or exactly or at most 717, at least or exactly or at most 718, at least or exactly or at most 719, at least or exactly or at most 720, at least or exactly or at most 721, at least or exactly or at most 722, at least or exactly or at most 723, at least or exactly or at most 724, at least or exactly or at most 725, at least or exactly or at most 726, at least or exactly or at most 727, at least or exactly or at most 728, at least or exactly or at most 729, at least or exactly or at most 730, at least or exactly or at most 731, at least or exactly or at most 732, at least or exactly or at most 733, at least or exactly or at most 734, at least or exactly or at most 735, at least or exactly or at most 736, at least or exactly or at most 737, at least or exactly or at most 738, at least or exactly or at most 739, at least or exactly or at most 740, or at least or exactly or at most 741 contiguous amino acid residues.

[0086] Insofar as embodiment b relates to SEQ ID NOs: 19-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 742, at least or exactly or at most 743, at least or exactly or at most 744, or at least or exactly or at most 745 contiguous amino acid residues.

[0087] Insofar as embodiment b relates to SEQ ID NOs: 20-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 746, at least

or exactly or at most 747, at least or exactly or at most 748, at least or exactly or at most 749, at least or exactly or at most 750, at least or exactly or at most 751, at least or exactly or at most 752, at least or exactly or at most 753, at least or exactly or at most 754, at least or exactly or at most 755, at least or exactly or at most 756, at least or exactly or at most 757, at least or exactly or at most 758, at least or exactly or at most 759, at least or exactly or at most 760, at least or exactly or at most 761, at least or exactly or at most 762, at least or exactly or at most 763, at least or exactly or at most 764, at least or exactly or at most 765, at least or exactly or at most 766, at least or exactly or at most 767, at least or exactly or at most 768, at least or exactly or at most 769, at least or exactly or at most 770, at least or exactly or at most 771, at least or exactly or at most 772, at least or exactly or at most 773, at least or exactly or at most 774, at least or exactly or at most 775, at least or exactly or at most 776, at least or exactly or at most 777, at least or exactly or at most 778, at least or exactly or at most 779, at least or exactly or at most 780, at least or exactly or at most 781, at least or exactly or at most 782, or at least or exactly or at most 783 contiguous amino acid residues.

[0088] Insofar as embodiment b relates to SEQ ID NOs: 21-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 784, at least or exactly or at most 785, at least or exactly or at most 786, at least or exactly or at most 787, at least or exactly or at most 788, at least or exactly or at most 789, at least or exactly or at most 790, at least or exactly or at most 791, at least or exactly or at most 792, at least or exactly or at most 793, at least or exactly or at most 794, at least or exactly or at most 795, at least or exactly or at most 796, at least or exactly or at most 797, at least or exactly or at most 798, at least or exactly or at most 799, at least or exactly or at most 800, at least or exactly or at most 801, at least or exactly or at most 802, at least or exactly or at most 803, at least or exactly or at most 804, at least or exactly or at most 805, at least or exactly or at most 806, at least or exactly or at most 807, at least or exactly or at most 808, at least or exactly or at most 809, at least or exactly or at most 810, at least or exactly or at most 811, at least or exactly or at most 812, at least or exactly or at most 813, at least or exactly or at most 814, at least or exactly or at most 815, at least or exactly or at most 816, at least or exactly or at most 817, at least or exactly or at most 818, at least or exactly or at most 819, at least or exactly or at most 820, at least or exactly or at most 821, at least or exactly or at most 822, at least or exactly or at most 823, at least or exactly or at most 824, at least or exactly or at most 825, at least or exactly or at most 826, at least or exactly or at most 827, at least or exactly or at most 828, at least or exactly or at most 829, at least or exactly or at most 830, at least or exactly or at most 831, at least or exactly or at most 832, at least or exactly or at most 833, at least or exactly or at most 834, at least or exactly or at most 835, at least or exactly or at most 836, at least or exactly or at most 837, at least or exactly or at most 838, at least or exactly or at most 839, at least or exactly or at most 840, at least or exactly or at most 841, at least or exactly or at most 842, at least or exactly or at most 843, at least or exactly or at most 844, at least or exactly or at most 845, at least or exactly or at most 846, at least or exactly or at most 847, at least or exactly or at most 848, at least or exactly or at most 849, or at least or exactly or at most 850 contiguous amino acid residues.

[0089] Insofar as embodiment b relates to SEQ ID NOs: 22-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 851, at least or exactly or at most 852, at least or exactly or at most 853, at least or exactly or at most 854, at least or exactly or at most 855, at least or exactly or at most 856, at least or exactly or at most 857, at least or exactly or at most 858, at least or exactly or at most 859, at least or exactly or at most 860, at least or exactly or at most 861, at least or exactly or at most 862, at least or exactly or at most 863, at least or exactly or at most 864, at least or exactly or at most 865, at least or exactly or at most 866, at least or exactly or at most 867, at least or exactly or at most 868, at least or exactly or at most 869, at least or exactly or at most 870, at least or exactly or at most 871, at least or exactly or at most 872, at least or exactly or at most 873, at least or exactly or at most 874, at least or exactly or at most 875, at least or exactly or at most 876, at least or exactly or at most 877, at least or exactly or at most 878, or at least or exactly or at most 879 contiguous amino acid residues.

[0090] Insofar as embodiment b relates to SEQ ID NOs: 23-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 880, at least or exactly or at most 881, at least or exactly or at most 882, at least or exactly or at most 883, at least or exactly or at most 884, at least or exactly or at most 885, at least or exactly or at most 886, at least or exactly or at most 887, at least or exactly or at most 888, at least or exactly or at most 889, at least or exactly or at most 890, at least or exactly or at most 891, at least or exactly or at most 892, at least or exactly or at most 893, at least or exactly or at most 894, at least or exactly or at most 895, at least or exactly or at most 896, at least or exactly or at most 897, at least or exactly or at most 898, at least or exactly or at most 899, at least or exactly or at most 900, at least or exactly or at most 901, at least or exactly or at most 902, at least or exactly or at most 903, at least or exactly or at most 904, at least or exactly or at most 905, at least or exactly or at most 906, at least or exactly or at most 907, at least or exactly or at most 908, at least or exactly or at most 909, at least or exactly or at most 910, at least or exactly or at most 911, at least or exactly or at most 912, at least or exactly or at most 913, at least or exactly or at most 914, at least or exactly or at most 915, at least or exactly or at most 916, at least or exactly or at most 917, or at least or exactly or at most 918 contiguous amino acid residues.

[0091] Insofar as embodiment b relates to SEQ ID NOs: 24-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 919, at least or exactly or at most 920, at least or exactly or at most 921, at least or exactly or at most 923, at least or exactly or at most 924, at least or exactly or at most 925, at least or exactly or at most 926, at least or exactly or at most 927, at least or exactly or at most 928, at least or exactly or at most 929, at least or exactly or at most 930, at least or exactly or at most 931, at least or exactly or at most 932, at least or exactly or at most 933, at least or exactly or at most 934, at least or exactly or at most

935, at least or exactly or at most 936, at least or exactly or at most 937, at least or exactly or at most 938, at least or exactly or at most 939, at least or exactly or at most 940, at least or exactly or at most 941, at least or exactly or at most 942, at least or exactly or at most 943, at least or exactly or at most 944, at least or exactly or at most 945, at least or exactly or at most 946, at least or exactly or at most 947, at least or exactly or at most 948, at least or exactly or at most 949, at least or exactly or at most 950, at least or exactly or at most 951, at least or exactly or at most 952, at least or exactly or at most 953, at least or exactly or at most 954, at least or exactly or at most 955, at least or exactly or at most 956, at least or exactly or at most 957, at least or exactly or at most 958, at least or exactly or at most 959, at least or exactly or at most 960, at least or exactly or at most 961, at least or exactly or at most 962, at least or exactly or at most 963, at least or exactly or at most 964, at least or exactly or at most 965, at least or exactly or at most 966, at least or exactly or at most 967, at least or exactly or at most 968, at least or exactly or at most 969, at least or exactly or at most 970, at least or exactly or at most 971, at least or exactly or at most 972, at least or exactly or at most 973, at least or exactly or at most 974, at least or exactly or at most 975, at least or exactly or at most 976, at least or exactly or at most 977, at least or exactly or at most 978, at least or exactly or at most 979, at least or exactly or at most 980, at least or exactly or at most 981, at least or exactly or at most 982, at least or exactly or at most 983, at least or exactly or at most 984, at least or exactly or at most 985, at least or exactly or at most 986, at least or exactly or at most 987, at least or exactly or at most 988, at least or exactly or at most 989, at least or exactly or at most 990, at least or exactly or at most 991, at least or exactly or at most 992, at least or exactly or at most 993, or at least or exactly or at most 994 contiguous amino acid residues.

[0092] Insofar as embodiment b relates to SEQ ID NOs: 25-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 995, at least or exactly or at most 996, at least or exactly or at most 997, at least or exactly or at most 998, at least or exactly or at most 999, at least or exactly or at most 1000, at least or exactly or at most 1001, at least or exactly or at most 1002, at least or exactly or at most 1003, at least or exactly or at most 1004, at least or exactly or at most 1005, at least or exactly or at most 1006, at least or exactly or at most 1007, at least or exactly or at most 1008, at least or exactly or at most 1009, at least or exactly or at most 1010, at least or exactly or at most 1011, at least or exactly or at most 1012, at least or exactly or at most 1013, at least or exactly or at most 1014, at least or exactly or at most 1015, at least or exactly or at most 1016, at least or exactly or at most 1017, at least or exactly or at most 1018, at least or exactly or at most 1019, at least or exactly or at most 1020, at least or exactly or at most 1021, at least or exactly or at most 1022, at least or exactly or at most 1023, at least or exactly or at most 1024, at least or exactly or at most 1025, at least or exactly or at most 1026, at least or exactly or at most 1027, at least or exactly or at most 1028, at least or exactly or at most 1029, at least or exactly or at most 1030, at least or exactly or at most 1031, at least or exactly or at most 1032, at least or exactly or at most 1033, at least or exactly or at most 1034, at least or exactly or at most 1035, at least or exactly or at most 1036, at least or exactly or at most 1037,

at least or exactly or at most 1038, at least or exactly or at most 1039, at least or exactly or at most 1040, at least or exactly or at most 1041, at least or exactly or at most 1042, at least or exactly or at most 1043, at least or exactly or at most 1044, at least or exactly or at most 1045, at least or exactly or at most 1046, at least or exactly or at most 1047, at least or exactly or at most 1048, at least or exactly or at most 1049, at least or exactly or at most 1050, at least or exactly or at most 1051, at least or exactly or at most 1052, at least or exactly or at most 1054, at least or exactly or at most 1054, at least or exactly or at most 1055, or at least or exactly or at most 1056 contiguous amino acid residues.

[0093] Insofar as embodiment b relates to SEQ ID NOs: 26-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 1057, at least or exactly or at most 1058, at least or exactly or at most 1059, at least or exactly or at most 1060, at least or exactly or at most 1061, at least or exactly or at most 1062, at least or exactly or at most 1063, at least or exactly or at most 1064, at least or exactly or at most 1065, at least or exactly or at most 1066, at least or exactly or at most 1067, at least or exactly or at most 1068, at least or exactly or at most 1069, at least or exactly or at most 1070, at least or exactly or at most 1071, at least or exactly or at most 1072, at least or exactly or at most 1073, at least or exactly or at most 1074, at least or exactly or at most 1075, at least or exactly or at most 1076, at least or exactly or at most 1077, at least or exactly or at most 1078, at least or exactly or at most 1079, at least or exactly or at most 1080, at least or exactly or at most 1081, at least or exactly or at most 1082, at least or exactly or at most 1083, at least or exactly or at most 1084, at least or exactly or at most 1085, at least or exactly or at most 1086, at least or exactly or at most 1087, at least or exactly or at most 1088, at least or exactly or at most 1089, at least or exactly or at most 1090, at least or exactly or at most 1091, at least or exactly or at most 1092, at least or exactly or at most 1093, at least or exactly or at most 1094, at least or exactly or at most 1095, at least or exactly or at most 1096, at least or exactly or at most 1097, at least or exactly or at most 1098, at least or exactly or at most 1099, at least or exactly or at most 1100, at least or exactly or at most 1101, at least or exactly or at most 1102, at least or exactly or at most 1103, at least or exactly or at most 1104, at least or exactly or at most 1105, at least or exactly or at most 1106, at least or exactly or at most 1107, at least or exactly or at most 1108, at least or exactly or at most 1109, at least or exactly or at most 1110, at least or exactly or at most 1111, at least or exactly or at most 1112, at least or exactly or at most 1113, at least or exactly or at most 1114, at least or exactly or at most 1115, at least or exactly or at most 1116, at least or exactly or at most 1117, at least or exactly or at most 1118, at least or exactly or at most 1119, at least or exactly or at most 1120, at least or exactly or at most 1121, at least or exactly or at most 1122, at least or exactly or at most 1123, at least or exactly or at most 1124, at least or exactly or at most 1125, at least or exactly or at most 1126, at least or exactly or at most 1127, at least or exactly or at most 1128, at least or exactly or at most 1129, at least or exactly or at most 1130, at least or exactly or at most 1131, at least or exactly or at most 1132, at least or exactly or at most 1133, at least or exactly or at most 1134, at least or exactly or at most 1135, at least or exactly or at most 1136, at least or exactly or at most 1137, at least or

exactly or at most 1138, at least or exactly or at most 1139, at least or exactly or at most 1140, at least or exactly or at most 1141, at least or exactly or at most 1142, at least or exactly or at most 1143, at least or exactly or at most 1144, at least or exactly or at most 1144, at least or exactly or at most 1146, at least or exactly or at most 1147, at least or exactly or at most 1148, at least or exactly or at most 1149, at least or exactly or at most 1150, at least or exactly or at most 1151, at least or exactly or at most 1152, at least or exactly or at most 1153, at least or exactly or at most 1154, at least or exactly or at most 1155, at least or exactly or at most 1155, at least or exactly or at most 1155, at least or exactly or at most 1159, or at least or exactly or at most 1159, or at least or exactly or at most 1159, or at least or exactly or at most 1159, or at least or exactly or at most 1159, or at least or exactly or at most 1159, or at least or exactly or at most 1159, or at least or exactly or at most 1159, or at least or exactly or at most 1159, or at least or exactly or at most 1150 contiguous amino acid residues.

[0094] Insofar as embodiment b relates to SEQ ID NOs: 27-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 1161, at least or exactly or at most 1162, at least or exactly or at most 1163, at least or exactly or at most 1164, at least or exactly or at most 1165, at least or exactly or at most 1166, at least or exactly or at most 1167, at least or exactly or at most 1168, at least or exactly or at most 1169, at least or exactly or at most 1170, at least or exactly or at most 1171, at least or exactly or at most 1172, at least or exactly or at most 1173, at least or exactly or at most 1174, at least or exactly or at most 1175, at least or exactly or at most 1176, at least or exactly or at most 1177, at least or exactly or at most 1178, at least or exactly or at most 1179, at least or exactly or at most 1180, at least or exactly or at most 1181, at least or exactly or at most 1182, at least or exactly or at most 1183, at least or exactly or at most 1184, at least or exactly or at most 1185, at least or exactly or at most 1186, at least or exactly or at most 1187, at least or exactly or at most 1188, at least or exactly or at most 1189, at least or exactly or at most 1190, at least or exactly or at most 1191, at least or exactly or at most 1192, at least or exactly or at most 1193, at least or exactly or at most 1194, at least or exactly or at most 1195, at least or exactly or at most 1196, at least or exactly or at most 1197, at least or exactly or at most 1198, at least or exactly or at most 1199, at least or exactly or at most 1200, at least or exactly or at most 1201, at least or exactly or at most 1202, at least or exactly or at most 1203, at least or exactly or at most 1204, at least or exactly or at most 1205, at least or exactly or at most 1206, at least or exactly or at most 1207, at least or exactly or at most 1208, at least or exactly or at most 1209, or at least or exactly or at most 1210 contiguous amino acid residues.

[0095] Insofar as embodiment b relates to SEQ ID NOs: 28-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 1211, at least or exactly or at most 1212, at least or exactly or at most 1213, at least or exactly or at most 1214, at least or exactly or at most 1215, at least or exactly or at most 1216, at least or exactly or at most 1218, at least or exactly or at most 1219, at least or exactly or at most 1220, at least or exactly or at most 1221, at least or exactly or at most 1221, at least or exactly or at most 1222, at least or exactly or at most 1223, at least or exactly or at most 1224, at least or exactly or at most 1225, at least or exactly or at most 1226, at least or exactly or at most 1227, at least or exactly or at most 1228, at least or exactly or at most 1229, at least or exactly or exactly or exactly or at most 1229, at least or exactly or at most 1229, at least or exactly or at most 1229, at least or exactly

or at most 1230, at least or exactly or at most 1231, at least or exactly or at most 1232, at least or exactly or at most 1233, at least or exactly or at most 1234, at least or exactly or at most 1235, at least or exactly or at most 1236, at least or exactly or at most 1237, at least or exactly or at most 1238, at least or exactly or at most 1239, at least or exactly or at most 1240, at least or exactly or at most 1241, at least or exactly or at most 1242, at least or exactly or at most 1243, at least or exactly or at most 1244, at least or exactly or at most 1245, at least or exactly or at most 1246, at least or exactly or at most 1247, at least or exactly or at most 1248, at least or exactly or at most 1249, at least or exactly or at most 1250, at least or exactly or at most 1251, at least or exactly or at most 1252, at least or exactly or at most 1253, at least or exactly or at most 1254, at least or exactly or at most 1255, at least or exactly or at most 1256, at least or exactly or at most 1257, at least or exactly or at most 1258, at least or exactly or at most 1259, at least or exactly or at most 1260, at least or exactly or at most 1261, at least or exactly or at most 1262, at least or exactly or at most 1263, at least or exactly or at most 1264, at least or exactly or at most 1265, at least or exactly or at most 1266, at least or exactly or at most 1267, at least or exactly or at most 1268, at least or exactly or at most 1269, at least or exactly or at most 1270, at least or exactly or at most 1271, at least or exactly or at most 1272, at least or exactly or at most 1273, at least or exactly or at most 1274, at least or exactly or at most 1275, at least or exactly or at most 1276, at least or exactly or at most 1277, at least or exactly or at most 1278, at least or exactly or at most 1279, at least or exactly or at most 1280, at least or exactly or at most 1281, at least or exactly or at most 1282, at least or exactly or at most 1283, at least or exactly or at most 1284, at least or exactly or at most 1285, at least or exactly or at most 1286, at least or exactly or at most 1287, at least or exactly or at most 1288, at least or exactly or at most 1289, at least or exactly or at most 1290, at least or exactly or at most 1291, at least or exactly or at most 1292, at least or exactly or at most 1293, at least or exactly or at most 1294, at least or exactly or at most 1295, at least or exactly or at most 1296, at least or exactly or at most 1297, at least or exactly or at most 1298, at least or exactly or at most 1299, at least or exactly or at most 1300, at least or exactly or at most 1301, at least or exactly or at most 1302, at least or exactly or at most 1303, at least or exactly or at most 1304, at least or exactly or at most 1305, at least or exactly or at most 1306, at least or exactly or at most 1307, at least or exactly or at most 1308, at least or exactly or at most 1309, at least or exactly or at most 1310, at least or exactly or at most 1311, at least or exactly or at most 1312, at least or exactly or at most 1313, at least or exactly or at most 1314, at least or exactly or at most 1315, at least or exactly or at most 1316, at least or exactly or at most 1317, at least or exactly or at most 1318, at least or exactly or at most 1319, at least or exactly or at most 1320, at least or exactly or at most 1321, at least or exactly or at most 1322, at least or exactly or at most 1323, at least or exactly or at most 1324, at least or exactly or at most 1325, at least or exactly or at most 1326, at least or exactly or at most 1327, at least or exactly or at most 1328, at least or exactly or at most 1329, at least or exactly or at most 1330, at least or exactly or at most 1331, at least or exactly or at most 1332, at least or exactly or at most 1333, at least or exactly or at most 1334, at least or exactly or at most 1335, at least or exactly or at most 1336, at least

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[0096] Insofar as embodiment b relates to SEQ ID NOs: 29-30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 2468, at least or exactly or at most 2469, at least or exactly or at most 2470, at least or exactly or at most 2471, at least or exactly or at most 2472, at least or exactly or at most 2473, at least or exactly or at most 2474, at least or exactly or at most 2475, at least or exactly or at most 2476, at least or exactly or at most 2477, at least or exactly or at most 2478, at least or exactly or at most 2479, at least or exactly or at most 2480, at least or exactly or at most 2481, at least or exactly or at most 2482, at least or exactly or at most 2483, at least or exactly or at most 2484, at least or exactly or at most 2485, at least or exactly or at most 2486, at least or exactly or at most 2487, at least or exactly or at most 2488, at least or exactly or 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[0097] Insofar as embodiment b relates to SEQ ID NO: 30, the at least 5 contiguous amino acids referred to in option b) in the definition of the first aspect of the invention may also constitute at least or exactly or at most 3535, at least or exactly or at most 3536, at least or exactly or at most 3537, at least or exactly or at most 3538, at least or exactly or at most 3540, at least or exactly or at most 3540, at least or exactly or at most 3541, at least or exactly or at most 3542, at least or exactly or at most 3544, at least or exactly or at most 3545, at least or exactly or at most 3546, at least or exactly or at most 3547, at least or exactly or at most 3548, at least or exactly or at most 3549, at least or exactly or at most 3549, at least or exactly or at most 3540, a

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at least or exactly or at most 5578, at least or exactly or at most 5579, at least or exactly or at most 5580, at least or exactly or at most 5581, at least or exactly or at most 5582, at least or exactly or at most 5583, at least or exactly or at most 5584, at least or exactly or at most 5585, at least or exactly or at most 5586, at least or exactly or at most 5587, at least or exactly or at most 5588, at least or exactly or at most 5589, at least or exactly or at most 5590, at least or exactly or at most 5591, at least or exactly or at most 5592, at least or exactly or at most 5593, at least or exactly or at most 5594, at least or exactly or at most 5595, at least or exactly or at most 5596, at least or exactly or at most 5597, at least or exactly or at most 5598, at least or exactly or at most 5599, at least or exactly or at most 5600, at least or exactly or at most 5601, at least or exactly or at most 5602, at least or exactly or at most 5603, at least or exactly or at most 5604, at least or exactly or at most 5605, at least or exactly or at most 5606, at least or exactly or at most 5607, at least or exactly or at most 5608, at least or exactly or at most 5609, at least or exactly or at most 5610, at least or exactly or at most 5611, at least or exactly or at most 5612, at least or exactly or at most 5613, at least or exactly or at most 5614, at least or exactly or at most 5615, at least or exactly or at most 5616, at least or exactly or at most 5617, at least or exactly or at most 5618, at least or exactly or at most 5619, at least or exactly or at most 5620, at least or exactly or at most 5621, at least or exactly or at most 5622, at least or exactly or at most 5623, at least or exactly or at most 5624, at least or exactly or at most 5625, or at least or exactly or at most 5626 contiguous amino acid residues.

[0098] 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%.

[0099] 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, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60 and 62 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.

**[0100]** 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 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73 and 74 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.

[0101] 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 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 and 100 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.

[0102] 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 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150 and 151 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.

[0103] 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 152, 153, 154, 155, 156, 157, 158, 159, 160, 171, 172, 173, 174 and 175 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.

[0104] 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 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227,  $228,\,229,\,230,\,231,\,232,\,233,\,234,\,235,\,236,\,237,\,238,\,239,\\$ 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 271, 272, 273, 274, 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 and 300 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.

[0105] 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 301, 302, 303, 304 and 305 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.

[0106] 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 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 and 336 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.

[0107] 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 337, 338, 339, 340, 341, 342 and 343 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.

[0108] 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 344, 345, 346, 347 and 348 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.

[0109] 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 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, 386, 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 and 416 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.

[0110] 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 417, 418, 419, 420, 421, 422 and 423 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.

[0111] 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 amino acid residue 424 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.

[0112] 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 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, 538, 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 and 564 in 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.

[0113] 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 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574 and 575 in 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  $\boldsymbol{L}$  is the number of amino acids defined for option b.

[0114] 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 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, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616 and 617 in 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.

[0115] 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 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, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683 and 684 in 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.

[0116] 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 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 and 738 in 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.

[0117] 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 739, 740, 741, and 742 in 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.

[0118] 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 743, 744, 745, 746, 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 and 780 in 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.

[0119] 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 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 and 847 in 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.

[0120] 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 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875 and 876 in 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.

[0121] 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 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 and 915 in 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 acids defined for option b.

[0122] 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 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, 942, 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 and 991 in 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.

[0123] 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 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, 1037, 1038, 1039, 1040, 1041, 1042, 1043, 1044, 1045, 1046, 1047, 1048, 1049, 1050, 1051, 1052 and 1053 in 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.

[0124] 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 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, 1085, 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, 1116, 1117, 1118, 1119, 1120, 1121, 1122, 1123, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, and 1157 in 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.

[0125] 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 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1170, 1171, 1172, 1173, 1174, 1175, 1176, 1177, 1178, 1179, 1180, 1181, 1182, 1183, 1184, 1185, 1186, 1187, 1188, 1189, 1190, 1191, 1192, 1193, 1194, 1195, 1196, 1197, 1198, 1199, 1200, 1201, 1202, 1203, 1204, 1205, 1206, and 1207 in 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.

[0126] 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 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, 1374, 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, 1492, 1493, 1494, 1495, 1496, 1497, 1498, 1499, 1500, 1501, 1502, 1503, 1504, 1505, 1506, 1507, 1508, 1509, 1510, 1511, 1512, 1513, 1514, 1515, 1516, 1517, 1518, 1519, 1520, 1521, 1522, 1523, 1524, 1525, 1526, 1527, 1528, 1529, 1530, 1531, 1532, 1533, 1534, 1535, 1536, 1537, 1538, 1539, 1540, 1541, 1542, 1543, 1544, 1545, 1546, 1547, 1548, 1549, 1550, 1551, 1552, 1553, 1554, 1555, 1556, 1557, 1558, 1559, 1560, 1561, 1562, 1563, 1564, 1565, 1566, 1567, 1568, 1569, 1570, 1571, 1572, 1573, 1574, 1575, 1576, 1577, 1578, 1579, 1580, 1581, 1582, 1583, 1584, 1585, 1586, 1587, 1588, 1589, 1590, 1591, 1592, 1593, 1594, 1595, 1596, 1597, 1598, 1599, 1600, 1601, 1602, 1603, 1604, 1605, 1606, 1607, 1608, 1609, 1610, 1611, 1612, 1613, 1614, 1615, 1616, 1617, 1618, 1619, 1620, 1621, 1622, 1623, 1624, 1625, 1626, 1627, 1628, 1629, 1630, 1631, 1632, 1633, 1634, 1635, 1636, 1637, 1638, 1639, 1640, 1641, 1642, 1643, 1644, 1645, 1646, 1647, 1648, 1649, 1650, 1651, 1652, 1653, 1654, 1655, 1656, 1657, 1658, 1659, 1660, 1661, 1662, 1663, 1664, 1665, 1666, 1667, 1668, 1669, 1670, 1671, 1672, 1673, 1674, 1675, 1676, 1677, 1678, 1679, 1680, 1681, 1682, 1683, 1684, 1685, 1686, 1687, 1688, 1689, 1690, 1691, 1692, 1693, 1694, 1695, 1696, 1697, 1698, 1699, 1700, 1701, 1702, 1703, 1704, 1705, 1706, 1707, 1708, 1709, 1710, 1711, 1712, 1713, 1714, 1715, 1716, 1717, 1718, 1719, 1720, 1721, 1722, 1723, 1724, 1725, 1726, 1727, 1728, 1729, 1730, 1731, 1732, 1733, 1734, 1735, 1736, 1737, 1738, 1739, 1740, 1741,

1742, 1743, 1744, 1745, 1746, 1747, 1748, 1749, 1750, 2338, 2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 1751, 1752, 1753, 1754, 1755, 1756, 1757, 1758, 1759, 2347, 2348, 2349, 2350, 2351, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2360, 2361, 2362, 2363, 2364, 1760, 1761, 1762, 1763, 1764, 1765, 1766, 1767, 1768, 2365, 2366, 2367, 2368, 2369, 2370, 2371, 2372, 2373, 1769, 1770, 1771, 1772, 1773, 1774, 1775, 1776, 1777, 1778, 1779, 1780, 1781, 1782, 1783, 1784, 1785, 1786, 2374, 2375, 2376, 2377, 2378, 2379, 2380, 2381, 2382, 2383, 2384, 2385, 2386, 2387, 2388, 2389, 2390, 2391, 1787, 1788, 1789, 1790, 1791, 1792, 1793, 1794, 1795, 2392, 2393, 2394, 2395, 2396, 2397, 2398, 2399, 2400, 1796, 1797, 1798, 1799, 1800, 1801, 1802, 1803, 1804, 2401, 2402, 2403, 2404, 2405, 2406, 2407, 2408, 2409, 1805, 1806, 1807, 1808, 1809, 1810, 1811, 1812, 1813, 2410, 2411, 2412, 2413, 2414, 2415, 2416, 2417, 2418, 1814, 1815, 1816, 1817, 1818, 1819, 1820, 1821, 1822, 2419, 2420, 2421, 2422, 2423, 2424, 2425, 2426, 2427, 1823, 1824, 1825, 1826, 1827, 1828, 1829, 1830, 1831, 2428, 2429, 2430, 2431, 2432, 2433, 2434, 2435, 2436, 1832, 1833, 1834, 1835, 1836, 1837, 1838, 1839, 1840, 2437, 2438, 2439, 2440, 2441, 2442, 2443, 2444, 2445, 1841, 1842, 1843, 1844, 1845, 1846, 1847, 1848, 1849, 2446, 2447, 2448, 2449, 2450, 2451, 2452, 2453, 2454, 1850, 1851, 1852, 1853, 1854, 1855, 1856, 1857, 1858, 2455, 2456, 2457, 2458, 2459, 2460, 2461, 2462, 2463 and 1859, 1860, 1861, 1862, 1863, 1864, 1865, 1866, 1867, 2464 in SEQ ID NOs: 28-30, if the length of the at least 5 1868, 1869, 1870, 1871, 1872, 1873, 1874, 1875, 1876, amino acid residues so permit—if the length of the at least 1877, 1878, 1879, 1880, 1881, 1882, 1883, 1884, 1885, 5 amino acids are higher than 5, the N-terminal first residue 1886, 1887, 1888, 1889, 1890, 1891, 1892, 1893, 1894, will not be higher numbered than N-L+1, where N is the 1895, 1896, 1897, 1898, 1899, 1900, 1901, 1902, 1903, number of amino acid residues of the reference sequence 1904, 1905, 1906, 1907, 1908, 1909, 1910, 1911, 1912, and L is the number of amino acids defined for option b. 1913, 1914, 1915, 1916, 1917, 1918, 1919, 1920, 1921, 1922, 1923, 1924, 1925, 1926, 1927, 1928, 1929, 1930, [0127] In the embodiments defined by option b) above, the 1931, 1932, 1933, 1934, 1935, 1936, 1937, 1938, 1939, polypeptide of the invention is also one that has at least 5 1940, 1941, 1942, 1943, 1944, 1945, 1946, 1947, 1948, contiguous amino acid residues defined for option b) above 1949, 1950, 1951, 1952, 1953, 1954, 1955, 1956, 1957, and also has its N-terminal amino acid residue correspond-1958, 1959, 1960, 1961, 1962, 1963, 1964, 1965, 1966, ing to any one of amino acid residues 2465, 2466, 2467, 1967, 1968, 1969, 1970, 1971, 1972, 1973, 1974, 1975, 2468, 2469, 2470, 2471, 2472, 2473, 2474, 2475, 2476, 1976, 1977, 1978, 1979, 1980, 1981, 1982, 1983, 1984, 2477, 2478, 2479, 2480, 2481, 2482, 2483, 2484, 2485, 1985, 1986, 1987, 1988, 1989, 1990, 1991, 1992, 1993, 2486, 2487, 2488, 2489, 2490, 2491, 2492, 2493, 2494, 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2495, 2496, 2497, 2498, 2499, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2513, 2514, 2515, 2516, 2517, 2518, 2519, 2520, 2521, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2522, 2523, 2524, 2525, 2526, 2527, 2528, 2529, 2530, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2531, 2532, 2533, 2534, 2535, 2536, 2537, 2538, 2539, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2540, 2541, 2542, 2543, 2544, 2545, 2546, 2547, 2548, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2549, 2550, 2551, 2552, 2553, 2554, 2555, 2556, 2557, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2558, 2559, 2560, 2561, 2562, 2563, 2564, 2565, 2566, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2567, 2568, 2569, 2570, 2571, 2572, 2573, 2574, 2575, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2576, 2577, 2578, 2579, 2580, 2581, 2582, 2583, 2584, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2603, 2604, 2605, 2606, 2607, 2608, 2609, 2610, 2611, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2612, 2613, 2614, 2615, 2616, 2617, 2618, 2619, 2620, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2621, 2622, 2623, 2624, 2625, 2626, 2627, 2628, 2629, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2630, 2631, 2632, 2633, 2634, 2635, 2636, 2637, 2638, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2639, 2640, 2641, 2642, 2643, 2644, 2645, 2646, 2647, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2648, 2649, 2650, 2651, 2652, 2653, 2654, 2655, 2656, 2156, 2157, 2158, 2159, 2160, 2171, 2172, 2173, 2174, 2657, 2658, 2659, 2660, 2661, 2662, 2663, 2664, 2665,  $2175,\ 2176,\ 2177,\ 2178,\ 2179,\ 2180,\ 2181,\ 2182,\ 2183,$ 2666, 2667, 2668, 2669, 2670, 2671, 2672, 2673, 2674, 2184, 2185, 2186, 2187, 2188, 2189, 2190, 2191, 2192, 2675, 2676, 2677, 2678, 2679, 2680, 2681, 2682, 2193, 2194, 2195, 2196, 2197, 2198, 2199, 2200, 2201, 2684, 2685, 2686, 2687, 2688, 2689, 2690, 2691, 2692, 2202, 2203, 2204, 2205, 2206, 2207, 2208, 2209, 2210, 2693, 2694, 2695, 2696, 2697, 2698, 2699, 2700, 2701, 2211, 2212, 2213, 2214, 2215, 2216, 2217, 2218, 2219, 2702, 2703, 2704, 2705, 2706, 2707, 2708, 2709, 2710, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2711, 2712, 2713, 2714, 2715, 2716, 2717, 2718, 2719. 2229, 2230, 2231, 2232, 2233, 2234, 2235, 2236, 2237, 2720, 2721, 2722, 2723, 2724, 2725, 2726, 2727, 2728. 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2729, 2730, 2731, 2732, 2733, 2734, 2735, 2736, 2737, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 2738, 2739, 2740, 2741, 2742, 2743, 2744, 2745, 2746, 2256, 2257, 2258, 2259, 2260, 2271, 2272, 2273, 2274, 2747, 2748, 2749, 2750, 2751, 2752, 2753, 2754, 2755, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2756, 2757, 2758, 2759, 2760, 2761, 2762, 2763, 2764, 2284, 2285, 2286, 2287, 2288, 2289, 2290, 2291, 2292, 2765, 2766, 2767, 2768, 2769, 2770, 2771, 2772, 2773, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2301, 2774, 2775, 2776, 2777, 2778, 2779, 2780, 2781, 2782, 2302, 2303, 2304, 2305, 2306, 2307, 2308, 2309, 2310, 2783, 2784, 2785, 2786, 2787, 2788, 2789, 2790, 2791, 2311, 2312, 2313, 2314, 2315, 2316, 2317, 2318, 2319, 2792, 2793, 2794, 2795, 2796, 2797, 2798, 2799, 2800, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2801, 2802, 2803, 2804, 2805, 2806, 2807, 2808, 2809, 2329, 2330, 2331, 2332, 2333, 2334, 2335, 2336, 2337, 2810, 2811, 2812, 2813, 2814, 2815, 2816, 2817, 2818.

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3416, 3417, 3418, 3419, 3420, 3421, 3422, 3423, 3424, 3425, 3426, 3427, 3428, 3429, 3430, 3431, 3432, 3433, 3434, 3435, 3436, 3437, 3438, 3439, 3440, 3441, 3442, 3443, 3444, 3445, 3446, 3447, 3448, 3449, 3450, 3451, 3452, 3453, 3454, 3455, 3456, 3457, 3458, 3459, 3460, 3461, 3462, 3463, 3464, 3465, 3466, 3467, 3468, 3469, 3470, 3471, 3472, 3473, 3474, 3475, 3476, 3477, 3478, 3479, 3480, 3481, 3482, 3483, 3484, 3485, 3486, 3487, 3488, 3489, 3490, 3491, 3492, 3493, 3494, 3495, 3496, 3497, 3498, 3499, 3500, 3501, 3502, 3503, 3504, 3505, 3506, 3507, 3508, 3509, 3510, 3511, 3512, 3513, 3514, 3515, 3516, 3517, 3518, 3519, 3520, 3521, 3522, 3523, 3524, 3525, 3526, 3527, 3528, 3529, 3530 and 3531 in SEQ ID NOs: 29-30, 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.

[0128] 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 3532, 3533, 3534, 3535, 3536, 3537, 3538, 3539, 3540, 3541, 3542, 3543, 3544, 3545, 3546, 3547, 3548, 3549, 3550, 3551, 3552, 3553, 3554, 3555, 3556, 3557, 3558, 3559, 3560, 3561, 3562, 3563, 3564, 3565, 3566, 3567, 3568, 3569, 3570, 3571, 3572, 3573, 3574, 3575, 3576, 3577, 3578, 3579, 3580, 3581, 3582, 3583, 3584, 3585, 3586, 3587, 3588, 3589, 3590, 3591, 3592, 3593, 3594, 3595, 3596, 3597. 3598, 3599, 3600, 3601, 3602, 3603, 3604, 3605, 3606. 3607, 3608, 3609, 3610, 3611, 3612, 3613, 3614, 3615, 3616, 3617, 3618, 3619, 3620, 3621, 3622, 3623, 3624, 3625, 3626, 3627, 3628, 3629, 3630, 3631, 3632, 3633, 3634, 3635, 3636, 3637, 3638, 3639, 3640, 3641, 3642, 3643, 3644, 3645, 3646, 3647, 3648, 3649, 3650, 3651, 3652, 3653, 3654, 3655, 3656, 3657, 3658, 3659, 3660, 3661, 3662, 3663, 3664, 3665, 3666, 3667, 3668, 3669, 3670, 3671, 3672, 3673, 3674, 3675, 3676, 3677, 3679, 3680, 3681, 3682, 3683, 3684, 3685, 3686, 3687, 3688, 3689, 3690, 3691, 3692, 3693, 3694, 3695, 3696, 3697, 3698, 3699, 3700, 3701, 3702, 3703, 3704, 3705, 3706, 3707, 3708, 3709, 3710, 3711, 3712, 3713, 3714, 3715, 3716, 3717, 3718, 3719, 3720, 3721, 3722, 3723, 3724, 3725, 3726, 3727, 3728, 3729, 3730, 3731, 3732, 3733, 3734, 3735, 3736, 3737, 3738, 3739, 3740, 3741, 3742, 3743, 3744, 3745, 3746, 3747, 3748, 3749, 3750, 3751, 3752, 3753, 3754, 3755, 3756, 3757, 3758, 3759. 3760, 3761, 3762, 3763, 3764, 3765, 3766, 3767, 3768. 3769, 3770, 3771, 3772, 3773, 3774, 3775, 3776, 3777, 3778, 3779, 3780, 3781, 3782, 3783, 3784, 3785, 3786, 3787, 3788, 3789, 3790, 3791, 3792, 3793, 3794, 3795. 3796, 3797, 3798, 3799, 3800, 3801, 3802, 3803, 3804. 3805, 3806, 3807, 3808, 3809, 3810, 3811, 3812, 3813, 3814, 3815, 3816, 3817, 3818, 3819, 3820, 3821, 3822, 3823, 3824, 3825, 3826, 3827, 3828, 3829, 3830, 3831, 3832, 3833, 3834, 3835, 3836, 3837, 3838, 3839, 3841, 3842, 3843, 3844, 3845, 3846, 3847, 3848, 3849, 3850, 3851, 3852, 3853, 3854, 3855, 3856, 3857, 3858, 3859, 3860, 3861, 3862, 3863, 3864, 3865, 3866, 3867, 3868, 3869, 3870, 3871, 3872, 3873, 3874, 3875, 3876, 3877, 3878, 3879, 3880, 3881, 3882, 3883, 3884, 3885,

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3980, 3981, 3982, 3983, 3984, 4573, 4574, 4575, 4576, 4577, 4578, 4579, 4580, 4581, 3985, 3986, 3987, 3988, 3989, 3990, 3991, 3992, 3993, 4582, 4583, 4584, 4585, 4586, 4587, 4588, 4589, 4590. 3994, 3995, 3996, 3997, 3998, 3999, 4000, 4001, 4002, 4591, 4592, 4593, 4594, 4595, 4596, 4597, 4598, 4599. 4003, 4004, 4005, 4006, 4007, 4008, 4009, 4010, 4011, 4600, 4601, 4602, 4603, 4604, 4605, 4606, 4607, 4608, 4012, 4013, 4014, 4015, 4016, 4017, 4018, 4019, 4020, 4609, 4610, 4611, 4612, 4613, 4614, 4615, 4616, 4617. 4021, 4022, 4023, 4024, 4025, 4026, 4027, 4028, 4029, 4618, 4619, 4620, 4621, 4622, 4623, 4624, 4625, 4626, 4030, 4031, 4032, 4033, 4034, 4035, 4036, 4037, 4038, 4627, 4628, 4629, 4630, 4631, 4632, 4633, 4634, 4635, 4039, 4040, 4042, 4043, 4044, 4045, 4046, 4047, 4048, 4636, 4637, 4638, 4639, 4640, 4641, 4642, 4643, 4644, 4049, 4050, 4051, 4052, 4053, 4054, 4055, 4056, 4057, 4645, 4646, 4647, 4648, 4649, 4650, 4651, 4652, 4653. 4058, 4059, 4060, 4061, 4062, 4063, 4064, 4065, 4066, 4654, 4655, 4656, 4657, 4658, 4659, 4660, 4661, 4662, 4067, 4068, 4069, 4070, 4071, 4072, 4073, 4074, 4075, 4663, 4664, 4665, 4666, 4667, 4668, 4669, 4670, 4671, 4076, 4077, 4078, 4079, 4080, 4081, 4082, 4083, 4084, 4672, 4673, 4674, 4675, 4676, 4677, 4678, 4679, 4680, 4085, 4086, 4087, 4088, 4089, 4090, 4091, 4092, 4093, 4681, 4682, 4683, 4684, 4685, 4686, 4687, 4688, 4689. 4094, 4095, 4096, 4097, 4098, 4099, 4100, 4101, 4102, 4690, 4691, 4692, 4693, 4694, 4695, 4696, 4697, 4698, 4103, 4104, 4105, 4106, 4107, 4108, 4109, 4110, 4110, 4699, 4700, 4701, 4702, 4703, 4704, 4705, 4706, 4707, 4111, 4112, 4113, 4114, 4115, 4116, 4117, 4118, 4119, 4120, 4708, 4709, 4710, 4711, 4712, 4713, 4714, 4715, 4716, 4121, 4122, 4123, 4124, 4125, 4126, 4127, 4128, 4129, 4717, 4718, 4719, 4720, 4721, 4722, 4723, 4724, 4725, 4130, 4131, 4132, 4133, 4134, 4135, 4136, 4137, 4138, 4726, 4727, 4728, 4729, 4730, 4731, 4732, 4733, 4734, 4139, 4140, 4141, 4142, 4143, 4144, 4145, 4146, 4147, 4735, 4736, 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[0129] 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.

[0130] 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 *Pseudomonas aeruginosa*. The polypeptide may in these cases induce a humeral and/or a cellular immune response.

[0131] A particularly preferred polypeptide of the invention is derived from SEQ ID NO: 17 and is otherwise as defined above.

## **Epitopes**

**[0132]** 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.

[0133] It is relatively uncomplicated to identify linear B-cell epitopes—one very simple approach entails that antibodies raised agains *Pseudomonas aeruginosa* or *Pseudomonas aeruginosa* 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 *Pseudomonas aeruginosa* polypeptide which are responsible for or contribute to binding to the antibodies can be identified.

[0134] 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.

[0135] Also, in silico methods for B-cell epitope prediction can be employed: useful state-of-the-art systems for  $\beta$ -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

[0136] 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).

[0137] 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, at least 153, at least 154, at least 155, at least 156, at least 157, at least 158, at least 159, at least 160, at least 171, at least 172, at least 173, at least 174, at least 175, at least 176, at least 177, at least 178, at least 179, at least 180, at least 181, at least 182, at least 183, at least 184, at least 185, at least 186, at least 187, at least 188, at least 189, at least 190, at least 191, at least 192, at least 193, at least 194, at least 195, at least 196, at least 197, at least 198, at least 199, at least 200 and at least 201 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.

[0138] 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%.

[0139] 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

[0140] 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

[0141] At any rate, certain vectors of the invention are capable of autonomous replication.

[0142] 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.

**[0143]** 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.

[0144] A more detailed discussion of vectors of the invention is provided in the following:

[0145] 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.

[0146] 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).

[0147] 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 organ-

ism. 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

[0148] 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.

[0149] 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 PCRTM, in connection with the compositions disclosed herein (see U.S. Pat. No. 4,683,202, U.S. Pat. No. 5,928,906, each incorporated herein by reference).

[0150] 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.

[0151] 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, Immunoglobulin Light Chain, T Cell Receptor, HLA DQa and/or DQ $\beta$ ,  $\beta$ -Interferon, Interleukin-2, Interleukin-2 Receptor, MHC Class II 5, MHC

Class II HLA-DRa, β-Actin, Muscle Creatine Kinase (MCK), Prealbumin (Transthyretin), Elastase I, Metallothionein (MTII), Collagenase, Albumin, α-Fetoprotein, γ-Globin, β-Globin, c-fos, c-HA-ras, Insulin, Neural Cell Adhesion Molecule (NCAM), al-Antitrypain, H2B (TH2B) Histone, Mouse and/or Type I Collagen, Glucose-Regulated Proteins (GRP94 and GRP78), Rat Growth Hormone, Human Serum Amyloid A (SAA), Troponin I (TN I), Platelet-Derived Growth Factor (PDGF), Duchenne Muscular Dystrophy, SV40, Polyoma, Retroviruses, Papilloma Virus, Hepatitis B Virus, Human Immunodeficiency Virus, Cytomegalovirus (CMV) IE, and Gibbon Ape Leukemia Virus. [0152] Inducible Elements include MT II—Phorbol Ester (TFA)/Heavy metals; MMTV (mouse mammary tumor virus)—Glucocorticoids; β-Interferon—poly(rl)x/poly(rc); Adenovirus 5 E2—EIA; Collagenase—Phorbol Ester (TPA): Stromelysin—Phorbol Ester (TPA): SV40—Phorbol Ester (TPA); Murine MX Gene—Interferon, Newcastle Disease Virus; GRP78 Gene—A23187; α-2-Macroglobulin— IL-6; Vimentin—Serum; MHC Class I Gene H-2κb—Interferon; HSP70-E1A/SV40 Large T Antigen; Proliferin-Phorbol Ester/TPA; Tumor Necrosis Factor—PMA; and Thyroid Stimulating Hormonea Gene—Thyroid Hormone. [0153] 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

[0154] 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.

[0155] 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.

[0156] 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- $\gamma$ .

[0157] 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)

[0158] 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.

[0159] 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. IRES elements from two members of the picornavirus family (polio and encephalomyocarditis) have been described, as well an IRES from a mammalian message. 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. Pat. Nos. 5,925,565 and 5,935,819, herein incorporated by reference).

# 2. Multiple Cloning Sites

[0160] 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

[0161] 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

[0162] 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.

[0163] In eukaryotic systems, the terminator region may also comprise specific DNA sequences that permit sitespecific 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 polyAtail 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. [0164] 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

[0165] 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

[0166] 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

[0167] 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.

[0168] 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

[0169] 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.

[0170] 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).

[0171] 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.

[0172] 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].

[0173] 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.

[0174] 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.

[0175] An interesting production system is the use of plants. For instance, proteins can be produced at low cost in plants using an *Agrobacterium* transfection system to genetically modify plants to express genes that encode the protein of interest. One commercially available platform are those provided by iBio CMO LLC (8800 HSC Pkwy, Bryan, Tex. 77807, USA) and iBio, Inc (9 Innovatoin Way, Suite 100, Newark, Del. 19711, USA) and disclosed in e.g. EP 2 853 599, EP 1 769 068, and EP 2 192 172. Hence, in such systems the vector is an *Agrobacterium* vector or other vector suitable for transfection of plants.

[0176] 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.

[0177] Further details on cells and cell lines are presented in the following:

[0178] 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 Kluvveromyces genus (e.g. K. lactis or K. fragilis) and members of the Schizosaccharomyces genus (e.g. S. pombe).

**[0179]** 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.

[0180] 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.

[0181] 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 and 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, DH5a, JMI 09, and KC8, as well as a number of commercially available bacterial hosts such as SURE® Competent Cells and SOLOP ACK<sup>TM</sup> Gold Cells (STRATAGENE®, La Jolla, Calif.). 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*.

[0182] 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.

[0183] 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**

[0184] 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.

[0185] 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. Pat. Nos. 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<sup>TM</sup> Baculovirus expression system from CLONTECH®

[0186] 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-REXTM (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

[0187] 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.

[0188] 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.

[0189] 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.

[0190] 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).

[0191] 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<sup>TM</sup>) which is described in detail in U.S. Pat. Nos. 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.

[0192] 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. Pat. Nos. 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

[0193] 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. Pat. Nos. 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), including microinjection (U.S. Pat. No. 5,789,215); by electroporation (U.S. Pat. No. 5,384,253); by calcium phosphate precipita-

tion; by using DEAE dextran followed by polyethylene glycol; by direct sonic loading; by liposome mediated transfection; by microprojectile bombardment (PCT Application Nos. WO 94/09699 and 95/06128; U.S. Pat. Nos. 5,610,042; 5,322,783 5,563,055, 5,550,318, 5,538,877 and 5,538,880); by agitation with silicon carbide fibers (U.S. Pat. Nos. 5,302,523 and 5,464,765); by Agrobacterium mediated transformation (U.S. Pat. Nos. 5,591,616 and 5,563,055); or by PEG mediated transformation of protoplasts (U.S. Pat. Nos. 4,684,611 and 4,952,500); by desiccation/inhibition mediated DNA uptake. Through the application of techniques such as these, organelle(s), cell(s), tissue(s) or organism(s) may be stably or transiently transformed. See also "Fish Vaccination", 2014, edited by Gudding R., Lillehaug A, and Evensen Ø, published by Wiley Blackwell, ISBN 978-0-470-67455-0, chapter 5, which deals specifically with DNA vaccination of fish.

The Antibodies of the Invention—and their Production/ Isolation

[0194] Antibodies directed against the proteins of the invention are useful for affinity chromatography, immuno-assays, and for distinguishing/identifying *Pseudomonas* proteins as well as for passive immunisation and therapy.

[0195] 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 10-200 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.

[0196] 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 I 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).

[0197] If desired, the antibodies (whether polyclonal or monoclonal) may be labeled using conventional techniques. Suitable labels include fluorophores, chromophores, radioactive atoms (particularly 32p and 1251), 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, 1251, 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.

[0198] 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')<sub>2</sub>, an scFV; cf. also the definition of the term "antibody" presented above.

Compositions of the Invention; Vaccines

[0199] 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).

[0200] In some embodiments of the invention, the pharmaceutical compositions such as vaccines include merely one single antigen, immunogen, polypeptide, protein, nucleic acid or vector of the invention, but in other embodiments, the pharmaceutical compositions comprise "cocktails" of the antigens or of the immunogens or of the polypeptides or of the protein or of the nucleic acids or of the vectors of the invention.

[0201] In particularly interesting embodiments, the pharmaceutical composition is an MVA vector mentioned herein, which encodes and can effect expression of at least 2 nucleic acid fragments of the invention.

[0202] An embodiment of a pharmaceutical composition of the invention comprises exactly Y or at least Y distinct (i.e. having non-identical primary structure) polypeptides of

the invention described above, where each of said Y or at least Y distinct polypeptides comprises an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-30 and wherein said Y or at least Y distinct polypeptides together comprise immunogenic amino acid sequences present in or derived from Y or at least Y of SEQ ID NOs. 1-30, wherein Y is an integer selected from 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, and 30.

[0203] Another embodiment of a pharmaceutical composition of the invention comprises a peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 1 in combination with at least one P. aeruginosa peptide/polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEO ID NOs: 2-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 2 in combination with at least one P. aeruginosa peptide/polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1, and 3-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 3 in combination with at least one P. aeruginosa peptide/polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1, 2, and 4-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 4 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-3, and 5-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 5 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-4, and 6-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 6 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-5, and 7-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 7 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-6, and 8-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 8 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEO ID NOs: 1-7, and 9-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 9 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEO ID NOs: 1-8, and 10-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 10 in combination with at least one *P. aeruginosa* peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-9, and 11-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 11 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-10, and 12-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 12 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-11, and 13-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 13 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-12, and 14-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 14 in combination with at least one *P. aeruginosa* peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-13, and 15-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 15 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-14, and 16-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 16 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEO ID NOs: 1-15, and 17-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 17 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEO ID NOs: 1-16, and 18-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 18 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-17, and 19-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 19 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-18, and 20-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 20 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-19, and 21-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 21 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-20, and 22-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 22 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-21, and 23-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 23 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-22, and 24-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 24 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEO ID NOs: 1-23, and 25-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 25 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-24, and 26-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 26 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-25, and 27-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 27 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-26, and 28-30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 28 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-27, 29, and 30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 29 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-28, and 30. Another embodiment of a pharmaceutical composition of the invention comprises a peptide/ polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from SEQ ID NO: 30 in combination with at least one P. aeruginosa peptide/ polypeptide, in particular with at least one peptide/polypeptide comprising or consisting of an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-29.

[0204] These embodiments entail combinations of peptides/polypeptides which are admixed with each other. Alternatively, the same combinations of peptides/polypeptides can be constructed as fusion polypeptides. Another alternative entails compositions where the immunogens are nucleic

acids encoding the peptide combinations or, preferably, encoding such fusion polypeptides.

[0205] Another embodiment of the pharmaceutical composition of the invention comprises Z or at least Z distinct nucleic acid molecules each encoding a polypeptide of the invention, where each of said Z or at least Z distinct nucleic acid molecules encodes an immunogenic amino acid sequence present in or derived from any one of SEQ ID NOs: 1-30 and wherein said at Z or least Z distinct nucleic acid molecules together encode immunogenic amino acid sequences present in or derived from at Z or least Z of SEQ ID NOs. 1-30, wherein Z is an integer selected from 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, and 30. Also, such a pharmaceutical composition may include nucleic acid that encode several immunogenic amino acid sequences disclosed herein, either as separate encoded species or as peptides fused to each other.

[0206] Vaccines of the invention typically 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 or targeting the protein/pathogen. 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.

[0207] 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.

[0208] 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:

[0209] 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, Mass.), (b) SAF, containing 10% Squalane, 0.4% Tween 80, 5% pluronicblocked 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, Mont.) 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 (Detox<sup>TM</sup>); (3) saponin adjuvants such as Stimulon<sup>TM</sup> (Cambridge Bioscience, Worcester, Mass.) 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<sup>TM</sup> adjuvants are preferred. [0210] As mentioned above, muramyl peptides include, but are not limited to, N-acetyl-muramyl-L-threonyl-Disoglutamine (thr-MDP), N-acetyl-normuramyl-L-alanyl-Disoglutamine (nor-MDP), N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2"-2'-dipalmitoyl-sn-glycero-3hydroxyphosphoryloxy)-ethylamine (MTP-PE), etc.

[0211] 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.

**[0212]** 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.

[0213] 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. nonhuman 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, often not higher than 5,000 μg), and very often in the range between 10 and 200 µg.

[0214] The immunogenic compositions are conventionally administered parenterally, eg, by injection, either subcutaneously, intramuscularly, or transdermally/transcutaneously (eg. WO98/20734). Additional formulations suitable for other modes of administration include oral, pulmonary and nasal formulations, suppositories, and transdermal applications. In the case of nucleic acid vaccination and antibody treatment, also the intravenous or intraarterial routes may be applicable.

[0215] Dosage treatment may be a single dose schedule or a multiple dose schedule. The vaccine may be administered in conjunction with other immunoregulatory agents.

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[0216] 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 ImIllunol 9: 271-283; Donnelly et al. (1997) Avnu Rev Innnunol 15: 617-648; later herein].

## Treatment Methods of the Invention

[0217] 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.

[0218] 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  $5,000~\mu g$  of the polypeptide of the invention per administration.

[0219] In preferred embodiments of the sixth aspect, the immunization scheme includes that the animal (e.g. the human) receives a priming administration and one or more booster administrations.

[0220] Preferred embodiments of the 6<sup>th</sup> aspect of the invention comprise that the administration is for the purpose of inducing protective immunity against *Pseudomonas aeruginosa*. In this embodiment it is particularly preferred that the protective immunity is effective in reducing the risk of attracting infection with *Pseudomonas aeruginosa* or is effective in treating or ameliorating infection with *Pseudomonas aeruginosa*.

[0221] 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 *Pseudomonas aeruginosa* and wherein said antibodies or B-lymphocytes producing said antibodies are subsequently recovered from the animal.

[0222] But, as also mentioned the method of the 6<sup>th</sup> aspect may also be useful in antibody production, so in other embodiments the administration is for the purpose of inducing antibodies specific for *Pseudomonas aeruginosa* and wherein B-lymphocytes producing said antibodies are subsequently recovered from the animal and used for preparation of monoclonal antibodies.

[0223] 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.

[0224] 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.

[0225] Reference is however made to the ranges for dosages of immunologically effective amounts of polypeptides, cf. above.

[0226] However, the effective amount for a given situation can be determined by routine experimentation and is within the judgement of the clinician.

[0227] 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.

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[0228] 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.

[0229] 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).

[0230] 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.

[0231] 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

- [0232] 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 *Pseudomonas aeruginosa*:
- [0233] 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 *Pseudomonas aeruginosa*;
- [0234] 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 *Pseudomonas aeruginosa*.
- [0235] 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 *Pseudomonas aeruginosa*.

# Example 1

[0236] The protective effect of PA1302-31-851, PA0931-29-742, PA2070-29-880, PA2070-173-880, PA2976-1-480, PA3901-33-784 and PA0041-34-550 in a murine model of pneumonia

[0237] The purpose of the experiment was to test the potentially protective effect of a combination of seven antigensof the invention in a well-characterized animal model of *Pseudomonas aeruginosa*-induced pneumonia. The primary parameter of comparison for this model is lung bacteriology, and secondly clinical symptoms, body temperature and weight loss.

# Materials and Methods

## Materials

[0238] NMRI mice, female (Janvier, France)

[0239] PA1302-31-851 (in 4 M urea; produced at University of Southern Denmark)

[0240] PA0931-29-742 (in 4 M urea; produced at University of Southern Denmark)

# Immunization

[0258] A group of 21 female NMRI mice were immunized with seven recombinant proteins in combination with adjuvant. The 7-valent combination vaccine consisted of PA1302-31-851, PA0931-29-742, PA2070-29-880, PA2070-173-880, PA2976-1-480, PA3901-33-784 and PA0041-34-550. A second group made up the negative control group, which was immunized only with adjuvant. The amount of adjuvant used for immunization of the control group was the same as the amount used when immunizing the vaccine group. Each mouse was immunized subcutaneously three times at approximately two week intervals (Table 1). At all three immunizations the mice in the vaccine group received 15 μg of each protein. For the first immunization the proteins were mixed with aluminum hydroxide (Al(OH)<sub>3</sub>) and Freund's incomplete adjuvant, whereas only Al(OH), was used for the subsequent immunizations. Due to restrictions on injection volume in mice the seven protein antigens were split into two separate volumes; three proteins, in combination with adjuvant, were injected on the left side of the mouse and the other four proteins were injected on the right side. This immunization routine was the same in all three rounds of immunization.

TABLE 1

iment. The two groups of mice were two week intervals. The length of the	
Immunization number	Challenge
_	

,	Imm	unization nu	mber	Challenge			
	1	2	3	Start	End		
Date Days before challenge start	06.17.15 39	06.29.15 27	07.10.15 16	07.26.15 0	07.30.15 +4		

[0241] PA2070-29-880 (in 4 M urea; produced at University of Southern Denmark)

[0242] PA2070-173-880 (in 4 M urea; produced at University of Southern Denmark)

[0243] PA2976-1-480 (in 2 M urea; produced at University of Southern Denmark)

[0244] PA3901-33-784 (in 2 M urea; produced at University of Southern Denmark)

[0245] PA0041-34-550 (in 2 M urea; produced at University of Southern Denmark)

[0246] Aluminum hydroxide (Alhydrogel 2.0%; Brenntag, cat. no. 21645-51-2)

[0247] Freund's incomplete adjuvant (Sigma, cat. no. F5506-10X10ML)

[0248] Isoflurane

[0249] Pseudomonas aeruginosa PA01 Iglewski

[0250] Luria broth agar plates

[0251] Luria broth medium

[0252] Seaweed alginate (Pronatal LF 10/60 FT sample; FMC Biopolymer)

[0253] Ketamine (50 mg/ml)

[0254] Xylazine (20 mg/ml)

[0255] Pentobarbital

[0256] Microtainer tubes with serum separator additive (BD, #365967)

[0257] Pseudomonas isolation agar (Sigma-Aldrich, #17208-500G)

Temperature Transponders

[0259] Four days before inoculation temperature transponders (BMDS, cat. no. IPTT-300) were inserted into each mouse. The mice were briefly anaesthetised by inhalation of isoflurane, and a temperature transponder inserted underneath the skin on the lower back or side of the mouse.

**[0260]** Using a compatible wireless scanner (BMDS Smart Probe; BMDS, cat. no. DAS-7007s) body temperature could be registered when placing the scanner close to the transponders underneath the skin of the mouse.

## Preparation of Bacterial Inoculum

[0261] A small amount of *Pseudomonas aeruginosa* PA01 Iglewski was extracted from a freeze stock (stored at -80° C.) and streaked out on a Luria broth agar plate. The plate was place at 37° C. over night. The following day a single colony was used to inoculate 100 ml sterile Luria broth medium. The culture was left to incubate at 37° C., with constant shaking, for 18 hours. After the 18 hours of incubation 50 ml of the bacterial culture was centrifuged at  $5000 \times g$  for 10 minutes at  $20^{\circ}$  C. The pellet was resuspended in 5 ml Luria broth medium. The bacterial suspension was mixed with seaweed alginate in a ratio of 0.5 ml bacterial suspension to 12 ml seaweed alginate, and small alginate beads were created as described in Bjarnsholt et al. (2014). The number of colony forming units (CFU) per ml alginate bead solution was determined by dissolving the alginate beads in saline.

## Challenge Setup

**[0262]** The mice were housed at the Biocenter at the University of Copenhagen. The animals were kept in an environment characterized by a 12 hours light-dark cycle and temperature and humidity control. They had access to food and water ad libitum. The experimental procedures were carried out in accordance with the guidelines of the Danish National Animal Ethics Committee (license number 2013-15-2934-00857).

[0263] Before inoculation the mice were anaesthetized with an intraperitoneal injection of ketamine (100 mg/kg) and xylazine (10 mg/kg). Once sedated each mouse was inoculated intranasally with 1.0×10<sup>7</sup> CFU of *Pseudomonas aeruginosa* PA01 Iglewski embedded in seaweed alginate beads. To ensure that the mice did not die from dehydration during the four day challenge, the mice received 1 ml of physiological saline subcutaneously once a day.

[0264] The mice were assessed daily to register symptoms and development of disease over the course of the four day challenge. To ensure a consistent evaluation of all animals each animal was scored individually following the scale of clinical symptoms given in table 2. Before the start of the challenge, the mouse cages were "blinded", leaving the scientist involved unaware of which treatment had been given to which animals. This ensured an unbiased scoring of the animals' clinical symptoms.

## TABLE 2

Scale of clinical symptoms. The mice were individually assessed on their physical appearance and behavior, specifically registering details of fur, posture, movement, eyes and breathing for each animal. The sum of the scores was used in the overall evaluation of animal welfare, and in relation to humane endpoints.

Fur	0-well groomed
	1-slightly ruffled
	2-very ruffled
Posture	0-normal
	1-slightly hunched back
	2-hunched back
Movement	0-normal
	1-decreased activity
	2-completely immobile
Eyes	0-normal
•	1-semi-closed
	2-closed
Breathing	0-normal
	1-affected/forced breathing

## Humane Endpoints.

[0265] Animals were euthanized if the sum of clinical scores reached 9, using the scale given in table 2, or if the body temperature was below  $30^{\circ}$  C.

# Organ Extraction and Bacteriology

[0266] Following registration of weight, temperature and clinical symptoms on day four after inoculation, the mice were euthanized by intraperitoneal injection of pentobarbital. Subsequently, the lungs were extracted aseptically, and placed in a tubes containing 4 ml sterile saline. Blood was collected after cardiac puncture and transferred to Microtainer tubes, in order to save serum for later ELISA analysis.

[0267] The lungs were homogenized, serially diluted and 100 µl of each dilution was plated on *Pseudomonas* Isolation

agar-plates. The plates were incubated at 37° C. over night, and the number of colony forming units was quantified the following day.

#### Results

# Clinical Symptoms

**[0268]** The animals were scored daily to register disease progression. The results of the clinical scoring are given in FIG. 1.

# Temperature and Weight Loss

[0269] Body weight and body temperature were registered daily, as part of the overall assessment of animal welfare. The results of the registration of weight and temperature are given in FIGS. 2 and 3, respectively. Note that there was a general issue of malfunctioning temperature transponders, especially in the group immunized with the 7-valent combination vaccine, hence the low number of data points.

## Bacteriology

[0270] Results are shown in FIG. 4.

## Antibody Titer

[0271] After challenge completion blood was collected from the mice. The serum was used for subsequent analysis of antibody titer, using ELISA. The antibody titer to the seven antigens were analysed for eight of the vaccinated mice. FIG. 5 shows the mean antibody response to the seven protein antigens—each curve is the mean of eight separate ELISA curves.

## Conclusions

[0272] The results indicate that the 7-valent combination vaccine protects mice from Pseudomonas aeruginosa PA01 Iglewski-induced pneumonia. The mice immunized with the combination vaccine had a significantly lower lung CFU compared to the negative controls. Similarly the clinical symptoms were significantly lower for mice immunized with the combination vaccine, hence these animals appeared less ill to an unbiased observer. Moreover, the animals immunized with the combination vaccine had a significantly smaller weight loss over the four days following inoculation, which is another indicator of a greater well-being. There was no significant difference in body temperature, when comparing the data from the two groups. It should, however, be noted that a great number of the animals in the vaccine group had been equipped with temperature transponders that were malfunctioning, hence the small number of data points. Analysis of the serum samples show that the mice immunized with the 7-valent combination vaccine had a relatively high antibody response to five of the seven protein antigens.

# Example 2

[0273] Confirmation of the protective effect of PA1302-31-851, PA0931-29-742, PA2070-29-880, PA2070-173-880, PA2976-1-480, PA3901-33-784 and PA0041-34-550 in a murine model of pneumonia ER\_ 0040

[0274] The purpose of the experiment was to verify the results of claim 1, i.e. that a 7-valent combination vaccine protected mice against a *Pseudomonas aeruginosa*-induced pneumonia. The primary parameter of comparison for this

model is lung bacteriology, and secondly clinical symptoms, body temperature and weight loss.

## Materials and Methods

## Materials

[0275] NMRI mice, female (Janvier, France)

[0276] PA1302-31-851 (in 4 M urea; produced at University of Southern Denmark)

[0277] PA0931-29-742 (in 4 M urea; produced at University of Southern Denmark)

[0278] PA2070-29-880 (in 4 M urea; produced at University of Southern Denmark)

the vaccine group. Each mouse was immunized subcutaneously three times at approximately two week intervals (Table 3). At all three immunizations the mice in the vaccine group received 15 µg of each protein. For the first immunization the proteins were mixed with aluminum hydroxide (Al(OH)<sub>3</sub>) and Freund's incomplete adjuvant, whereas only Al(OH)<sub>3</sub> was used for the subsequent immunizations (see appendix 5). Due to restrictions on injection volume in mice the seven protein antigens were split into two separate volumes; three proteins, in combination with adjuvant, were injected on the left side of the mouse and the other four proteins were injected on the right side. This immunization routine was the same at all three rounds of immunization.

TABLE 3

Time line of experiment. The two groups of mice were immunized simultaneously
at approximately two week intervals. The length of the challenge was four days.

	Imm	unization nu	mber	Challenge				
	1	2	3	Start	End			
Date Days before challenge start	11.26.15 44	12.11.15 29	12.26.15 14	01.09.16 0	01.14.16 +4			

[0279] PA2070-173-880 (in 4 M urea; produced at University of Southern Denmark)

[0280] PA2976-1-480 (in 2 M urea; produced at University of Southern Denmark)

[0281] PA3901-33-784 (in 2 M urea; produced at University of Southern Denmark)

[0282] PA0041-34-550 (in 2 M urea; produced at University of Southern Denmark)

[0283] Aluminum hydroxide (Alhydrogel 2.0%; Brenntag, cat. no. 21645-51-2)

[0284] Freund's incomplete adjuvant (Sigma, cat. no. F5506-10X10ML)

[0285] Isoflurane

[0286] Pseudomonas aeruginosa PA01 Iglewski

[0287] Luria broth agar plates

[0288] Luria broth medium

[0289] Seaweed alginate (Pronatal LF 10/60 FT sample; FMC Biopolymer)

[0290] Ketamine (50 mg/ml)

[0291] Xylazine (20 mg/ml)

[0292] Pentobarbital

[0293] Microtainer tubes with serum separator additive (BD, #365967)

[0294] Pseudomonas isolation agar (Sigma-Aldrich, #17208-500G)

# Immunization

[0295] A group of 32 female NMRI mice were immunized with seven recombinant proteins in combination with adjuvant. The 7-valent combination vaccine consisted of PA1302-31-851, PA0931-29-742, PA2070-29-880, PA2070-173-880, PA2976-1-480, PA3901-33-784 and PA0041-34-550.

[0296] A second group made up the negative control group, which was immunized only with adjuvant. The amount of adjuvant used for immunization of the control group was the same as the amount used when immunizing

#### Temperature Transponders

[0297] Four days before inoculation temperature transponders (BMDS, cat. no. IPTT-300) were inserted into each mouse. The mice were briefly anaesthetised by inhalation of isoflurane, and a temperature transponder inserted underneath the skin on the lower back or side of the mouse.

**[0298]** Using a compatible wireless scanner (BMDS Smart Probe; BMDS, cat. no. DAS-7007s) body temperature could be registered when placing the scanner close to the transponders underneath the skin of the mouse.

# Preparation of Bacterial Inoculum

[0299] A small amount of Pseudomonas aeruginosa PA01 Iglewski was extracted from a freeze stock (stored at -80° C.) and streaked out on a Luria broth agar plate. The plate was place at 37° C. over night. The following day a single colony was used to inoculate 100 ml sterile Luria broth medium. The culture was left to incubate at 37° C., with constant shaking, for 18 hours. After the 18 hours of incubation 50 ml of the bacterial culture was centrifuged at 5000×g for 10 minutes at 20° C. The pellet was resuspended in 5 ml Luria broth medium. The bacterial suspension was mixed with seaweed alginate in a ratio of 0.5 ml bacterial suspension to 12 ml seaweed alginate, and small alginate beads were created as described in Bjarnsholt et al (2014). The number of colony forming units (CFU) per ml alginate bead solution was determined by dissolving the alginate beads in saline.

## Challenge Setup

**[0300]** The mice were housed at the Biocenter at the University of Copenhagen. The animals were kept in an environment characterized by a 12 hours light-dark cycle and temperature and humidity control. They had access to food and water ad libitum. The experimental procedures

were carried out in accordance with the guidelines of the Danish National Animal Ethics Committee (license number 2013-15-2934-00857).

[0301] Before inoculation the mice were anaesthetized with an intraperitoneal injection of ketamine (100 mg/kg) and xylazine (10 mg/kg). Once sedated each mouse was inoculated intranasally with 1.0×10<sup>7</sup> CFU of *Pseudomonas aeruginosa* PA01 Iglewski embedded in seaweed alginate beads. To ensure that the mice did not die from dehydration during the four day challenge, the mice received 1 ml of physiological saline subcutaneously once a day.

[0302] The mice were assessed daily to register symptoms and development of disease over the course of the four day challenge. To ensure a consistent evaluation of all animals each animal was scored individually following the scale of clinical symptoms given in table 2 in Example 1. Before the start of the challenge, the mouse cages were "blinded", leaving the scientist involved unaware of which treatment had been given to which animals. This ensured an unbiased scoring of the animals' clinical symptoms.

## Humane Endpoints.

[0303] Animals were euthanized if the sum of clinical scores reached 9, using the scale given in table 2, or if the body temperature was below  $30^{\circ}$  C.

# Organ Extraction and Bacteriology

[0304] Following registration of weight, temperature and clinical symptoms on day four after inoculation, the mice were euthanized by intraperitoneal injection of pentobarbital. Subsequently, the lungs were extracted aseptically, and placed in a tubes containing 4 ml sterile saline. Blood was collected after cardiac puncture and transferred to Microtainer tubes, in order to save serum for later ELISA analysis. [0305] The lungs were homogenized, serially diluted and 100 µl of each dilution was plated on *Pseudomonas* Isolation agar-plates. The plates were incubated at 37° C. over night, and the number of colony forming units was quantified the following day.

# Results

# Clinical Symptoms

[0306] The animals were scored daily to register disease progression. The results of the clinical scoring are given in FIG. 6.

## Temperature and Weight Loss

[0307] Body weight and body temperature were registered daily, as part of the overall assessment of animal welfare. The results of the registration of weight and temperature are given in FIGS. 7 and 8, respectively.

## Bacteriology

[0308] Results are shown in FIG. 9, and the pooled results with those of Example 1 are shown in FIG. 10.

# Antibody Titer

[0309] After challenge completion blood was collected from the mice. The serum was used for subsequent analysis of antibody titer, using ELISA. The antibody titer to the seven antigens were analysed for all of the surviving vac-

cinated mice, i.e. 26 mice. FIG. **6** shows the mean antibody response to the seven protein antigens—each curve is the mean of 26 separate ELISA curves.

## Conclusions

[0310] Generally the results indicate that the 7-valent combination vaccine protects mice from Pseudomonas aeruginosa PA01 Iglewski-induced pneumonia—results also found in Example 1. Analysis of the primary parameter of comparison—the lung bacteriology—did not suggest a protective effect of treatment with the 7-valent vaccine, as there was no significant difference in lung CFU when comparing the two groups. Only when the CFU results from both Examples 1 and 2 were analysed together, did a significant effect of the protein vaccine appear. The other parameters of interest collectively suggest that the proteinimmunized mice had a better recovery from infection. The vaccinated group had significantly lower clinical scores in addition to a significantly higher body temperature and a significantly lower weight loss. Analysis of the serum samples show that the mice immunized with the 7-valent combination vaccine had a relatively high antibody response to five of the seven protein antigens.

## Biologic Sequence Information

[0311] The full-length, native polypeptides of the invention have the following designations used herein:

SEQ ID NO:	Polypeptide name	
1	PA1034	
2 3	PA1592	
3	PA3284	
4 5	PA4107	
	PA0912	
6	PA0070	
7	PA5060	
8	PA1954	
9	PA0971	
10	PA5253	
11	PA0724	
12	PA1441	
13	PA5133	
14	PA3716	
15	PA4016	
16	PA1805	
17	PA3729	
18	PA0931	
19	PA2688	
20	PA3901	
21	PA1302	
22	PA2070	
23	PA3115	
24	PA3535	
25	PA2976	
26	PA4554	
27	PA4282	
28	PA1874	
29	PA0041	
30	PA2462	

[0312] A number of the polypeptides of the invention are fragments of the full-length, native polypeptides. Such fragments as follows: PAXXXX-Y-Z, where XXXX is the number in the polypeptide name, X is the number of the N-terminal amino acid residue in the fragment and Z is the number of the C-terminal amino acid residue. For instance,

PA2070-29-880 is the polypeptide having the amino acid sequence SEQ ID NO: 22, residues 29-880.

[0313] The polypeptides of the present invention have the following amino acid sequences:

SEQ ID NO: 1

 ${\tt MSQEPHVHGPNCNHDHDHHHDHGHGHVHGPHCNHSHEPVRNPLKAVGRND}\\ {\tt PCPCGSEKKPKKCHGA}$ 

SEO ID NO: 2

MKKTVTLALLLAASLGLAACDKKEEDKAAAPAAPATETQPSAPATPPAEP SAPAPSSDTPATPQTPAPTPEQPQQNQQ

SEQ ID NO: 3

MKKI SLASSVVGAALLGVASVGAHAAQNPFAVQELSSGYSVAAAEKAKEG SCGEAKCGADKGKREASKAGHEGSCGADKAKEGSCGGEKKAGEGNCGAD KKKS

SEQ ID NO: 4

 ${\tt MSVFDSRQKTSASLLGAVLVGGMLLGGSAFAVEPLGQGLQVAAASAGEGK}$   ${\tt CGEGKCGSGGSAKTPAKAGAEGKCGEGKCGDASFARTDTDHDGKVSRAEF}$ 

LAVAKDRAGEFDSIDSDHDGFISEAEAYEHLRKTYEANGKPMPAGLFSKL

EQGQH

SEO ID NO: 5

MRSLSLLLLLSLASTCEAAAVFRCEDASGHVSFTQLGCPAGQAGETVVAD

NPPPGGRSVTPMAETKTKKASIGRKSVPLAVIGEREDRCGRRLDEKERRK

AIVEQRIMAGMTRSDVERALGKPDRVSGNNAEVRYQYKADKRRGARSVSF

DQEGCVKGREGTGWSESIPGAKAGPSSYR

SEQ ID NO: 6
MSQPSENRLITSARYALCLLTASGVLLSGCASSGVGSVAQTTRAEYYPSC

YEPVSHLRSTDNAVRNSAITGAITGGLLGGLAGGLASDENRGRNAALAAA GGALAGGAAGYYMEKQKQISDDRARIGSYGTDVDRSTVEINRSVAYAKSA

OSCYOSOFKALLDGRKNKSINEAEGRKRLAEIVSGLOETNALLVAANGRA

GENI SNYTQAYEKDLQQVGVPRAEVTKVAEAENRASTTKGGSKPKTGSNP

KVPKEAVATEQTIRKAQDAQSEGNKVASQGQGMIREVCNSPDMGDWAPPS

CAKA

SEQ ID NO: 7

 ${\tt MAGKKKSEKESSWIGEIEKYSRQIWLAGLGAYSKVSKDGSKLFETLVKDG}$ 

EKAEKEAKSDVDAQVGAAKASARSAKSKVDEVRDRALGKWSELEEAFDKR

LNSAISRLGVPSRNEVKELHSKVDTLTKQIEKLTGVSVKPAAKAAAKPAA

KPAAKPAAKKPAAKKPAAKPAAKPAAPAASSSAPAAPAATPAASAPAAN

APATPSSQG

SEQ ID NO: 8

MKATMVLTPLALAMAAVLSVSAYAGNEGGWHPPKPNPQSNNKGGATALVV DTOONYNNKVSNFGTLNNASVSGSIKDASGNVGVNVAAGDNNOOANAAAL

ASADAS FVFGTATASTSVLOSGYGNTLNNYSNPNTASLSNSANNVSGNLG

VNVAAGNFNQQKNDLAAAVSNGQYSTAGSAASQTSTGNTTVNSANYAYGG

TYVSLKLNADGSYKGTSDQIGDVYLDTWEGQTHPGGSNTGHIDVDSQAQG

-continued

AKDLNHDGGAFAFKEKGDVDLKGTVSGFIPAIVGFKTPVTNNASLSNSLQ

NVSGNVGVNIAAGGGNQQSNSLSIAAGCSSCPAGGESLGF

SEQ ID NO: 9

 ${\tt MKQQFERSPSESYFWPVVLAVVLHVLIFAMLFVSWAFAPELPPSKPIVQA}$ 

 ${\tt TLYQLKSKSQATTOTNQKIAGEAKKTASKQYEVEQLEQKKLEQQKLEQQK}$ 

 ${\tt LEQQQVAAAKAAEQKKADEARKAEAQKAAEAKKADEAKKAAEAKAAEQKK}$ 

QADI AKKRAEDEAKKKAAEDAKKKAAEDAKKKAAEEAKKKAAAEAAKKKA

AVEAAKKKAAAAAAARKAAEDKKARALAELLSDTTERQQALADEVGSEV

 ${\tt TGSLDDLIVNLVSQQWRRPPSARNGMSVEVLIEMLPDGTITNASVSRSSG}$ 

 ${\tt DKPFDSSAVAAVRNVGRIPEMQQLPRATFDSLYRQRRIIFKPEDLSL}$ 

SEQ ID NO: 10

 ${\tt MSANKKPVTTPLHLLQQLSHSLVEHLEGACKQALVDSEKLLAKLEKQRGK}$ 

AQEKLHKARTKLQDAAKAGKTKAQAKARETISDLEEALDTLKARQADTRT

YIVGLKRDVQESLKLAQGVGKVKEAAGKALESRKAKPATKPAAKAAAKPA

VKTVAAKPAAKPAAKPAAKPAAKPAAKPAAKPAAKPAAKPA

 ${\tt AKTAAAKPAAKPAAKPVAKPAAKPAAKPAAKPAAKPAAKPVAKPTAKPA}$ 

AKPVAAKPAATKPATAPAAKPAATPSAPAAASSAASATPAAGSNGAAPTS

AS

SEQ ID NO: 11

 ${\tt MWGLTMKFASLILMLLFATVARAEDYYWKIQSLPERFSSPSAACAAWAKA}$ 

 ${\tt TGRPGEFTFTGSMKARDQTSFWCEFTNNETGKTAAGYGPAGRYGDSCPEG}$ 

 ${\tt TEYDKATGVCKSPPQECKEGELFPAKGPDSPVVTSGGRNYVGDGGAPTAC}$ 

 ${\tt YQSCEYGGNPSPASCYLVKGSTTTGFCNYILKGTGQNCGADSYTFSQTGD}$ 

SLNPPDTPNTDPSDPNDPGCPPGWSWSGTTCVKAPTDPTDPTDPTTPGSD

GGGDGNGGGNNNGGGNDGGTGNGGDGSGGGDGNGGGDGSGTGGD

 ${\tt GNGTCDPAKENCSTGPEGPGGELKEPTPGTWDDAIATWEKKVEDAKQELK}$ 

 ${\tt TKVKANVDQMKGAFDLNLAEGGGQLPCESMTIWGKSYSLCISDYAGQLSS}$ 

LRVALLLMAALIAALILLKD

SEQ ID NO: 12

MAVAPGVLLPPTPDVKPKAAAPKSQQKTPEPSNDKTSSFSDMYAKETAKK

PAERADGPAKGSRDKPRDAGKDAAEAQPTDAVRQPAVAEDGKPLPADGQA

KADGEDKVETPVDPLOLLGLGGGAVPLLDENTOATLLPPAVPTASSAPASL

TEASSDPTLVKLNGVPAVNMALEQGAQDAAQTAKGGPAKSADPRQANLGD

ALAGLTSDSLTKAVDGKALEAQLQQTAEPAVASAASESLLESKAEPRGEP

 ${\tt FAAKLNGLTQAMAQQALTNRPVNGTVPGQPVAMQQNGWSEAVVDRVMWMS}$ 

 ${\tt SQNLKSAEIQLDPAELGRLDVRIHMTADQTQVTFASPNAGVRDALESQMH}$   ${\tt RLRDMFSQQGMNQLDVNVSDQSLARGWQGQQQGEGGSARGRGLAGEASGD}$ 

EETLAGVSEIRSRPGASAARGLVDYYA

SEQ ID NO: 13

MLRLLPLLLSLACLAPAFADERADTQRQLEQTQKDIGELKKLLDGIQQEK

SGVQKQLKSTETEMGDLEKQIKALQDELDKSEAELKRLDGEKKKLQDARI

EQQRLLAIQARAAYQSGREEYLKLLLNQEHPEKFSRTLTYYDYINKARLE
QLASFNETLRQLANVEQDISAQKAEQLSKQGELDSRREALAATRKERQQA
LAKLNSDYRERDQKLKSRQQDQAELAKVLRTIEETLARQAREAAAAAERE
RQRALAAERERARQQQAAPGRVTSPPREPAPGPLVSSTGAVYGGAFGSAR
GKLPWPVNGRVVARFGSQRGDDPRAKWDGVLISASAGSTVRAVHGGRVVF
ADWLRGAGLLVILDHGGGYLSLYGHNQSLLKDAGDTVKAGDPIATVGTSG
GQSSPAVYFAIRFIQGRPADPTTWCRAQG

SEQ ID NO: 14
MQRLSRIGRNTLAVSVSTLLLSACNQGDDAPKPAAVAPQPAAPSMAALSI
PLCLNGQCAVIDQDAKLLVPFDNDYDNIVASAYQGTLMAAREERWNLIQA
KDGKVLRDDIGEALSLLTPNLYGFVRDGKYGVVDGQGKEVQAPRFDDIYP
NSANEFIIYEIDGKRGILDAKGKQLTEALYDTTLVNGSVAEHGGLISAER
GEEKWIINLATGEQKAVAYESLGDLHDGVMSASVIGKGSQLVDAKGDVVG
DGKSYDYLGTPANGLVAFREKYDSPCGYLDYQGKVAIAAQFAGCGAFGKQ
GGLAQQRMEDGSSGKYGLIDRSGAWKVQPQYDSADSAGLTALGYTVDVPG
LAAVGVSTGLFSADFGIFNLDEGSEWVKPGYAQIGALGNDLFVVAKKGGP
QKTVSFMGSESQVPVVGLMDRSGKMLLEPDELISIQSAYDGRFLEGLDGM
DNAAHTVLLDRQGRTLVPALWQKLEVNPQQGYILGYEVSGTGDEATETLR
ALYDLNGKPRFTVATTDCGAEQLLDGNGKAIWPQDPTPYCQSDDEQDDEG
EPEQEPAPVEESEETSES

SEQ ID NO: 15
MLRPARSLSLCSALVILLAACGEGEPLLPADARLPDGARYRGELVDGRLE
GQGRLDYDNGAWYAGRFEHGLLHGHGTWQGADGSRYSGGFAAGLFDGQGR
LAMADGSVYQGGFRQGLFDGEGSLEQQGTRYRGGFRKGLYSGQGTLDGSD
GSRYQGSFRQGRLEGEGSFSDSQGNQYAGTFRDGQLNGKGRWSGPDGDRY
VGQFKDNQFHGQGRYESASGDVWIGRFSEGALNGPGELLGADGSRYRGGF
QFWRFHGQGLLEQLDGTRYEGGFAAGAYAGQGTLDRADGSREQGLWADGK
RIRDAAGKALPDTLEVGLLAQGRLLDEELRKIPASTPASELYALSLGGDG
RQGVFLREADYAGDLLGQRFAARGVIRLVNHRDHFGDRPLATRESLSRAV
RTLAERSGPEDLVFIYLTSHGSSDHQLALDMPGLNLGDLPAAELAELLAP
LRQRDKVLVVSACYSGGFIPPLKDERTLILTAARADRVSFGCSDDADFTY
FGRALLANALNRTDDLSKAFELAKEEVRQREKEEGFEASEPQAWLPERVL
AHWRTLRGOOAERALASREGKTGEGAAGK

SEQ ID NO: 16
MLQNIRDNSQGWIAKTIIGVIIVLLSLTGFDAIIRATDHSNVAAKVNGDD
ISLNEVQQAVDMQRRQLLQRLGKDFDPSMLDDKLLKEAALKGLIERTLLL
QAAKDDKFAFSDQALDQLILQTPEFQVDGKFNADRFDQVIRQMNYSRMQF
RQMLGQEMLIGQLRAGLAGTGFVTDNELQSFARLEKQTRDFATLAIKADA
SKSSVSDDEVKAFYEGHKSEFMTPEQVVVEYVELKKSSFFDQVKVKQEDL
EALYQKEIANLSEQRDAAHILIEVNDKVGDEQAKAKIDEIKARLAKGEDF

AALAKEFSQDIGSAATGGDLGYAGRGVYDPAFEEALYALKQGEVSAPVKT
PYGYHLIKLLGVQAPEVPSLESLKPKLEDELKKQMVEQRFVEATKDLESS
AYEAADLSQPAQEMGLKVQTSQPFGRSGGDGIAANRQIVQTAFSAEVLEE

AANSGAIELDPDTVVVLRVKEHNKPKEQPLEQVAANIRERLAAEKAAEEA

continued

QKRGEALIAELREGRTSSAAGESWKVVEAASRGHEGVDPKLLQAVFRMQR PEAKDKPSFSGVTLANGDYVVIRLNGVSEPEEAISDDEKAMYRRFLASRS

GQADFAAFRRQLQDKAEVEKY

SEQ ID NO: 17

MDMTSLMPLLLGVGLVVLLVVGLLALFKAFYIKVPQGTALIVNDMSSTPK
VHFTGALVYPVIHLKEFMRISLITLEVDRRGKDGLICRDNMRADITVAFY
LRVNETQDDVLKVAKAIGVDRASDRSAVNELFNAKFSEALKTVGKQFDFV
QLFENRQDFRDRIIEVIGNDLNGYVLEDVAIDYLEQTAKNSLDPSNILDA
EGIRKITELTATQNVITNELERNEELAIKKKNVETREAALALERQQADAE
ARQKREIETIRAREEAETARVKEEERLKAEQARIQAQQEIDVRTENHQRE
VEVAQQNRQRAVVIEVEKVTRAKDLEIVAREREVELQKIEKEKALEEQRK
NIANVIRERVAVEKTVAQEEERIKEVREVSEAERVKQVILLQAQAEAEQE
LVRQVKQAEADEARSKHKAVEINTMAQAELEAASKQAEAKKRLAEGIEAE
RAAPGLADARVLEVTAAAKEKDGLAAARVRAEQUAEARGDEERGLADARV
LEAQAAAKEKDGLAEAKVLAEKLGAQARGEEQLGAAKAKATKDQGSAEAE
VLLQRLNAEAEGLGKKFGALDALSDSARQHEEFRMQLEKSFEEAMAAIAA
NKDIAKDQAEVLATALGKANIEIVGGEGDFFNSFAKSLSVGKAIEGVVGK
SPVVQDVLARLLNGRGAAAAVMPERKSGHENEPAAEV

SEQ ID NO: 18 DERAESVVQLGDEV

MYPQFRRGHLAAAVLFASSSLLGGQALAEDERLEELDERAESVVQLGDEV

VLGTAEQELKQAPGVSIITAEDIRKRPPVNDLSEIIRTMPGVNLTGNSSS

GQRGNNRQIDIRGMGPENTLILVDGKPVSSRNSVRYGWRGERDTRGDSNW

VPPEEVERIEVLRGPAAARYGSGAAGGVVNIITKRPTDRLRGSMTVFTNI

PESSKDGATRRANFSLSGPLTEALSFRAYGSANKTDSDDTDINLGHTVNP

SRTVAGREGVRNRDLSGMLSWQVTPDQVVDFEAGFSRQGNIYAGDTQNNN

GTANTQGLADDGAETNRMYRENYAITHNGTWSGTSRFVAQYDSTRNNRLE

EGLAGSVEGQIGADRSFSASKLENYRLSGELNLPLHALFEQVLTVGAEWN

KETLNDPSSLKQGFVGSDSLPGTPAAGSRSPKSKAEIRALYVEDNIELRP

GTMLTPGLRLDDHSDFGLNWSPSLNASQTLGEYFTVKAGIARAFKAPNLY

QSNPNYLLYTRGNGCPIQTSSGGCYLVGNENLDAETSVNKELGIEFRRDG

WVAGLTYFRNDYKNKIVAPLDVMGQTGTGNNILQWSNAKKAVVEGLEGNL

LVPLHEDLSWSTNLTYMWSKDKDTGNPLSVIPEYTLNSTLDWQASERLST

QLTSTIYGRQEPPKHGTSRNTPVVSRKEVGTYGIWGVSAGYTFSENLSVR

SEQ ID NO: 19 MSSRALPAVPFLLLSSCLLANAVHAAGQGDGSVIELGEQTVVATAQEETK QAPGVSIITAEDIAKRPPSNDLSQIIRTMPGVNLTGNSSSGQRGNNRQID

IRGMGPENTLILVDGKPVSSRNSVRYGWRGERDSRGDTNWVPADQVERIE
VIRGPAAARYGNGAAGGVVNIITKQAGAETHGNLSVYSNFPQHKAEGASE
RMSFGLNGPLTENLSYRVYGNIAKTDSDDWDINAGHESNRTGKQAGTLPA
GREGVRNKDIDGLLSWRLTPEQTLEFEAGFSRQGNIYTGDTQNTNSNNYV
KQMLGHETNRMYRETYSVTHRGEWDFGSSLAYLQYEKTRNSRINEGLAGG
TEGIFDPNNAGFYTATLRDLTAHGEVNLPLHLGYEQTLTLGSEWTEQKLD
DPSSNTQNTEEGGSIPGLAGKNRSSSSSARIFSLFAEDNIELMPGTMLTP
GLRWDHHDIVGDNWSPSLNLSHALTERVTLKAGIARAYKAPNLYQLNPDY
LLYSRGQGCYGQSTSCYLRGNDGLKAETSVNKELGIEYSHDGLVAGLTYF
RNDYKNKIESGLSPVDHASGGKGDYANAAIYQWENVPKAVVEGLEGTLTL
PLADGLKWSNNLTYMLQSKNKETGDVLSVTPRYTLNSMLDWQATDDLSLQ
ATVTWYGKQKPKKYDYHGDRVTGSANDQLSPYAIAGLGGTYRLSKNLSLG

SEO ID NO: 20 MSPSRALSPLSRALLLACLGGPVLVSAGSACAAEIRTDARQYYRLPAEPL EOALNHLGROAGVLIAFSPEOTAARRSOALDGEYTLEEALAALLVGSGLE ARARGDGAYTLEALPVEDPANLQALTVVGDWLADASAADVFEHPGARDVV RREQFQAQGAASTREVLERIPGVSAPLNNGTGSHDLALNFGIRGLNPRLA  ${\tt SRSTVLMDGIPVPFAPYGQPQLSLAPVSIGNMDAVDVVRGGGAVRYGPQN}$ VGGIVNFVTRAIPEDFATKLDVHSELSPSSSQDGLKTTHNVLIGGTGANG LGGALLYSGTRGGDWREHSDTRIDDLILKGRFQPSDEHTFSAMTQYYDGE ADMPGGLGTAAYHDDPYOSTRPYDKFWGRRTLASASYEYTPNASOKLNVT GFFTKTLRSGYLDQGRNLTLSPREYWVRGLETRFSQGFELGESRHEVGIG HRYVNEASHELRYWTRADSGOLPSTGSRNDRDTRGSTEANAFYIDDRIDI GNWTITPGIRYEKIDSEOKNLLKNSKDSGRYNASLPALNVIYHLTPSWNL YANTEGSFGTVQYSQMGKAVRSGDIEPEKARTWELGSRYDDGILRAELGA FLINFDNQYESNQQTDSVTARGKTRHKGIEAAIAYDLADLDPLLSGFDVY ASYAYVDASIREDGPNKGNQVPFSSKHKGTLGANYRTGAWSYNLDGSFQT SQYADNANTESESADGSTGRIAGWMVWSARGTYDFGPQLNDLKLGLGVKN LFDRRYYTRSFDDNNKGLYVGOPRTLYVOASVGF

SEQ ID NO: 21
MTLPFTRAAWRPLCSAAVLGAALWAAGASAAERRFDLPAQPLAASLSRLA
QQAQVQVLFDESLLRGLRAPALSGSYGVREALERLLVGSELELVEAGGGY
VVRRRQVDAYSDNALQLDAQTIVGNGREVDASNVGRSTLTRRDIERQQAD
NIPSLLQTLPGVTMGGSPKPGGQTTNIWGLGDAEDVPYTLDGAQKSGFER
YQQGTVFIEPEMIKRIEVEKGPHSVFTGNGGFGGTVHMETKDAPDLLREG
RDVGAMLKYGYHSNDQQKIYSGAVFGRSEDRRVDALLYLNGRDGRDMKLA
DNLPLSPTDYPINPKRLPNSAQDEKTGLFKLNLHPTEEHDLGFTYLRSKS
SRWTPFSASSYPTPPSQWTIDRYGYELGLTRLLAHRDTTDTTWTGKYNYH
PLDNPWIDLQLSYSDARTEQLDRREDTAFYQLATGGKRMRTEYQDKVLEL

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RNTSRFDTGALQHELTLGAALHKHKRDILMHMPGKTYETPRYNYGWLQPA
FMPAGKQDTQSFYIQDAITYGSLTVTPSMRFDSVRNDGQANLAPIYDNPK
LGHDYRAQTYSGWSPRLSVFWTATPNLAFFADYTETWRAPVIDEQYEVQN
SSTIGGSSRDLDAERIHAIRGGSVINLPDLLVAGDSLQIRTTLFQNRIKD
EIFRTRSVGCRQQSIDNGSIGGSCGDMLPLSNYRNLPGLTIKGFEIESFY
DSQRLFGSLSYSWMTGKHDGAYSNPWGPNVWARDIPPPKWVAMLGLKVPE
WDAKLGWQGEFVRKTDRLPSDRYSGGMGTGSGDIYWDHAANDSYDTHRLF
AEWVPAKLGLKDTRIDFTVDNLFNRSYRQPLGGDLVYSQGRNAKISVTQF

SEO ID NO: 22  ${\tt MHRSLHTDAPLGAALLLALQLAPGSAAAAEEQAPVDPPTVQLQRIEVTGS}$ AIRRVDAETAVPISVLRAEELROOGVTSTEELIGRLSGNOGVYNSSRSVG SATGGASFADI.RGTGANKTI.VI.I.NGRRI.ANNATDGSAVDI.NTTPFAATDR VEVLRDGASALYGTDAIGGVINFITRKSLNEGRFDSGYASPTHDGGGNOR NVSASWGFGELEEDRFNVFAVANYDKQERLGAKDRGYTYNYQPGRGLDYS SGTAFPGNWSOGANASNPLAAGGCKGADLIPRNGICROSLWRYLDLVPET EKTSVFSRATGKLADEHNVSLEYFWSRSDNATQVGPGTLTGLQIDPGTAF  ${\tt YPGNGITPGPGGFVLDPSRPVEVNWRQSVLGPRLQSSQNTGQRLLLGFDG}$  ${\tt QFAGWDYDIGASYNQNKVVDHIHSGYVDDRAAALGIANGTLNPFGPQTDA}$  ${\tt GLAYLGSHALSGDFRTSVGRVKGLDARASREIGDWFGAGPAALALGGEFR}$  ${\tt KEAFHQDIQDFAGNVQSLGVDPAATVSGERNLKAQYAELNVPVLDSLELS}$ AAIRHDKYSDFGSTSNPKYSFRFOPFROLVLRGAYSEGFRAPSLYELYNP TFTTYTSANYDDPRLCAGGQPSQGGIANRDCAQQFYNATGGNTDLRPETA RNVTLGLVYQPLRDLSVGLDFWWIRIANQIAEFPEAAIFADPQAYAGRIV RKADGSIDHVVTGLANLGKVKTSGVDLSLDYRFPASRYGOFGLDLOGTYV SRYDFQQQIGGQYLDNVGDFQGVGVIARWKHVANATWSRDAWQATLSNRY TSGYNDYDRASHGKVGSWNLWDLAGSYRLSHALGLTLGVKNLFDREPPFS NQTYTFQSGYDPRYTDPYGRILFGRLSYSF

SEQ ID NO: 23
MVRLRTLVRAIAAASVLTSGMAHGLGLGEITLKSALNGLDAEIELLEVRD

LGSGEVIPSLASPEEFSKAGVDRLYYLTDLKFTPVVKPNGKSVIRVTSSK

PVQEPYLNFLVQVLWPNGRLLREYTVLLDPPLYSPQAAASAPQAPVSAPR

ATGAPRAPQAPAPVRTTAPAGSDTYRTVSNDTLWEIAQRNRTDRVSVPQA

MLAFQELNPGAFVDGNINRLKSGQVLRIPTEQQMLERSPREALSQVQAQN

QSWRGSRNPAAGSAGAQLDATQRNAAGSAPSKVDATDNLRLVSGEGKASK

GADKGGKGDSKAIADTLAVTKESLDSTRRENEELQSRMQDLQSQLDKLQK

LIQLKDAQLAKLQGQLGAEGQGAAQPNAALPDASQPNAAAQAPAQPGTPA

AAAPTPAPAGEAPAAPAQPPVAPPPAPAAEKPPAPAVPAPAPVQAAEQPA

PSFLDELLANPLWLAVIGGSALLALLVLLMILSRRNAQKEKEEAQAFAAD

TGEEQEDALDLGKDGFDDLTLDEPEPQVAAVAPQVEKTTAQTSDALGEAD

IYIAYGRFNQAAELLQNAIYDEPQRTDLRLKLMEVYAEMGDREGFARQNE
LREIGGAQPQVEQLKSRYPAMVAVAAVAGLAGAKLAQDELDSFSLDDLSL
DDSGHAAKPDAAGQDLDDAFDLSLDDLGGDDVQADLKSDSGALDDLTLDS
DLDLAASTPADKPVDDLDFGLDFAELAETPSQPKHDDLGDFSLDLDAPED
KLSDDDFLLSLNDEVPAAAPADNEFTLDTEAAEEPALSLPDDFDLSLADE
PTEPAAPEKGEDSFAAQLDEVSAQLDELASNLDEPKSATPSFSAEDAAVA
SALDGDADDDFDFLSGADEAATKLDLARAYIDMGDSEGARDILDEVLAEG
NDSQQAEARELLERLA

SEO ID NO: 24 MTDDHSFRPRPTSLSAALLLGAWIAOPATAAYVEAGRPGDPASWRSAEYO ODWGLERMRADOAYAAGIDGOGVKIGEMDSGFDPSHPDTPASRYOPVTAS GTYVDGTPFSVSGAMNGNNDSHGTHVGGTLGASRDGVGMHGVAYAAOVYV ANTHONDS FLEGPT PDPNYFKAAYOALADAGVRAINNSWGSOPKVSYETL DGLHAAYAOHYGRSTWLDAAAGVSROGVINVFSAGNSGYANASVRSALPY FOPDLEGHWLAVSGLDOONGORYNRCGIAKYWCITTPGRLINSTMPGGGY ANKSGTSMAAPHATGALALVMORYPLNNEOALOVLLTTATOLDGTPTGAP TDTVGWGVPDLGRAMHGPGOLLGRFEANLPAGLRDEWSNPISDSALLORO AEDAAEHAAWQRTLKDKGWENGLPAGASQQERTDYAIGMARDQAAAQRQY QGSLVKAGAGSLVLSGDSTYRGPTLVDGGLLSVDGSLLSAVEVNAGGTLG  ${\tt GSGRIGGLLARSGGTVAAGNSIGTLEVAGDLRFESGSTYAVELSESASDR}$ IVASGKASIAGGNVTLAMENSPDLLSQSQVESLVGRRYDILDAAGGIDGR FDAVLPNYLFLGGTLDYAANAIRLDIGRNGTTLASVAOTPNOAAVAGAVE TLGAGNPVYESLLLSENAATAQRAFQQLSGEIYPALAGLLLNDSRYLRDS VGERLROTSDGEAGGEAPEGWFKALGSWGKSADGSHGSEGYRHSVGGFLL GVDSQVASDTRLGLVAGYSNSSLNMDSSLQSSASIDSYHLGAYLGRQLQQ WRLSLGAAHAWHRAEVKRDLQYGAVAGKQKAKLDAQSSQLFAEAAYALGW  ${\tt RSLELEPFAGLAYVHVASDDFRERGSAAALEGGDDNLDAAFTTLGLRAKR}$ HFELDAGRRLALSGTLGWRHNLSDTTPQRHLAFASGSQPFSVESVALSRD AALLGVDASLAVNREVSVRLGYNGLLGSREKDHGVGLAVDWRF

SEQ ID NO: 25
MKRMLINATQPEELRVALVDGQRLFDLDIESGAREQKKANIYKGRITRVE

PSLEAAFVDFGAERHGFLPLKEISREYFKKSPEGRINIKEVLSEGQEVIV

QVEKEERGNKGAALTTFISLAGRYLVLMPNNPRAGGISRRIEGEERNELR

EALNGLNAPADMGLIVRTAGLGRSTEELQWDLDYLLQLWSAIKEASGERG

APFLIYQESNVIIRAIRDYLRQDIGEVLIDSIDAQEEALNFIRQVMPQYA

SKVKLYQDSVPLFNRFQIESQIETAFQREVKLPSGGSIVIDPTEALVSID

INSARATKGGDIEETALQTNLEAAEEIARQLRLRDIGGLIVIDFIDMTPA

KNQRAVEERVREALEADRARVQVGRISRFGLLEMSRQRLRPSLGETSGIV

CPRCNGQGIIRDVESLSLAILRLIEEEALKDRTAEVRARVPFQVAAFLLN

EKRNAITKIELRTRARIFILPDDHLETPHFEVQRLRDDSPELVAGQTSYE

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MATVEHEEAQPVSSTRTLVRQEAAVKTVAPQQPAPQHTEAPVEPAKPMPE
PSLFQGLVKSLVGLFAGKDQPAAKPAETSKPAAERQTRQDERRNGRQQNR
RRDGRDGNRRDEERKPREERAERQPREERAERPNREERSERRREERAERP
AREERQPREGREERAERTPREERQPREGREGREERSERRREERAERPARE
ERQPREGREERAERPAREERQPREDRQARDAAALEAEALPNDESLEQDEQ
DDTDGERPRRRSRGQRRRSNRRERQREVSGELEGSEATDNAAAPLNTVAA
AAAAGIAVASEAVEANVEQAPATTSEAASETTASDETDASTSEAVETQGA
DSEANTGETADIEAPVTVSVVRDEADQSTLLVAQATEEAPFASESVESRE
DAESAVQPATEAAEEVAAPVPVEVAAPSEPAATEEPTPAIAAVPANATGR
ALNDPREKRRLQREAERLAREAAAAAEAAAQAAPAVEEIPAVASEEASAQ
EEPAAPQAEEITQADVPSQADEAQEAVQAEPEASGEGAADTEHAKKTEES
ETSRPHA

SEO ID NO: 26 MKSVLHQIGKTSLAAALSGAVLLSAQTTHAAALSVSQQPLMLIQGVAPNM LVTLDDSGSMAFAYAPDSISGYGNYTFFASNSFNPMYFDPNTQYKLPKKL TLVNGOVOIODYPAPNFSSAWRNGFTRSGSINLSNSYKVTIEYGRGYDKE STIKADAAYYYDFTGSSSCNRTNQACYTRRYVSTEQRQNFANWYSFYRTR  $\verb|ALATQTAANLAFYSLPENARVSWQLLNDSNCNQMGSGSSSGNCFSNYLRD|$  ${\tt FTGQHRVNFFNWLEKLSVNGGTPLRQAMTRAGEFLKKTGVNGPYAYRPGT}$  ${\tt QTAPEYSCRGSYHILMTDGLWNNDSANVGNADSTARNLPDGKSYSSQTPY}$  ${\tt RDGTFDTLADQAFHYWATDARPDIDDNIKPYIPYPDQANPSAEYWNPRND}$ PATWQHMVTYTLGLGLTTSLTSPRWEGSTFSGGYNDIVAGNLSWPRASNN DSNNVYDLWHAAVNSRGEFFSADSPDQLVAAFQDILNRISGKDLPASRPA  ${\tt ISSSLQEDDTGDKLTRFAYQTSFASDKNWAGDLTRYSLTTQDKATVQTKL}$ WSAQSILDAMPNGGAGRKIMMAGSGTSGLKEFTWGSLSADQQRQLNRDPD RNDVADTKGQDRVAFLRGDRRKENSDNFRTRNSILGDIINSSPATVGKAQ YLTYLAQPIEPSGNYSTFAEAQKTRAPRVYVGANDGMLHGFDTDGNETFA FIPSAVFEKLHKLTARGYQGGAHQFYVDGSPVVADAFFGGAWHTVLIGSL RAGGKGLFALDVTDPANIKLLWEIGVDQEPDLGYSFPKPTVARLHNGKWA VVTGNGYSSLNDKAALLIIDLETGAITRKLEVTGRTGVPNGLSSPRLADN NSDGVADYAYAGDLOGNLWRFDLIAGKVNODDPFSRANDGPAVASSFRVS FGGQPLYSAVDSAGAAQAITAAPSLVRHPTRKGYIVIFGTGKYFENADAR ADTSRAOTLYGIWDOOTKGEAAGSTPRLTRGNLOOOTLDLOADSTFASTA RTIRIASONPVNWLNNDGSTKOSGWYLDFMVNGTLKGEMLIEDMIAIGOV VLLQTITPNDDPCADGASNWTYGLDPYTGGRTSFTVFDLARQGVVDSKSD YSYNKONVAVSGTEOKGLGGLTLSTNEOGNPEVCSSGECLTVNPGPNTRG RONWRPIEGKN

SEQ ID NO: 27 MKILAIRLKNLASLAGEQEIDFTREPLSSAGLFAITGPTGAGKSTVLDAL CLALFGSTPRLESTSASSKVPDGRNELSSNDERNLLRRGCASGYAEVDFV

GIDGHRYRARWETRRSRDKADGALQKSQQSLQDLETQQMLAANKKSEFRE QLEQKLGLNFAQFTRAVLLAQSEFSAFLKASDNDRGALLEKLTDTGLYSQ LSKAAYQRASQADEQRKQLEQRLEGSLPLAEQARAGLEAALESHAQARLQ EQQALQRLEGQQQWFTEEQRLLQSCEHAQGQLAEARQAWDALATERETLQ WLERLAPVRGLIERLKQLEQELRHSEQQQRQRTEQQAAGTERLQGLQARL QEARERQAQADNHLRQAQAPLREAFQLESEARRLERTLAERQELHRQSNQ RHAOOSDAAROLDMEOORHVAEOAOLOAALRDSOALAALGDAWVTHOGOL ATFVQRRQRALESQAQLPELEKSLAHAGEPLERLQAQWTALHGSEPDDLA ARLVELRROTDSLEROOALHKEWOOVLDORAGLARRLGELDORMVEOEOA LLDLKRQGSQCAEEVKAAEQALQVTRELLQRQRLARSASVEQLRAGLVDG EACPVCGSOEHPYHHSEOLLAALGEHDDOEOVRAEOSLERLROTLVGLRE GYSSQRERLNQSRQEQQELTGQLAALDRQLDQWTLPEELRLLQPSAQLEW LAQRLDDLAGQRQQCQRDFDRLIARQRQTQQLQQELRAAETILQQRQQAL TEQRORYEHLOQOVEEDSQQLRPLLSDEHWQRWQADPLRTFQALGESIEQ  $\tt RRQQQARLQQIEQRLQELKQRCDESSWQLKQSDEQRNEARQAEERAQAEL$ AELNGRLGAHLGQHACAQDWQLSLEHAAQAAQSAVETLQAPLDSLREEQL RLAEALEHLQQQRQRQQDEFQRLQADWQAWRERQDNLDDSRLDALLGLSE EQATQWREQLQRLQEEITRQQTLEAERQAQLLQHRRQRPETDREALEDNL RQQRERLAASEQAYLETYSQLQADNQRREQSQALLAELERARAEFRRWGR LNELIGSSSGDKFRRIAQGYNLDLLVQHSNVQLRQLARRYRLQRGGSELG LLVVDTEMGDELRSVYSLSGGETFLISLALALGLASMASSKLRIESLFID EGFGSLDPESLQLAMDALDNLQAQGRKVAVISHVQEMHERIPVQVRVQRE GNGMSSLKVVG

SEO ID NO: 28 MSIQAKVTPIDQSISSAAAVEVPENGILKLSQSSNVALDVAPESVAGYSK SGSDLIVQLKTGESVRIANFYAEGQPSSQLFLADKDKLVAVDLPPVAADG PLMAGYIPQESLAGFESLTGAGVLGGMSAGTALLVGAAAIGAGVAISNSS GGGGGGGSSVPPDTTPPKAASGLKIAPDGSSISGQAEAGASVGIDTNGDG KPDLTVIADANGNFTAPLNPPLTNGOTVTVVVTDPAGNASPPAOVTAPDT TAPAPATDVOVAPDGSSVTGKAEPGSTVGVDTDGDGOPDTTVVVGPGGSF EVPLNPPLTNGETVTVIVTDPAGNNSTPVTVEAPDTTAPAPATDVOVAPD GSSVTGNAEPGATVGVDTDGDGOPDTTVVVGPGGSFEVPLNPPLTNGETV TVIVTDPAGNSSTPVTAEAPDFPDAPOVNASNGSVLSGTAEAGVTIVITD GNGNPIGOTSADANGNWSFPGSOLPDGTVVNVVARDAAGNSSPATSITVD GVAPNAPVVEPSNGSELSGTAEPGSSVTLTDGNGNPIGQTTADANGNWSF TPSTPLPDGTVVNVVARDAAGNSSPPASVTVDAVAPATPTVDPSNGTTLS GAEPGSSVTLTDGNGNPIGOVTADGSGNWTFTPSTPLPNGTVVNATATDP SGNASSPASVTVDAVAPATPVVNPSNGTTLSGTAEPGATVTLTDGNGNPI GQVTADGSGNWSFTPTTPLPNGTVVNATATDASGNTSAGSSVTVDSVAPA

continued TPVINPSNGTTLSGTAEPGSSVTLTDGNGNPIGQVTADGSGNWSFTPSTP LADGTVVNATATDPAGNTSGQGSTTVDGVAPTTPTVNLSNGSSLSGTAEP GSTVILTDGNGNPIAEVTADGSGNWTYTPSTPIANGTVVNVVAQDAAGNS  ${\tt SPGASVTVDSQAPAAPVVNPSNGTTLSGTAEPGATVTLTDGNGNPIGQVT}$ ADGSGNWSFTPGTPLANGTVVNATASDPTGNTSAPASTTVDSVAPAAPVV NPSNGAEISGTAEPGATVTLTDGSGNPIGQVTADGSGNWSFTPSTPLADG TVVNATATDPAGNTGGQGSTTVDAIAPATPTVNLSNGSSLSGTAEPGSTV ILTDGNGNPIAEVTADGSGNWTYTPSTPIANGTVVNVVAODASGNSSPPA TVTVDSSAPPAPVINPSNGVVISGTAEAGATVTLTDAGGNPIGOVTADGS GNWSFTPGTPLANGTVIVATATDPTGNTGPOAATTVDAVAPPAPVIDPSN GTTISGTAEAGAKVILTDGNGNPIGETTADGSGNWSFTPGTPLANGTVVN AVAODPAGNTGPOGSTTVDAVAPNTPVVNPSNGNLLNGTAEPGSTVTLTD GNGNPTGOTTADGSGNWSFTPGSOLPNGTVVNVTASDAAGNTSLPATTTV DSSLPSIPOVDPSNGSVISGTADAGNTIIITDGNGNPIGOVTADGSGNWS FTPGIPLPDGTVVNVVARSPSNVDSAPAVITVDGVAPAAPVIDPSNGTEI SGTAEAGATVILTDGGGNPIGOATADGSGNWTFTPSTPLANGTVINAVAO DPAGNTSGPASVTVDAIAPPAPVINPSNGVVISGTAEAGATVILTDGNGN  ${\tt PIGQVTADGSGNWSFTPGTPLANGSVINALAQDAAGNNSSPTSATVDSLA}$  ${\tt PAAPVIDPSNGSVIAGTAEAGATVILTDGNGNPIGQVTADGSGNWSFTPG}$  ${\tt TPLSNGTVVNAVAQDAAGNTSGPVSTTVDAVAPATPVIDPSNGVELSGTA}$  ${\tt EPGVRVILTDGNGNPIGQTLADGSGNWSFTPGTPLANGTVVNAVAQDPAG}$ NTSGPASTTVDTVAPATPVINPSNGSVITGTAEVGAKVILTDGNGNPIGE TTADGSGNWTFTPGTPLANGTVINAVAEDAAGNASGPASTTVDSVAPSAP LLSISADGALLTGTAEPNSOVRIVVNGDTANPITVTVDGAGNFSLPFAPP LITGELIAGVAVDAAGNVSGPATINAPDLAPPTISVPEAADTWINAAEIG  ${\tt DGIQVDVTVRPTMQVGQVVTVKFAGQNGYEAEVSHTLTAGDIAAGNLTLT}$ LTPPGGMGPFPEGASTVTADINGGTASTPVPFTIDTIPPATPVLSLVGNI LTISAEPGTELTVTVDVGGVTATATVTADNSGLASLNLLTDLDIDFSWDQ LLNAOVSVVGRDPAGNPSNTASIGVGTSIEOPVTIGNFGLDVSLNPLNPR FGFSGTTEPDSSVVIRVITPALNVELLPIOADSSGNFSLNLLSPTILTOL GLNITDILNLGSO1SFNLVSTDSNGNDSAAYGITLTPNGLSLNIGOIDVN GTSGDDVLSGANGSSEHINGGDGSDLIFNVGTGDHVVAGNGNDTIOITAT DEVSTDGGAGEDTI.VI.ANGTDI.DYNAVGVGTI.SNI.ERTDI.GKGDSGSVI.T LTAAEVDAITDANNTLQITGENNDTLNVVGAVNTGTTQLINGITYDVYTF

SEQ ID NO: 29
MDIRSPLNQCIALSLAGILFLNPIVAAAAGLALDKAAGGNTGLGQAGNGV
PIVNIATPNDAGLSNNHFRDYNVGANGLILNNATGKTQGTQLGGIILGNP
NLKGQAAQVILNQVTGGNRSTLAGYTEVAGQSARVIVANPHGITCQGCGF
INTPRATLTTGKPIMDGQRLERFQVDGGDIVVEGAELNVGNLEQFDLITR

GSTTLLIEDNTVOVVV

# -continued saklnaklyaknlnivtgrndvoadsloatpraadgsekpolaidssalg

 ${\tt GMYAGAIRLVGTEQGVGVRLAGDMAASGGDIRIDASGKLSLAQASSQGDL}$ KIAAQAVELNGKTYAGGSAEIRSAEELVNRQSLAARERIVLEAAHIDNAG VIEAGVEPDERRNARGDLELRSGTLRNAGSLVASRALEAKASQALDNQGG  ${\tt SLKGATVRVDAGHLDNRGGKLLAEGELRVEASSLDNRQDGLLQSRDRAVV}$ KTRGDLDNRGGQVIGLNDLEVGAATLDNGQQGLLGSQQSTRVSAQALVNR  ${\tt GDGEVSGKRVEARVGSLDNRGGKLIGDDLLVVASGAIDNRLGLFSAANRL}$ DLRARSLDNSGKGTLSSRGGLEVSLGGLLDNRDEGNLLSQGAQRVTVGQL DNRAGGLLSSRSELNVHGASLDNRGGVLVADAGLSATGGAFDNRDGGSAS GKAGVRVEVASI RNDOGGKLI SDGRI DI AANAVGNAGGRI AAKGDI OATI. GSLAQQGGELVSEKTLKVAADTLDNSQSGLIAANGGIAIEARQVDNRAGE ISSTSKVAVNAREQLDNRGGKVIGDSGLRLTVQRLLNQAKGVLAGRDGLS  $\verb|LDGGELFNGDGGRLDSQNSLSVSLGGVLDNQGGALVSEGSLTARAARLDN|$ RGGTFSSAGALALTSQAALDNQGGRLLSDAGVTLQGASLDNSRSGVISAK  ${\tt GAVDIRTGVLDNSRNGGIGSNAGITLVAARLDNGQQGRVSAKGLLDANLK}$  ${\tt GLDQRGGGVLISETGVTLDLNGGTLVNRDGGLIATPGALLLRQLGAVDNG}$ AGGEISSDRAFTLAAASLDNRGGRLIGAANLTLRIAQALDNSLAGVISGA AGLDIAAARLDNSAKGTLASRAGIDLRVDGALDNHAEGTVSGARLTLASA  ${\tt SLDNSGKGLLSGNAGLSVATGALDNAEGGQLISQGVLDVSSADLDNRGGA}$ LSGKQSLRLSAANLDNRGGLLTSDGELELTAGRVDSADGGEISARGDLRL TVERLVQRQGRLVGERGVSLDLRGGDLDNQGGLISARGPLSIERLSVLDN RQGGEISSQQGFELLARRIDNGQQGRIISAGKLRLDADALGNAGAGLLSG WQGLTVTGGSLDNSAGGTLSSKDGELAISLGGALDNHGQGALVSKGAQRI  ${\tt DAASLDNAQGIVSGESDVTLSIAGKLDNGQGGLVSAQRALSFERDDTLLN}$  ${\tt NAGGRINGGSLLLKGASLDNSDGQLISQGRLDAILGGALVNTGAARLASG}$ GDLLLRSASVDNRGGKLVSQGLLEISAGSLDNSASGTLASQAGMSLRLGG  ${\tt GALRNQQDGLIFSQAGALDVQAGSLDNRQGTLQAQGDNRLRIGGALDNQG}$ GRLDSRAGNLDLQSGSLDNGAGGVLNSAKGWLKLVTGLFDNSAGVTQAQS LEIRAGOGVRNOOGHLSALGGDNRIVTADFDNOGGGLYASGLLSLDGORF LNOGAAAGOGGKVGAGRIDFSLAGALANRFGOLESESELHLRAAAIDNSG GSLRALGRSGSTRLVAGGLNNAYGVLESANODLDLOLGSLANAGGRILHT GNGTFGLDSGOVIRAGGELTTNGLLDIRASEWTNSSVLOAGRLNLDIGTF RQTAEGKLLAVQSFTGRGGDWSNDGLLASDGSFRLDLSGGYRGNGRATSL GDFALNAASLDLGNAASLAGGANVTLGAGNLLVNRGRITAAGDLVASAAS LNNYGTLGGGGNLRLNAPALLNERGLLFSGADMTLRAGDITNLYGDVYSL GRLDIARDDAGNRAASLRNLSGVIESGKDFSLRASLIENRRAVLESKSGL YTAKMEQTACIEGVNAGDCSGKRNAIWTITQRDKTEVTASSAMGQLLAGG DFAIDGGTLNNLSSLIGSGGNLTANLEVLDNOGLETGELETIRVLRTARG GDIGGIDQKSRNFTNLYWYQSANFDPARAGEIPAALNAILSDWSFEYEFP

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SKGPTPISSGDQSYAAVIQAAGDVTVNASTRIDNGVTRPGYTFVGSGRQV GDSAVGGSGVSVVVPLTSQLPPDLARRQVNPVTLPGFSLPQGDNGLFRLS  $\tt SRFAEDGNGSAALGAGADRTQGGSGVSVGQQGAGNAAGTWQGQGVRVDGL$  ${\tt AGAANVQGQGGSTLGGSLPGVARVQGVPGNATPSASKYLIETNPALTELK}$  ${\tt QFLNSDYLLSGLGMNPDDSKKRLGDGLYEQRLIRDAVVARTGQRYIDGLS}$ SDEALFRYLMDNAIAYKDQLHLQLGVGLSAEQMAALTHDIVWLEEVEVNG EKVLAPVVYLAQAEGRLAPNGALIQGRDVKLVSGGDLHNVGTLRARNDLS ATADNLDNSGLIEAGKRLDLLAGDSIRNRQGGVIAGRDSLTALTGDVINE RSVTRYDSALDGRTWERSFADSAARVEAANSLNVOAGRDIANLGGVLOSR GDLSLDAGRDVTVAAVEDROGOTRWSTSRLOSVTOLGAEVSAGRDLNVSA GRDLTAVASTLEARRDIALSAGRDVTLAAAANEEHAYSKTRKVTYOEDKV AQQGTRVDAGGDLAINAGQDLRLIASQASAGDEAYLVAGDKLELLAANDS NYYLYDKKKKGDFGRKETRRDEVTDVKAVGSQISSGGDLTLLSGGDQTYQ GAKLESGNDLAIVSGGAVTFEAVKDLHQESHEKSKGDLAWNSAKGKGQTD  $\verb"ETLRQTQIVAQGNLAIKAVEGLKIDLKHIDQKTVSQTIDAMVQADPQLAW"$  $\verb|LKEAEQRGDVDWRMVQEVHDSWKYSNSGMGPATQIAVAIAAAAIGGMAAA|$  ${\tt GALSGAGVGASSFAMGAGVGAAGSLSGTAAVSLINNKGDLGKVLKDSFSS}$  ${\tt DSLKQIAIASLTGGLTAEYFDGILQTKTDPLTGKVTVDLSSLSGVGRFAA}$ NQAMQNATSTVLSQALGQGGSLNEALKSALYNSFAAAGFNFVGDIGQEYS LKPGDPSMVTMHALMGGLAAQVSGGDFATGAAAAGANEALVAKLDQAFKS LSPENREAMVTMGSQLVGVLAAAVRDPDVTGKALESAAWVAKNSTQYNFL NHQDVADLDNALQKCKSQGNCRQVEEEFKARSDENRRRLNGCVAVGNCAE IRAEIDAGSTALNELVAROETANPGGSDSDIAYGFLMGRNVVDWTTAGOL  $\verb+LLEQTANLWWNGNPQWQKEVGAYLDQTGFNPFGIGVPAMGGAAGKVTAKA$  $\verb|LMNALKAGELPKGEVAPGKANLPTIGALADAEAGMPYTHPVKLAAKATGT|$  ${\tt AGKIKIEAGAIPDANEVRAGQGLSGLGYDVTHQTTASAKGIQGQRTADLH}$ VDGLGSIDVYTPKNLDPTKIVRAIEKKSNQAGGVLVQADLPSTDMSSIAA RMWGKTNAQSIKTIFFQKPDGSLVRFDRPAGGG

SEQ ID NO: 30
MDIRSPLNQCIALSLAGILFLNPIVAAAAGLALDKAAGGNTGLGQAGNGV
PIVNIATPNGAGLSNNHFRDYNVGANGLILNNATGKTQGTQLGGIILGNP
NLKGQAAQVILNQVTGGNRSTLAGYTEVAGQSARVIVANPHGITCQGCGF
INTPRATLTTGKPIMDGQRLERFQVDGGDIVVEGAELNVGNLEQFDLITR
SAKLNAKLYAKNLNIVTGRNDVQADSLQATPRAADGSEKPQLAIDSSALG
GMYAGAIRLVGTEQGVGVKLAGDMAASGGDIRIDASGKLSLAQASSQGDL
KIAAQAVELNGKTYAGGSAEIRSAEELVNRQSLAARERIALEAAHIDNAG
VIEAGVEPDERRNARGDLELRSGTLRNAGSLVASRALEAKASQALDNQGG
SLKGATVRVDGGHLDNRGGKLLAEGELRVEASSLDNRQDGLLQSRDRAVV
KTRGDLDNRGGQVVGLNELQVQAAALDNRSAGLLSSKGDMDIEFARLDNS

AGGKLVSERRTLLKADRLDNRSGRIVAGQDLDLSSRLIDNRAGDISSTSR VVASAREQLDNRGGKIVGDSGLDITTPRMLNQDKGVLASRDGLRLSATEL FNGAGGLLSSOKGIDVSLAGAFDNOAGSLDSRGFLTVKSAWLDNOGGTLS SAGALAVTSQGALNNQGGRLASDAGLSLSSASLDNSQAGAISGKGAVEIR TGNLNNSRKASIGSDAGLTLVAARVDNSQAGRIAAKGVIDADLQGLDQHD RGNLVSDTGITLDLNKGSLVNRAQGLIATPGTLLLRQLGVVDNSGGEISS DRAFTLATSALNNQGGRLLSGGALTLRIAQALDNSLEGIVSGAGGLDIQA FVLDNRSGSIGSKGAIDIGVTRLENDAGTLIAERGLKLVADEANSSKGRI AANGSLHAKVGTLSOKGGELTSODSLTLDLGILNNNAGRIAGNOGVDITA ROVDNSVGEIASOGVVALNLTEOLDNRGGKIVGDSGLGITAPHVLNODKG VLASRDGLRLSATELFNGAGGLLSSOKGIDVSLAGAFDNOAGSLDSRGFL TVKSAWLDNOGGTLSSAGALAVTSOGALNNOGGRLASDAGLSLSSASLDN SOAGATSGKGAVETRTGNI,NNSRKASTGSDAGI,TI,VAARVDNSOAGRTAA KGAIDAALQGLDQHDRGSLVSDTGITLDLNKGSLVNRAQGLIATPGTLLL RQLGVVDNSGGEISSDRAFTLATSALNNQGGRLLSGGALTLRIAQALDNS LEGIVSGAGGLDIOAFVLDNRSGSIGSKGAIDIGVTRLENDAGTLIAERG LKLAADEANNSKGRIVAKDELRAKLGALVQNGGELTTQGALALDADKVDN GAGRIAGNRGVVIDARQVDNRAGEIASQGVATLNLTEQLDNRGGKVVADS  ${\tt GLGITAPRVLNQDKGVIASRDGLRLSGTELFNGNAGLLSSQRHIEVTLDG}$  $\verb|VLDNQGKGALLSDGTLTVSAGRIHNQDATLSSAGALRLSSQEAVDNRGGK| \\$  $\verb|LVTDSSLRLTSASLDNSRSGIISANAAAEIHTGVLNNSQKGNLGSNDGLG|$ LIATEVDNSOEGRITAKGMIDANIKGLDOOGKGRLVSNAGIILDLNEGTL  ${\tt ANGAQGLIATPGTLLLRQLGMVDNSGGEISSDRAFTLTTSALTNQGGRLR}$ SGGVLTLRIAOALDNSLEGVLSGTGGLDIRALALDNRSGSIGSKGAVDID VSRLENDDGDLLSEGRLKLTAERANSVRGRIAARGDLHASVTAFNOAGGE LSSEGALMLEADSLDNRSGGLVSADGNLTVSARRIDNRAGEIASPGQVTL DVAEQLDNRGKAIGDSGLRLAAPRVLNQDGGVLASRDGLRLNGAELFNGN GGLLSSQQSIDVILDGVLGNQAGSLSSQGRLSVKSGRLDNQGGAVSSAGT LSLSSOGALNNOGGRVVTDAGAVLRSASLDNSOGGIVSAKGAAEIRTGSL NNSOKGGIGSGAGLALVADLVDNSONGRITAKGAIDANLKGLDOOGSGRL VSDTAIALDLRGGELVNRAOGLIATPGALLLROLGVVDNSGGGEISSDRS FTLAATALSNRGGRVISGDSLTLRIAQALDNSLQGVLSASGGLDVAALVF DNHSGIVASKGDTHIGVNRLENEAGRVVSEGALDLTAKOVSSAKGRIAAK GDLOVTVGTLEOOGGELASOGTLTLDADSLDNRNGGLVSADGGVTAEARO IDNRGGEISSVAKVALAVREQLDNRGGKVIGDSELSLTVQRLLNQAKGVL ASRDGLHLDGAELLNGDGGLLSSQRLVDVTLSGALDNQGSGALVSEESLT VKADOVNNOAGTFSSAGSLLVTSRGELNNOGGRLVTDAGATLNSTGFDNS RAGLVSAKGAVAIRTGALNNSQKGSIGGNTGVTLVAGLVDNGREGRISTK GTLDANLKGLLQQGGGSLVGERGVTLDLNGGTLDNHDLGLVSTPGALLLR

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QLGMVDNSVGGEISSDRAFTLAANTLNNQGGRLISSEALTLRIAKTLDNS LKGQVLATDGLAIESQVLDNRAGTIGSKGDARISVTSLDNAEQGSLVSEG RLELVADOVSNGNOGRIAARGVLEAAVGTLLOOGGELVSOGSLDLRADTL DNSQSGLIAANGGIAIEARQVDNRAGEISSTSKVAVNAREQLDNRGGKVI GDSGLRLTVQRLLNQAKGVLAGRDGLSLDGGELFNGDGGRLDSQNSLSVS  $\verb|LGGVLDNQGGALVSEGSLTARAARLDNRGGTFSSAGALALTSQAVLDNQG|$ GRLLSDAGVTLKGASLDNSRSGVISAKGAVDIRTGVLDNSRNGGIGSNAG ITLVAARLDNGOOGRVSAKGLLDANLKGLDORGGGVLVSETGVTLDLNGG TLVNRDGGLIATPGALLLROLGAVDNGAGGEISSDRAFTLAAASLDNRGG RLIGADSLTLRIAOADNSLAGVISGAAGLDIAAARLDNSAKGTLASRAGI DLRVDGALDNHAEGTVSGARLTLASASLDNSGKGLLSGNAGLSVATGALD NAEGGOLTSOGVLDVSSADLDNRGGALSGKOSLRLSAANLDNRGGLLTSD GEEL TAGRYDSADGGET SARGDI.RI.TVERI.VOROGRI.TGERGVSI.DI.RGG DLDNQGGLISARGPLSIERLNVLDNRQGGEIYSQQGFELLARRIDNGQQG RIISAGKLRLDADALGNAGAGLLSGWOGLTVTGGSLDNSAGGTLSSKDGE LAISLGGALDNHGOGALVSKGAORIDAASLDNAOGIVSGESDVTLSIAGK LDNGQGGLVSAQRALSFERDDTLLNNAGGRINGGSLLLKGASLDNSDGQL ISQGRLDAILGGALVNAGAARLASGGDLLLRSASVDNRGGKLVSQGLLEI SAGSLDNSASGTLASQADMSLRLGGGALRNQQDGLIFSQAGALEVQAGSL  ${\tt DNRQGTLQAQGDNRLRIGGALDNQAGRLDSRAGNLDLQSGSLDNGAGGVL}$  ${\tt NSAKGWLKLVTGLFDNSAGVTQAQSLEIRAGQGVRNQQGHLSALGGDNRI}$ VTADFDNOGGGLYASGLLSLDGORFLNOGAAAGOGGKVGAGRIDFSLAGA LANRFGQLESESELHLRAAAIDNSGGSLRALGRSGSTRLVAGDLNNAYGV LESANODLDLOLGSLANAGGRILHTGNGTFGLDSGOVIRAGGELTTNGLL  ${\tt DIRASEWTNSSVLQAGRLNLDIGTFRQTAEGKLLAVQSFTGRGGDWSNDG}$ LLASNGSLRLELSGGYRGNGRATSLGDFALNAASLDLGNAASLAGGANVT LGAGNLLVNRGRITAAGDLVASAASLNNYGTLGGGGNLRLNAPALLNERG LLFSGADMTLRAGDITNLYGDVYSLGRLDIARDDAGGWANRLENISGNLE STGDMRFSVSSLLNRRETLE1EGDLONSAIGVRCTGCOLSERWGKTRSSS ELVWIREYKSTLGDSSAAASITAGRDLLVVGASLONIASNISAVRDATLS LSNFENKGYALGEYAVRGVYSPPSKFGEELLMRILAYNAVNDPSYGEGYA STGGRLPNIHYFDKNFNEKVSPLEVIHGNGKNGGPGWHLYFGTLDVEYPD TDRWNKATGRIPAPNYSSKKTDATPDLLKGLAPLDELTINKGANSTVGAV VOAGGRVTVNAAESFNNSVLOGFOAVOETOLPHODIAVSSTTSAVVTLKS QLPADLARQQINPLTLPGFSLPQGQNGLFRLASQGAQVNQASGALKSASD LTQSGHGVSVSAQTGSGASGWSTQARRVGDDRVTSLAGSAYQGRVAEAID ALRASAPISGDGGNTGRFOAGEHOATTGLGGLVEGNASGHSGNGVILADL RGGLPSFSSLPASDHVOGTVPGHDGNGTILANWOGAOATVOASPSTVRVE GVVSSPGGNGSILADLPAEQSSVQALPSAVRAQGSLPRLEERSALLAEPP

VGQPALQTLPSVARVEGVPSNATPSNSHKYLIETNPALTELKQFLNSDYL
LGGLGINPDDSKKRLGDGLYEQRLVREAIVQRTGQRFIAGLNSDEAMFRY
LMDNAIASKDVLGLTPGVTLSAAQVAALTHDIVWLEEVEVNGEKVLAPVV
YLAQAEGRLGPNGALIQGRDVNLITGGDLRNAGTLRAQNDLSATAGNIDN
SGLIEAGNRLDLLASGSIRNDQGGIIAGREVSLSALTGDVINERTVTQHQ
SSYRGTGTTEAFADSAARIEAAQKLTVSAGRDVANIGGVIDSKGDLALQG
GRDVLVSAAVAERGWTAGSQAYQTQTTQMGAEVVAGRDISVSAGRDISVV
GSRIDARRDVTFEAGRDVGLVAAANEEHAYGKTKKVTFQDDKITQQATRV
DAGGDLAINAGQDLRLVASQASAGDEAYLVAGDKLELLAANDSSYYLYDK
KSKGSFGSKKTRRDEITDVTAVGSQISSGGDLTLLSGGDQTYQGAKLESG
NDLAIVSGGAVTFEAVKDLHQESHEKSKGDLAWQSSKGKGQTDETVRQSQ
IVAQGNLAIKAVEGLKIDLKHIDQKTVSQTIDAMVQADPQLAWLKQMEQR
GDVDWRRVQELHDSWKYSNSGLGVGAQLAIAIVVAYFTAGAASAALGSMA
GVGAGSGSMMAAAGSTAMVQAGTAVGTAAAGWANAAGTAVAMGMASNGAI

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STINNRGNLGDVVKDVTSSDALRGYVVAGTTAGLTAGVYDKWTSTQTGTS

TALPNTGAVAPAAGLGTWQGVGQFTSNQLLQNGTSVLLDRALGGKGSLGD
ALQNSLANAFAAYGFKLIGDTTHGVLDDGSLGKIGLHALMGGLAAEAVGG
DFRTGALAAGVNEALVDSLAKQYASLPIDDKKGLLIMSSQLIGVLAASTQ
GDADAKSLQTGAWVAGNATQHNYLSHWQEEKKRQEVDGCKDKQLCKTGIE
AKWAIISAQQDVGIVVGVGGGIGLSTAETAVGVYELVKNWRETYAALEQL
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**[0314]** The corresponding nucleic acid sequences (DNA in SEQ ID NOs. 31-60 and RNA in SEQ ID NOs. 61-90) are set forth in the electronic sequence listing that forms part of the present application.

#### SEQUENCE LISTING

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<2113 < 400 Met 1 Ala Gln Glu Gly 65 Ser Asp Ala	L> LE2> TY 3> OF Leu Phe Lys 50 Asp Glu Ala	ENGTHERS AND	PRT ISM: UCE: Leu Asp 20 Ile Gly Glu Ile Ile Ino Ser	Pset 13 Leu 5 Glu Gly Val Lys Leu 85 Glu Gly	Pro Arg Glu Gln Gln 70 Lys Gln Arg	Leu Ala Leu Lys 55 Ile Arg Gln Glu	Leu Asp Lys 40 Gln Lys Leu Arg Glu 120	Leu Thr 25 Lys Leu Ala Asp Leu 105	Ser 10 Gln Leu Lys Leu Gly 90 Leu	Arg Leu Ser Gln 75 Glu Ala	Gln Asp Thr 60 Asp Lys Lleu Leu	Leu Gly 45 Glu Glu Lys Gln Leu 125	Glu 30 Ile Thr Leu Lys Ala 110	Gln Glu Asp Leu 95 Arg	Thr Gln Met Lys 80 Gln Ala Gln

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

Leu	Ser	Lys	Gln 180	Gly	Glu	Leu	Asp	Ser 185	Arg	Arg	Glu	Ala	Leu 190	Ala	Ala
Thr	Arg	Lys 195	Glu	Arg	Gln	Gln	Ala 200	Leu	Ala	Lys	Leu	Asn 205	Ser	Asp	Tyr
Arg	Glu 210	Arg	Asp	Gln	Lys	Leu 215	Lys	Ser	Arg	Gln	Gln 220	Asp	Gln	Ala	Glu
Leu 225	Ala	ГÀз	Val	Leu	Arg 230	Thr	Ile	Glu	Glu	Thr 235	Leu	Ala	Arg	Gln	Ala 240
Arg	Glu	Ala	Ala	Ala 245	Ala	Ala	Glu	Arg	Glu 250	Arg	Gln	Arg	Ala	Leu 255	Ala
Ala	Glu	Arg	Glu 260	Arg	Ala	Arg	Gln	Gln 265	Gln	Ala	Ala	Pro	Gly 270	Arg	Val
Thr	Ser	Pro 275	Pro	Arg	Glu	Pro	Ala 280	Pro	Gly	Pro	Leu	Val 285	Ser	Ser	Thr
Gly	Ala 290	Val	Tyr	Gly	Gly	Ala 295	Phe	Gly	Ser	Ala	Arg 300	Gly	Lys	Leu	Pro
Trp 305	Pro	Val	Asn	Gly	Arg 310	Val	Val	Ala	Arg	Phe 315	Gly	Ser	Gln	Arg	Gly 320
Asp	Asp	Pro	Arg	Ala 325	Lys	Trp	Asp	Gly	Val 330	Leu	Ile	Ser	Ala	Ser 335	Ala
Gly	Ser	Thr	Val 340	Arg	Ala	Val	His	Gly 345	Gly	Arg	Val	Val	Phe 350	Ala	Asp
Trp	Leu	Arg 355	Gly	Ala	Gly	Leu	Leu 360	Val	Ile	Leu	Asp	His 365	Gly	Gly	Gly
Tyr	Leu 370	Ser	Leu	Tyr	Gly	His 375	Asn	Gln	Ser	Leu	Leu 380	Lys	Asp	Ala	Gly
Asp 385	Thr	Val	Lys	Ala	Gly 390	Asp	Pro	Ile	Ala	Thr 395	Val	Gly	Thr	Ser	Gly 400
Gly	Gln	Ser	Ser	Pro 405	Ala	Val	Tyr	Phe	Ala 410	Ile	Arg	His	Gln	Gly 415	Arg
Pro	Ala	Asp	Pro 420	Thr	Thr	Trp	Cha	Arg 425	Ala	Gln	Gly				
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	> TY > OF			Pseu	ıdomo	nas	aeru	ıgino	sa						
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Pro	Ala	Ala 35	Val	Ala	Pro	Gln	Pro 40	Ala	Ala	Pro	Ser	Met 45	Ala	Ala	Leu
Ser	Ile 50	Pro	Leu	Cys	Leu	Asn 55	Gly	Gln	Сув	Ala	Val 60	Ile	Asp	Gln	Asp
Ala 65	ГÀа	Leu	Leu	Val	Pro 70	Phe	Asp	Asn	Asp	Tyr 75	Asp	Asn	Ile	Val	Ala 80
Ser	Ala	Tyr	Gln	Gly 85	Thr	Leu	Met	Ala	Ala 90	Arg	Glu	Glu	Arg	Trp 95	Asn

Leu	Ile	Gln	Ala 100	Lys	Asp	Gly	Lys	Val 105	Leu	Arg	Asp	Asp	Ile 110	Gly	Glu
Ala	Leu	Ser 115	Leu	Leu	Thr	Pro	Asn 120	Leu	Tyr	Gly	Phe	Val 125	Arg	Asp	Gly
Lys	Tyr 130	Gly	Val	Val	Asp	Gly 135	Gln	Gly	ГЛа	Glu	Val 140	Gln	Ala	Pro	Arg
Phe 145	Asp	Asp	Ile	Tyr	Pro 150	Asn	Ser	Ala	Asn	Glu 155	Phe	Ile	Ile	Tyr	Glu 160
Ile	Asp	Gly	Lys	Arg 165	Gly	Ile	Leu	Asp	Ala 170	Lys	Gly	Lys	Gln	Leu 175	Thr
Glu	Ala	Leu	Tyr 180	Asp	Thr	Thr	Leu	Val 185	Asn	Gly	Ser	Val	Ala 190	Glu	His
Gly	Gly	Leu 195	Ile	Ser	Ala	Glu	Arg 200	Gly	Glu	Glu	ГЛа	Trp 205	Ile	Ile	Asn
Leu	Ala 210	Thr	Gly	Glu	Gln	Lys 215	Ala	Val	Ala	Tyr	Glu 220	Ser	Leu	Gly	Asp
Leu 225	His	Asp	Gly	Val	Met 230	Ser	Ala	Ser	Val	Ile 235	Gly	ГЛа	Gly	Ser	Gln 240
Leu	Val	Asp	Ala	Lys 245	Gly	Asp	Val	Val	Gly 250	Asp	Gly	ГЛа	Ser	Tyr 255	Asp
Tyr	Leu	Gly	Thr 260	Pro	Ala	Asn	Gly	Leu 265	Val	Ala	Phe	Arg	Glu 270	Lys	Tyr
Asp	Ser	Pro 275	Cys	Gly	Tyr	Leu	Asp 280	Tyr	Gln	Gly	Lys	Val 285	Ala	Ile	Ala
Ala	Gln 290	Phe	Ala	Gly	CAa	Gly 295	Ala	Phe	Gly	Lys	Gln 300	Gly	Gly	Leu	Ala
Gln 305	Gln	Arg	Met	Glu	Asp 310	Gly	Ser	Ser	Gly	Lys 315	Tyr	Gly	Leu	Ile	Asp 320
Arg	Ser	Gly	Ala	Trp 325	Lys	Val	Gln	Pro	Gln 330	Tyr	Asp	Ser	Ala	Asp 335	Ser
Ala	Gly	Leu	Thr 340	Ala	Leu	Gly	Tyr	Thr 345	Val	Asp	Val	Pro	Gly 350	Leu	Ala
Ala	Val	Gly 355	Val	Ser	Thr	Gly	Leu 360	Phe	Ser	Ala	Asp	Phe 365	Gly	Ile	Phe
Asn	Leu 370	Asp	Glu	Gly	Ser	Glu 375	Trp	Val	Lys	Pro	Gly 380	Tyr	Ala	Gln	Ile
Gly 385	Ala	Leu	Gly	Asn	390	Leu	Phe	Val	Val	Ala 395	Lys	ГÀа	Gly	Gly	Pro 400
Gln	Lys	Thr	Val	Ser 405	Phe	Met	Gly	Ser	Glu 410	Ser	Gln	Val	Pro	Val 415	Val
Gly	Leu	Met	Asp 420	Arg	Ser	Gly	Lys	Met 425	Leu	Leu	Glu	Pro	Asp 430	Glu	Leu
Ile	Ser	Ile 435	Gln	Ser	Ala	Tyr	Asp 440	Gly	Arg	Phe	Leu	Glu 445	Gly	Leu	Asp
Gly	Met 450	Asp	Asn	Ala	Ala	His 455	Thr	Val	Leu	Leu	Asp 460	Arg	Gln	Gly	Arg
Thr 465	Leu	Val	Pro	Ala	Leu 470	Trp	Gln	Lys	Leu	Glu 475	Val	Asn	Pro	Gln	Gln 480
Gly	Tyr	Ile	Leu	Gly 485	Tyr	Glu	Val	Ser	Gly 490	Thr	Gly	Asp	Glu	Ala 495	Thr

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#### -continued

Glu Thr Leu Arg Ala Leu Tyr Asp Leu Asn Gly Lys Pro Arg Phe Thr Val Ala Thr Thr Asp Cys Gly Ala Glu Gln Leu Leu Asp Gly Asn Gly Lys Ala Ile Trp Pro Gln Asp Pro Thr Pro Tyr Cys Gln Ser Asp Asp Glu Gln Asp Asp Glu Gly Glu Pro Glu Gln Glu Pro Ala Pro Val Glu Glu Ser Glu Glu Thr Ser Glu Ser <210> SEQ ID NO 15 <211> LENGTH: 579 <212> TYPE: PRT <213 > ORGANISM: Pseudomonas aeruginosa <400> SEQUENCE: 15 Met Leu Arg Pro Ala Arg Ser Leu Ser Leu Cys Ser Ala Leu Val Ile 10 Leu Leu Ala Ala Cys Gly Glu Gly Glu Pro Leu Leu Pro Ala Asp Ala 25 Arg Leu Pro Asp Gly Ala Arg Tyr Arg Gly Glu Leu Val Asp Gly Arg  $35 \ \ 40 \ \ 45$ Leu Glu Gly Gln Gly Arg Leu Asp Tyr Asp Asn Gly Ala Trp Tyr Ala Gly Arg Phe Glu His Gly Leu Leu His Gly His Gly Thr Trp Gln Gly Ala Asp Gly Ser Arg Tyr Ser Gly Gly Phe Ala Ala Gly Leu Phe Asp Gly Gln Gly Arg Leu Ala Met Ala Asp Gly Ser Val Tyr Gln Gly Gly Phe Arg Gln Gly Leu Phe Asp Gly Glu Gly Ser Leu Glu Gln Gln Gly 120 Thr Arg Tyr Arg Gly Gly Phe Arg Lys Gly Leu Tyr Ser Gly Gln Gly Thr Leu Asp Gly Ser Asp Gly Ser Arg Tyr Gln Gly Ser Phe Arg Gln Gly Arg Leu Glu Gly Glu Gly Ser Phe Ser Asp Ser Gln Gly Asn Gln Tyr Ala Gly Thr Phe Arg Asp Gly Gln Leu Asn Gly Lys Gly Arg Trp 180 185 190 Ser Gly Pro Asp Gly Asp Arg Tyr Val Gly Gln Phe Lys Asp Asn Gln Phe His Gly Gln Gly Arg Tyr Glu Ser Ala Ser Gly Asp Val Trp Ile Gly Arg Phe Ser Glu Gly Ala Leu Asn Gly Pro Gly Glu Leu Leu Gly Ala Asp Gly Ser Arg Tyr Arg Gly Gly Phe Gln Phe Trp Arg Phe His Gly Gln Gly Leu Leu Glu Gln Leu Asp Gly Thr Arg Tyr Glu Gly Gly 265 Phe Ala Ala Gly Ala Tyr Ala Gly Gln Gly Thr Leu Asp Arg Ala Asp 280

295 Ala Ala Gly Lys Ala Leu Pro Asp Thr Leu Glu Val Gly Leu Leu Ala Gln Gly Arg Leu Leu Asp Glu Glu Leu Arg Lys Ile Pro Ala Ser Thr Pro Ala Ser Glu Leu Tyr Ala Leu Ser Leu Gly Gly Asp Gly Arg Gln Gly Val Phe Leu Arg Glu Ala Asp Tyr Ala Gly Asp Leu Leu Gly Gln Arg Phe Ala Ala Arg Gly Val Ile Arg Leu Val Asn His Arg Asp His Phe Gly Asp Arg Pro Leu Ala Thr Arg Glu Ser Leu Ser Arg Ala Val 390 395 Arg Thr Leu Ala Glu Arg Ser Gly Pro Glu Asp Leu Val Phe Ile Tyr 405 410 Leu Thr Ser His Gly Ser Ser Asp His Gln Leu Ala Leu Asp Met Pro 425 Gly Leu Asn Leu Gly Asp Leu Pro Ala Ala Glu Leu Ala Glu Leu Leu 440 Ala Pro Leu Arg Gln Arg Asp Lys Val Leu Val Val Ser Ala Cys Tyr 455 Ser Gly Gly Phe Ile Pro Pro Leu Lys Asp Glu Arg Thr Leu Ile Leu 470 475 Thr Ala Ala Arg Ala Asp Arg Val Ser Phe Gly Cys Ser Asp Asp Ala Asp Phe Thr Tyr Phe Gly Arg Ala Leu Leu Ala Asn Ala Leu Asn Arg 505 Thr Asp Asp Leu Ser Lys Ala Phe Glu Leu Ala Lys Glu Glu Val Arg 520 Gln Arg Glu Lys Glu Glu Gly Phe Glu Ala Ser Glu Pro Gln Ala Trp Leu Pro Glu Arg Val Leu Ala His Trp Arg Thr Leu Arg Gly Gln Gln Ala Glu Arg Ala Leu Ala Ser Arg Glu Gly Lys Thr Gly Glu Gly Ala Ala Gly Lys <210> SEQ ID NO 16 <211> LENGTH: 621 <212> TYPE: PRT <213 > ORGANISM: Pseudomonas aeruginosa <400> SEOUENCE: 16 Met Leu Gln Asn Ile Arg Asp Asn Ser Gln Gly Trp Ile Ala Lys Thr 10 Ile Ile Gly Val Ile Ile Val Leu Leu Ser Leu Thr Gly Phe Asp Ala Ile Ile Arg Ala Thr Asp His Ser Asn Val Ala Ala Lys Val Asn Gly 40 Asp Asp Ile Ser Leu Asn Glu Val Gln Gln Ala Val Asp Met Gln Arg

Gly Ser Arg Glu Gln Gly Leu Trp Ala Asp Gly Lys Arg Ile Arg Asp

Arg 65	Gln	Leu	Leu	Gln	Arg 70	Leu	Gly	Lys	Asp	Phe 75	Asp	Pro	Ser	Met	Leu 80
Asp	Asp	Lys	Leu	Leu 85	Lys	Glu	Ala	Ala	Leu 90	Lys	Gly	Leu	Ile	Glu 95	Arg
Thr	Leu	Leu	Leu 100	Gln	Ala	Ala	Lys	Asp 105	Asp	Lys	Phe	Ala	Phe 110	Ser	Asp
Gln	Ala	Leu 115	Asp	Gln	Leu	Ile	Leu 120	Gln	Thr	Pro	Glu	Phe 125	Gln	Val	Asp
Gly	Lys 130	Phe	Asn	Ala	Asp	Arg 135	Phe	Asp	Gln	Val	Ile 140	Arg	Gln	Met	Asn
Tyr 145	Ser	Arg	Met	Gln	Phe 150	Arg	Gln	Met	Leu	Gly 155	Gln	Glu	Met	Leu	Ile 160
Gly	Gln	Leu	Arg	Ala 165	Gly	Leu	Ala	Gly	Thr 170	Gly	Phe	Val	Thr	Asp 175	Asn
Glu	Leu	Gln	Ser 180	Phe	Ala	Arg	Leu	Glu 185	Lys	Gln	Thr	Arg	Asp 190	Phe	Ala
Thr	Leu	Ala 195	Ile	ГЛа	Ala	Asp	Ala 200	Ser	Lys	Ser	Ser	Val 205	Ser	Asp	Asp
Glu	Val 210	Lys	Ala	Phe	Tyr	Glu 215	Gly	His	Lys	Ser	Glu 220	Phe	Met	Thr	Pro
Glu 225	Gln	Val	Val	Val	Glu 230	Tyr	Val	Glu	Leu	Lys 235	Lys	Ser	Ser	Phe	Phe 240
Asp	Gln	Val	Lys	Val 245	Lys	Gln	Glu	Asp	Leu 250	Glu	Ala	Leu	Tyr	Gln 255	Lys
Glu	Ile	Ala	Asn 260	Leu	Ser	Glu	Gln	Arg 265	Asp	Ala	Ala	His	Ile 270	Leu	Ile
Glu	Val	Asn 275	Asp	Lys	Val	Gly	Asp 280	Glu	Gln	Ala	Lys	Ala 285	Lys	Ile	Asp
Glu	Ile 290	Lys	Ala	Arg	Leu	Ala 295	Lys	Gly	Glu	Asp	Phe 300	Ala	Ala	Leu	Ala
Lys 305	Glu	Phe	Ser	Gln	Asp 310	Ile	Gly	Ser	Ala	Ala 315	Thr	Gly	Gly	Asp	Leu 320
Gly	Tyr	Ala	Gly	Arg 325	Gly	Val	Tyr	Asp	Pro 330	Ala	Phe	Glu	Glu	Ala 335	Leu
Tyr	Ala	Leu	Lys 340	Gln	Gly	Glu	Val	Ser 345	Ala	Pro	Val	ГЛа	Thr 350	Pro	Tyr
Gly	Tyr	His 355	Leu	Ile	Lys	Leu	Leu 360	Gly	Val	Gln	Ala	Pro 365	Glu	Val	Pro
Ser	Leu 370	Glu	Ser	Leu	Lys	Pro 375	Lys	Leu	Glu	Asp	Glu 380	Leu	Lys	ГÀа	Gln
Met 385	Val	Glu	Gln	Arg	Phe 390	Val	Glu	Ala	Thr	Lys 395	Asp	Leu	Glu	Ser	Ser 400
Ala	Tyr	Glu	Ala	Ala 405	Asp	Leu	Ser	Gln	Pro 410	Ala	Gln	Glu	Met	Gly 415	Leu
Lys	Val	Gln	Thr 420	Ser	Gln	Pro	Phe	Gly 425	Arg	Ser	Gly	Gly	Asp 430	Gly	Ile
Ala	Ala	Asn 435	Arg	Gln	Ile	Val	Gln 440	Thr	Ala	Phe	Ser	Ala 445	Glu	Val	Leu
Glu	Glu 450	Ala	Ala	Asn	Ser	Gly 455	Ala	Ile	Glu	Leu	Asp 460	Pro	Asp	Thr	Val

Jul. 19, 2018

Sin   Sin	Val 465	Val	Leu	Arg	Val	Lys 470	Glu	His	Asn	Lys	Pro 475	Lys	Glu	Gln	Pro	Leu 480
Sing	Glu	Gln	Val	Ala		Asn	Ile	Arg	Glu		Leu	Ala	Ala	Glu		Ala
515	Ala	Glu	Glu		Gln	Lys	Arg	Gly		Ala	Leu	Ile	Ala		Leu	Arg
S30	Glu	Gly		Thr	Ser	Ser	Ala		Gly	Glu	Ser	Trp		Val	Val	Glu
560 Gly Val Thr Leu Ala San Gly Asp Tyr Val Val Ile Arg Leu San Gly San Tyr San Val Ile Arg Leu San Gly San Tyr San Val Ile Arg Leu San Gly San Tyr San Val Ile Arg Leu San Gly San San Gly San Tyr San San Glu Lys Ala Met Tyr San	Ala		Ser	Arg	Gly	His		Gly	Val	Asp	Pro		Leu	Leu	Gln	Ala
See   Glu   Pro   Glu   Glu   Ala   Ile   See   Asp   Asp   Glu   Lys   Ala   Ala   Pro   See   Asp   See   Asp   See   See   Asp   See   See   Asp   See   See   See   Asp   See   See   See   Asp   See   See   See   See   Asp   See   See   See   Asp   See   See   See   Asp   See   See		Phe	Arg	Met	Gln	_	Pro	Glu	Ala	Lys	_	Lys	Pro	Ser	Phe	
Secondary   Seco	Gly	Val	Thr	Leu		Asn	Gly	Asp	Tyr		Val	Ile	Arg	Leu		Gly
Arg Arg Gln Leu Gln Asp Lys Ala Glu Val Glu Lys Tyr 610	Val	Ser	Glu		Glu	Glu	Ala	Ile		Asp	Asp	Glu	Lys		Met	Tyr
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					38											
Met 1         Asp Met 1         Thr Ser Ser Leu Met 1         Pro Leu Leu Leu Leu Leu Leu Leu Leu Gly Val Gly Leu Met 1         Leu Ala Leu Leu Gly Val Gly Leu Met 25         Leu Ala Leu Leu Leu Leu Leu Leu Ala Leu Heu Met 25         Leu Met Leu Val Met 30         Tyr Ile 30           Lys Val Pro Son Glu Gly Thr Ala Leu	<213	3 > OF	RGAN:	ISM:	Pse	adomo	onas	aeru	ıgino	sa						
1       5       10       15       11         Val       Leu       Val       Val       Val       Leu       Val       Asp       Asp       Ser       Ser       Thr         Pro       Lys       Val       His       Phe       Thr       Ser       Leu       1eu       Val       Tyr       Pro       Val       His       His       Leu         Lys       Glu       Phe       Met       Arg       Fro       Ser       Leu       Iu       Thr       Leu       Pro       Val       Arg	< 400	)> SI	EQUEI	ICE :	17											
Lys       Val       Pro So       Gln       Gly       Thr       Ala       Leu Ao       Ile       Val       Ass       Ass       Met Aps       Ser       Ser       Thr         Pro So       Lys       Val       His       Phe       Thr       Gly       Ala       Leu       Val       Pro Go       Val       His       His       Leu         Lys       Glu       Phe       Met       Arg       70       Ser       Leu       Ile       Val       Tyr       Gu       Val       His       His       Pro Ro       Arg		Asp	Met	Thr		Leu	Met	Pro	Leu		Leu	Gly	Val	Gly		Val
Pro       Lys       Val       His       Phe       Thr       G1y       Ala       Leu       Val       Tyr       Pho       Val       Ile       His       Leu         Lys       Glu       Phe       Met       Arg       55       Aleu       Ile       Thr       660       Val       Ile       His       Leu         Lys       Glu       Phe       Met       Arg       Ala       Arg       Ile       I	Val	Leu	Leu		Val	Gly	Leu	Leu		Leu	Phe	ГÀЗ	Ala		Tyr	Ile
50	ГÀз	Val		Gln	Gly	Thr	Ala		Ile	Val	Asn	Asp		Ser	Ser	Thr
65       70       75       80         Gly Lys Asp Sap Gly Leu Sap	Pro		Val	His	Phe	Thr		Ala	Leu	Val	Tyr		Val	Ile	His	Leu
95  Val Ala Phe Tyr Leu Arg Val Asn Glu Thr Gln Asp Asp Val Leu Lys 1100  Val Ala Lys Ala Ile Gly Val Asp Arg Ala Ser Asp Arg Ser Ala Val 125  Asn Glu Leu Phe Asn Ala Lys Phe Ser Glu Ala Leu Lys 140  Lys Gln Phe Asp Phe Val Gln Leu Phe Glu Asn Asp Arg Ser Asp Phe Arg 145  Asp Arg Ile Ile Glu Val Ile Gly Asn Asp Leu Asn Gly Tyr Val Leu Glu Asp Arg Val Ala Ile Asp Tyr Leu Glu Gln Thr Ala Lys Asn Ser Leu		Glu	Phe	Met	Arg		Ser	Leu	Ile	Thr		Glu	Val	Asp	Arg	
The color of the	Gly	Lys	Asp	Gly		Ile	Cys	Arg	Asp		Met	Arg	Ala	Asp		Thr
115 120 125 125 125 125 125 125 125 125 125 125	Val	Ala	Phe		Leu	Arg	Val	Asn		Thr	Gln	Asp	Asp		Leu	Lys
130 135 140  Lys Gln Phe Asp Phe Val Gln Leu Phe Glu Asn Arg Gln Asp Phe Arg 160  Asp Arg Ile Ile Glu Val Ile Gly Asn Asp Leu Asn Gly Tyr Val Leu 175  Glu Asp Val Ala Ile Asp Tyr Leu Glu Gln Thr Ala Lys Asn Ser Leu	Val	Ala		Ala	Ile	Gly	Val		Arg	Ala	Ser	Asp		Ser	Ala	Val
145       150       155       160         Asp Arg Ile Ile Glu Val 11e Gly Asn Asp Leu Asn Gly Tyr Val 165       170 <t< td=""><td>Asn</td><td></td><td>Leu</td><td>Phe</td><td>Asn</td><td>Ala</td><td>-</td><td>Phe</td><td>Ser</td><td>Glu</td><td>Ala</td><td></td><td>Lys</td><td>Thr</td><td>Val</td><td>Gly</td></t<>	Asn		Leu	Phe	Asn	Ala	-	Phe	Ser	Glu	Ala		Lys	Thr	Val	Gly
165 170 175  Glu Asp Val Ala Ile Asp Tyr Leu Glu Gln Thr Ala Lys Asn Ser Leu	-	Gln	Phe	Asp	Phe		Gln	Leu	Phe	Glu		Arg	Gln	Asp	Phe	-
	Asp	Arg	Ile	Ile		Val	Ile	Gly	Asn	_	Leu	Asn	Gly	Tyr		Leu
	Glu	Asp	Val		Ile	Asp	Tyr	Leu		Gln	Thr	Ala	ГЛа		Ser	Leu
Asp Pro Ser Asn Ile Leu Asp Ala Glu Gly Ile Arg Lys Ile Thr Glu 195 200 205	Asp	Pro		Asn	Ile	Leu	Asp		Glu	Gly	Ile	Arg		Ile	Thr	Glu

Leu	Thr 210	Ala	Thr	Gln	Asn	Val 215	Ile	Thr	Asn	Glu	Leu 220	Glu	Arg	Asn	Glu
Glu 225	Leu	Ala	Ile	Lys	Lys 230	Lys	Asn	Val	Glu	Thr 235	Arg	Glu	Ala	Ala	Leu 240
Ala	Leu	Glu	Arg	Gln 245	Gln	Ala	Asp	Ala	Glu 250	Ala	Arg	Gln	Lys	Arg 255	Glu
Ile	Glu	Thr	Ile 260	Arg	Ala	Arg	Glu	Glu 265	Ala	Glu	Thr	Ala	Arg 270	Val	Lys
Glu	Glu	Glu 275	Arg	Leu	Lys	Ala	Glu 280	Gln	Ala	Arg	Ile	Gln 285	Ala	Gln	Gln
Glu	Ile 290	Asp	Val	Arg	Thr	Glu 295	Asn	His	Gln	Arg	Glu 300	Val	Glu	Val	Ala
Gln 305	Gln	Asn	Arg	Gln	Arg 310	Ala	Val	Val	Ile	Glu 315	Val	Glu	Lys	Val	Thr 320
Arg	Ala	ГЛа	Asp	Leu 325	Glu	Ile	Val	Ala	Arg 330	Glu	Arg	Glu	Val	Glu 335	Leu
Gln	Lys	Ile	Glu 340	ГÀа	Glu	ГÀв	Ala	Leu 345	Glu	Glu	Gln	Arg	150	Asn	Ile
Ala	Asn	Val 355	Ile	Arg	Glu	Arg	Val 360	Ala	Val	Glu	ГЛа	Thr 365	Val	Ala	Gln
Glu	Glu 370	Glu	Arg	Ile	rÅa	Glu 375	Val	Arg	Glu	Val	Ser 380	Glu	Ala	Glu	Arg
Val 385	Lys	Gln	Val	Ile	Leu 390	Leu	Gln	Ala	Gln	Ala 395	Glu	Ala	Glu	Gln	Glu 400
Leu	Val	Arg	Gln	Val 405	ГÀЗ	Gln	Ala	Glu	Ala 410	Asp	Glu	Ala	Arg	Ser 415	Lys
His	Lys	Ala	Val 420	Glu	Ile	Asn	Thr	Met 425	Ala	Gln	Ala	Glu	Leu 430	Glu	Ala
Ala	Ser	Lys 435	Gln	Ala	Glu	Ala	Lys 440	ГÀЗ	Arg	Leu	Ala	Glu 445	Gly	Ile	Glu
Ala	Glu 450	Arg	Ala	Ala	Pro	Gly 455	Leu	Ala	Asp	Ala	Arg 460	Val	Leu	Glu	Val
Thr 465	Ala	Ala	Ala	ГÀа	Glu 470	ГÀа	Asp	Gly	Leu	Ala 475	Ala	Ala	Arg	Val	Arg 480
Ala	Glu	Gln	Leu	Ile 485	Ala	Glu	Ala	Arg	Gly 490	Asp	Glu	Glu	Arg	Gly 495	Leu
Ala	Asp	Ala	Arg 500	Val	Leu	Glu		Gln 505	Ala	Ala	Ala	Lys	Glu 510	ГÀа	Asp
Gly	Leu	Ala 515	Glu	Ala	ГÀа	Val	Leu 520	Ala	Glu	Lys	Leu	Gly 525	Ala	Gln	Ala
Arg	Gly 530	Glu	Glu	Gln	Leu	Gly 535	Ala	Ala	ГÀа	Ala	Lys 540	Ala	Thr	Lys	Asp
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Arg	Glu	Gly	Val 260	Arg	Asn	Arg	Asp	Leu 265	Ser	Gly	Met	Leu	Ser 270	Trp	Gln
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Jul. 19, 2018

745 Gly Val Asp Ser Gln Val Ala Ser Asp Thr Arg Leu Gly Leu Val Ala 760 Gly Tyr Ser Asn Ser Ser Leu Asn Met Asp Ser Ser Leu Gln Ser Ser Ala Ser Ile Asp Ser Tyr His Leu Gly Ala Tyr Leu Gly Arg Gln Leu Gln Gln Trp Arg Leu Ser Leu Gly Ala Ala His Ala Trp His Arg Ala Glu Val Lys Arg Asp Leu Gln Tyr Gly Ala Val Ala Gly Lys Gln Lys Ala Lys Leu Asp Ala Gln Ser Ser Gln Leu Phe Ala Glu Ala Ala Tyr Ala Leu Gly Trp Arg Ser Leu Glu Leu Glu Pro Phe Ala Gly Leu Ala Tyr Val His Val Ala Ser Asp Asp Phe Arg Glu Arg Gly Ser Ala Ala 870 875 Ala Leu Glu Gly Gly Asp Asp Asn Leu Asp Ala Ala Phe Thr Thr Leu Gly Leu Arg Ala Lys Arg His Phe Glu Leu Asp Ala Gly Arg Arg Leu 905 Ala Leu Ser Gly Thr Leu Gly Trp Arg His Asn Leu Ser Asp Thr Thr 920 Pro Gln Arg His Leu Ala Phe Ala Ser Gly Ser Gln Pro Phe Ser Val 935 Glu Ser Val Ala Leu Ser Arg Asp Ala Ala Leu Leu Gly Val Asp Ala 950 Ser Leu Ala Val Asn Arg Glu Val Ser Val Arg Leu Gly Tyr Asn Gly Leu Leu Gly Ser Arg Glu Lys Asp His Gly Val Gly Leu Ala Val Asp 985 Trp Arg Phe <210> SEQ ID NO 25 <211> LENGTH: 1057 <212> TYPE: PRT <213> ORGANISM: Pseudomonas aeruginosa <400> SEQUENCE: 25 Met Lys Arg Met Leu Ile Asn Ala Thr Gln Pro Glu Glu Leu Arg Val Ala Leu Val Asp Gly Gln Arg Leu Phe Asp Leu Asp Ile Glu Ser Gly 25 Ala Arg Glu Gln Lys Lys Ala Asn Ile Tyr Lys Gly Arg Ile Thr Arg Val Glu Pro Ser Leu Glu Ala Ala Phe Val Asp Phe Gly Ala Glu Arg His Gly Phe Leu Pro Leu Lys Glu Ile Ser Arg Glu Tyr Phe Lys Lys Ser Pro Glu Gly Arg Ile Asn Ile Lys Glu Val Leu Ser Glu Gly Gln

Glu	Val	Ile	Val 100	Gln	Val	Glu	Lys	Glu 105	Glu	Arg	Gly	Asn	Lys 110	Gly	Ala
Ala	Leu	Thr 115	Thr	Phe	Ile	Ser	Leu 120	Ala	Gly	Arg	Tyr	Leu 125	Val	Leu	Met
Pro	Asn 130	Asn	Pro	Arg	Ala	Gly 135	Gly	Ile	Ser	Arg	Arg 140	Ile	Glu	Gly	Glu
Glu 145	Arg	Asn	Glu	Leu	Arg 150	Glu	Ala	Leu	Asn	Gly 155	Leu	Asn	Ala	Pro	Ala 160
Asp	Met	Gly	Leu	Ile 165	Val	Arg	Thr	Ala	Gly 170	Leu	Gly	Arg	Ser	Thr 175	Glu
Glu	Leu	Gln	Trp 180	Asp	Leu	Asp	Tyr	Leu 185	Leu	Gln	Leu	Trp	Ser 190	Ala	Ile
Lys	Glu	Ala 195	Ser	Gly	Glu	Arg	Gly 200	Ala	Pro	Phe	Leu	Ile 205	Tyr	Gln	Glu
Ser	Asn 210	Val	Ile	Ile	Arg	Ala 215	Ile	Arg	Asp	Tyr	Leu 220	Arg	Gln	Asp	Ile
Gly 225	Glu	Val	Leu	Ile	Asp 230	Ser	Ile	Asp	Ala	Gln 235	Glu	Glu	Ala	Leu	Asn 240
Phe	Ile	Arg	Gln	Val 245	Met	Pro	Gln	Tyr	Ala 250	Ser	Lys	Val	Lys	Leu 255	Tyr
Gln	Asp	Ser	Val 260	Pro	Leu	Phe	Asn	Arg 265	Phe	Gln	Ile	Glu	Ser 270	Gln	Ile
Glu	Thr	Ala 275	Phe	Gln	Arg	Glu	Val 280	Lys	Leu	Pro	Ser	Gly 285	Gly	Ser	Ile
Val	Ile 290	Asp	Pro	Thr	Glu	Ala 295	Leu	Val	Ser	Ile	Asp 300	Ile	Asn	Ser	Ala
Arg 305	Ala	Thr	Lys	Gly	Gly 310	Asp	Ile	Glu	Glu	Thr 315	Ala	Leu	Gln	Thr	Asn 320
Leu	Glu	Ala	Ala	Glu 325	Glu	Ile	Ala	Arg	Gln 330	Leu	Arg	Leu	Arg	Asp 335	Ile
Gly	Gly	Leu	Ile 340	Val	Ile	Asp	Phe	Ile 345	Asp	Met	Thr	Pro	Ala 350	Lys	Asn
Gln	Arg	Ala 355	Val	Glu	Glu	Arg	Val 360	Arg	Glu	Ala	Leu	Glu 365	Ala	Asp	Arg
Ala	Arg 370	Val	Gln	Val	Gly	Arg 375	Ile	Ser	Arg	Phe	Gly 380	Leu	Leu	Glu	Met
Ser 385	Arg	Gln	Arg	Leu	Arg 390	Pro	Ser	Leu	Gly	Glu 395	Thr	Ser	Gly	Ile	Val 400
Cys	Pro	Arg	Cys	Asn 405	Gly	Gln	Gly	Ile	Ile 410	Arg	Asp	Val	Glu	Ser 415	Leu
Ser	Leu	Ala	Ile 420	Leu	Arg	Leu	Ile	Glu 425	Glu	Glu	Ala	Leu	Lys 430	Asp	Arg
Thr	Ala	Glu 435	Val	Arg	Ala	Arg	Val 440	Pro	Phe	Gln	Val	Ala 445	Ala	Phe	Leu
Leu	Asn 450	Glu	Lys	Arg	Asn	Ala 455	Ile	Thr	Lys	Ile	Glu 460	Leu	Arg	Thr	Arg
Ala 465	Arg	Ile	Phe	Ile	Leu 470	Pro	Asp	Asp	His	Leu 475	Glu	Thr	Pro	His	Phe 480
Glu	Val	Gln	Arg	Leu 485	Arg	Asp	Asp	Ser	Pro 490	Glu	Leu	Val	Ala	Gly 495	Gln
Thr	Ser	Tyr	Glu	Met	Ala	Thr	Val	Glu	His	Glu	Glu	Ala	Gln	Pro	Val

			500					505					510		
Ser	Ser	Thr 515		Thr	Leu	Val	Arg 520		Glu	Ala	Ala	Val 525		Thr	Val
Ala	Pro 530	Gln	Gln	Pro	Ala	Pro 535	Gln	His	Thr	Glu	Ala 540	Pro	Val	Glu	Pro
Ala 545	Lys	Pro	Met	Pro	Glu 550	Pro	Ser	Leu	Phe	Gln 555	Gly	Leu	Val	ГЛа	Ser 560
Leu	Val	Gly	Leu	Phe 565	Ala	Gly	Lys	Asp	Gln 570	Pro	Ala	Ala	Lys	Pro 575	Ala
Glu	Thr	Ser	580	Pro	Ala	Ala	Glu	Arg 585	Gln	Thr	Arg	Gln	Asp 590	Glu	Arg
Arg	Asn	Gly 595	Arg	Gln	Gln	Asn	Arg 600	Arg	Arg	Asp	Gly	Arg 605	Asp	Gly	Asn
Arg	Arg 610	Asp	Glu	Glu	Arg	Lys 615	Pro	Arg	Glu	Glu	Arg 620	Ala	Glu	Arg	Gln
Pro 625	Arg	Glu	Glu	Arg	Ala 630	Glu	Arg	Pro	Asn	Arg 635	Glu	Glu	Arg	Ser	Glu 640
Arg	Arg	Arg	Glu	Glu 645	Arg	Ala	Glu	Arg	Pro 650	Ala	Arg	Glu	Glu	Arg 655	Gln
Pro	Arg	Glu	Gly 660	Arg	Glu	Glu	Arg	Ala 665	Glu	Arg	Thr	Pro	Arg 670	Glu	Glu
Arg	Gln	Pro 675	Arg	Glu	Gly	Arg	Glu 680	Gly	Arg	Glu	Glu	Arg 685	Ser	Glu	Arg
Arg	Arg 690	Glu	Glu	Arg	Ala	Glu 695	Arg	Pro	Ala	Arg	Glu 700	Glu	Arg	Gln	Pro
Arg 705	Glu	Gly	Arg	Glu	Glu 710	Arg	Ala	Glu	Arg	Pro 715	Ala	Arg	Glu	Glu	Arg 720
Gln	Pro	Arg	Glu	Asp 725	Arg	Gln	Ala	Arg	Asp 730	Ala	Ala	Ala	Leu	Glu 735	Ala
Glu	Ala	Leu	Pro 740	Asn	Asp	Glu	Ser	Leu 745	Glu	Gln	Asp	Glu	Gln 750	Asp	Asp
Thr	Asp	Gly 755	Glu	Arg	Pro	Arg	Arg 760	Arg	Ser	Arg	Gly	Gln 765	Arg	Arg	Arg
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Ser 785	Glu	Ala	Thr	Asp	Asn 790	Ala	Ala	Ala	Pro	Leu 795	Asn	Thr	Val	Ala	Ala 800
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Val	Glu	Gln	Ala 820	Pro	Ala	Thr	Thr	Ser 825	Glu	Ala	Ala	Ser	Glu 830	Thr	Thr
Ala	Ser	Asp 835	Glu	Thr	Asp	Ala	Ser 840	Thr	Ser	Glu	Ala	Val 845	Glu	Thr	Gln
Gly	Ala 850	Asp	Ser	Glu	Ala	Asn 855	Thr	Gly	Glu	Thr	Ala 860	Asp	Ile	Glu	Ala
Pro 865	Val	Thr	Val	Ser	Val 870	Val	Arg	Asp	Glu	Ala 875	Asp	Gln	Ser	Thr	Leu 880
Leu	Val	Ala	Gln	Ala 885	Thr	Glu	Glu	Ala	Pro 890	Phe	Ala	Ser	Glu	Ser 895	Val
Glu	Ser	Arg	Glu 900	Asp	Ala	Glu	Ser	Ala 905	Val	Gln	Pro	Ala	Thr 910	Glu	Ala

Ala Glu Glu Val Ala Ala Pro Val Pro Val Glu Val Ala Ala Pro Ser 920 Glu Pro Ala Ala Thr Glu Glu Pro Thr Pro Ala Ile Ala Ala Val Pro Ala Asn Ala Thr Gly Arg Ala Leu Asn Asp Pro Arg Glu Lys Arg Arg Leu Gln Arg Glu Ala Glu Arg Leu Ala Arg Glu Ala Ala Ala Ala Ala Glu Ala Ala Gln Ala Ala Pro Ala Val Glu Glu Ile Pro Ala Val Ala Ser Glu Glu Ala Ser Ala Gln Glu Glu Pro Ala Ala Pro Gln Ala Glu Glu Ile Thr Gln Ala Asp Val Pro Ser Gln Ala Asp Glu Ala 1015 Gln Glu Ala Val Gln Ala Glu Pro Glu Ala Ser Gly Glu Gly Ala 1030 1035 Ala Asp Thr Glu His Ala Lys Lys Thr Glu Glu Ser Glu Thr Ser 1040 1045 Arg Pro His Ala 1055 <210> SEQ ID NO 26 <211> LENGTH: 1161 <212> TYPE: PRT <213> ORGANISM: Pseudomonas aeruginosa <400> SEQUENCE: 26 Met Lys Ser Val Leu His Gln Ile Gly Lys Thr Ser Leu Ala Ala Ala Leu Ser Gly Ala Val Leu Leu Ser Ala Gln Thr Thr His Ala Ala Ala 25 Leu Ser Val Ser Gln Gln Pro Leu Met Leu Ile Gln Gly Val Ala Pro Asn Met Leu Val Thr Leu Asp Asp Ser Gly Ser Met Ala Phe Ala Tyr Ala Pro Asp Ser Ile Ser Gly Tyr Gly Asn Tyr Thr Phe Phe Ala Ser Asn Ser Phe Asn Pro Met Tyr Phe Asp Pro Asn Thr Gln Tyr Lys Leu Pro Lys Lys Leu Thr Leu Val Asn Gly Gln Val Gln Ile Gln Asp Tyr Pro Ala Pro Asn Phe Ser Ser Ala Trp Arg Asn Gly Phe Thr Arg Ser Gly Ser Ile Asn Leu Ser Asn Ser Tyr Lys Val Thr Ile Glu Tyr Gly 135 Arg Gly Tyr Asp Lys Glu Ser Thr Ile Lys Ala Asp Ala Ala Tyr Tyr 150 155 Tyr Asp Phe Thr Gly Ser Ser Cys Asn Arg Thr Asn Gln Ala Cys Tyr Thr Arg Arg Tyr Val Ser Thr Glu Gln Arg Gln Asn Phe Ala Asn Trp Tyr Ser Phe Tyr Arg Thr Arg Ala Leu Ala Thr Gln Thr Ala Ala

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Leu 225	Leu	Asn	Asp	Ser	Asn 230	Cys	Asn	Gln	Met	Gly 235	Ser	Gly	Ser	Ser	Ser 240
Gly	Asn	Cys	Phe	Ser 245	Asn	Tyr	Leu	Arg	Asp 250	Phe	Thr	Gly	Gln	His 255	Arg
Val	Asn	Phe	Phe 260	Asn	Trp	Leu	Glu	Lys 265	Leu	Ser	Val	Asn	Gly 270	Gly	Thr
Pro	Leu	Arg 275	Gln	Ala	Met	Thr	Arg 280	Ala	Gly	Glu	Phe	Leu 285	Lys	Lys	Thr
Gly	Val 290	Asn	Gly	Pro	Tyr	Ala 295	Tyr	Arg	Pro	Gly	Thr 300	Gln	Thr	Ala	Pro
Glu 305	Tyr	Ser	Cys	Arg	Gly 310	Ser	Tyr	His	Ile	Leu 315	Met	Thr	Asp	Gly	Leu 320
Trp	Asn	Asn	Asp	Ser 325	Ala	Asn	Val	Gly	Asn 330	Ala	Asp	Ser	Thr	Ala 335	Arg
Asn	Leu	Pro	Asp 340	Gly	Lys	Ser	Tyr	Ser 345	Ser	Gln	Thr	Pro	Tyr 350	Arg	Asp
Gly	Thr	Phe 355	Asp	Thr	Leu	Ala	360	Gln	Ala	Phe	His	Tyr 365	Trp	Ala	Thr
Asp	Ala 370	Arg	Pro	Asp	Ile	Asp 375	Asp	Asn	Ile	Lys	Pro 380	Tyr	Ile	Pro	Tyr
Pro 385	Asp	Gln	Ala	Asn	Pro 390	Ser	Ala	Glu	Tyr	Trp 395	Asn	Pro	Arg	Asn	Asp 400
Pro	Ala	Thr	Trp	Gln 405	His	Met	Val	Thr	Tyr 410	Thr	Leu	Gly	Leu	Gly 415	Leu
Thr	Thr	Ser	Leu 420	Thr	Ser	Pro	Arg	Trp 425	Glu	Gly	Ser	Thr	Phe 430	Ser	Gly
Gly	Tyr	Asn 435	Asp	Ile	Val	Ala	Gly 440	Asn	Leu	Ser	Trp	Pro 445	Arg	Ala	Ser
Asn	Asn 450	Asp	Ser	Asn	Asn	Val 455	Tyr	Asp	Leu	Trp	His 460	Ala	Ala	Val	Asn
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Ser	Arg	Pro	Ala 500	Ile	Ser	Ser	Ser	Leu 505	Gln	Glu	Asp	Asp	Thr 510	Gly	Asp
ГÀа	Leu	Thr 515	Arg	Phe	Ala	Tyr	Gln 520	Thr	Ser	Phe	Ala	Ser 525	Asp	Lys	Asn
Trp	Ala 530	Gly	Asp	Leu	Thr	Arg 535	Tyr	Ser	Leu	Thr	Thr 540	Gln	Asp	Lys	Ala
Thr 545	Val	Gln	Thr	ГЛа	Leu 550	Trp	Ser	Ala	Gln	Ser 555	Ile	Leu	Asp	Ala	Met 560
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Ser	Gly	Leu	Lys 580	Glu	Phe	Thr	Trp	Gly 585	Ser	Leu	Ser	Ala	Asp 590	Gln	Gln
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Gly	Gln 610		Arg	Val	Ala	Phe 615	Leu	Arg	Gly	Asp	Arg 620	Arg	Lys	Glu	Asn
Ser 625	Asp	Asn	Phe	Arg	Thr 630	Arg	Asn	Ser	Ile	Leu 635	Gly	Asp	Ile	Ile	Asn 640
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Gln	Pro	Ile	Glu 660	Pro	Ser	Gly	Asn	Tyr 665	Ser	Thr	Phe	Ala	Glu 670	Ala	Gln
ГÀа	Thr	Arg 675	Ala	Pro	Arg	Val	Tyr 680	Val	Gly	Ala	Asn	Asp 685	Gly	Met	Leu
His	Gly 690	Phe	Asp	Thr	Asp	Gly 695	Asn	Glu	Thr	Phe	Ala 700	Phe	Ile	Pro	Ser
Ala 705	Val	Phe	Glu	ГÀа	Leu 710	His	ГЛа	Leu	Thr	Ala 715	Arg	Gly	Tyr	Gln	Gly 720
Gly	Ala	His	Gln	Phe 725	Tyr	Val	Asp	Gly	Ser 730	Pro	Val	Val	Ala	Asp 735	Ala
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Gly	Gly	Lув 755	Gly	Leu	Phe	Ala	Leu 760	Asp	Val	Thr	Asp	Pro 765	Ala	Asn	Ile
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785					790			Arg		795					800
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Asp	Asn 850	Asn	Ser	Asp	Gly	Val 855	Ala	Asp	Tyr	Ala	Tyr 860	Ala	Gly	Asp	Leu
Gln 865	Gly	Asn	Leu	Trp	Arg 870	Phe	Asp	Leu	Ile	Ala 875	Gly	Lys	Val	Asn	Gln 880
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Phe	Arg	Val	Ser 900	Phe	Gly	Gly	Gln	Pro 905	Leu	Tyr	Ser	Ala	Val 910	Asp	Ser
Ala	Gly	Ala 915	Ala	Gln	Ala	Ile	Thr 920	Ala	Ala	Pro	Ser	Leu 925	Val	Arg	His
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Arg	Leu	Thr	Arg 980	Gly	Asn	Leu	Gln	Gln 985	Gln	Thr	Leu	Asp	Leu 990	Gln	Ala
Asp	Ser	Thr 995	Phe	Ala	Ser	Thr	Ala 1000		g Thi	r Ile	e Arç	g Il.		la Se	er Gln

Asn	Pro 1010		. Asr	Trp	Leu	. Asr 101		sn i	Asp	GlΣ	/ Se:		r 20	Lys	Gln	Ser
Gly	Trp 1025		Leu	ı As <u>r</u>	) Phe	Met 103		al i	Asn	GlΣ	Th:		eu 135	Lys	Gly	Glu
Met	Leu 1040	Ile	: Glu	ı Asp	) Met	Ile 104		la :	Ile	GlΣ	/ Glı		1 50	Val	Leu	Leu
Gln	Thr 1055	Ile	Thi	Pro	) Asn	Asp 106		sp 1	Pro	Суа	a Ala		p 165	Gly	Ala	Ser
Asn	Trp 1070		Туг	Gl <sub>y</sub>	/ Leu	Ası 107		ro '	Tyr	Thi	Gl		.у 980	Arg	Thr	Ser
Phe	Thr 1085	Val	Ph∈	e Asp	Leu	Ala 109		rg (	Gln	Glγ	√ Vai		ı1 95	Asp	Ser	Lys
Ser	Asp 1100		Sei	ту1	Asn	Lys 110		ln i	Asn	Va]	Ala		1 .10	Ser	Gly	Thr
Glu	Gln 1115		Gly	/ Let	ı Gly	Gl <sub>3</sub>		eu '	Thr	Leu	ı Se:		ır .25	Asn	Glu	Gln
Gly	Asn 1130		Glu	ı Val	L Cys	Se:		er (	Gly	Glu	ι Су		eu .40	Thr	Val	Asn
Pro	Gly 1145		Asr	1 Thi	Arg	Gl <sub>3</sub>		rg (	Gln	Asr	ı Trj		g .55	Pro	Ile	Glu
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Phe		Ile 35	Thr	Gly	Pro	Thr	Gly 40	Al	a G	Ly I	nys :	Ser	Thr 45	: Val	l Leu	ı Asp
Ala	Leu 50	Сув	Leu	Ala		Phe 55	Gly	Se	r Tl	ır E		Arg 60	Leu	ı Glı	ı Sei	Thr
Ser 65	Ala	Ser	Ser	Lys	Val 70	Pro	Asp	Gl:	y Ai		Asn ( 75	Glu	Leu	ı Sei	r Sei	Asn 80
Asp	Glu	Arg	Asn	Leu 85	Leu	Arg	Arg	Gl:	y C <u>y</u> 90		Ala :	Ser	Glγ	туз	r Ala 95	a Glu
Val	Asp	Phe	Val 100	Gly	Ile	Asp	Gly	Hi:		rg T	Tyr i	Arg	Ala	Arg		Glu
Thr	_	Arg 115	Ser	Arg	Asp	ГÀа	Ala 120	Asj	p GI	Ly A	Ala 1	Leu	Glr 125		s Sei	Gln
Gln	Ser 130	Leu	Gln	Asp		Glu 135	Thr	Gli	n G	ln N		Leu 140	Ala	a Alá	a Asr	ı L'Aa
Lys 145	Ser	Glu	Phe	Arg	Glu 150	Gln	Leu	Gl	u G		.55 .ys 1	Leu	Glγ	Let	ı Asr	n Phe 160
Ala	Gln	Phe	Thr	Arg 165	Ala	Val	Leu	Le	u A:		3ln :	Ser	Glu	ı Phe	e Sei 175	Ala
Phe	Leu	Lys	Ala 180	Ser	Asp	Asn	Asp	Arg		ly A	Ala 1	Leu	Leu	190		s Leu

Thr	Asp	Thr 195	Gly	Leu	Tyr	Ser	Gln 200	Leu	Ser	Lys	Ala	Ala 205	Tyr	Gln	Arg
Ala	Ser 210	Gln	Ala	Asp	Glu	Gln 215	Arg	Lys	Gln	Leu	Glu 220	Gln	Arg	Leu	Glu
Gly 225	Ser	Leu	Pro	Leu	Ala 230	Glu	Gln	Ala	Arg	Ala 235	Gly	Leu	Glu	Ala	Ala 240
Leu	Glu	Ser	His	Ala 245	Gln	Ala	Arg	Leu	Gln 250	Glu	Gln	Gln	Ala	Leu 255	Gln
Arg	Leu	Glu	Gly 260	Gln	Gln	Gln	Trp	Phe 265	Thr	Glu	Glu	Gln	Arg 270	Leu	Leu
Gln	Ser	Cys 275	Glu	His	Ala	Gln	Gly 280	Gln	Leu	Ala	Glu	Ala 285	Arg	Gln	Ala
Trp	Asp 290	Ala	Leu	Ala	Thr	Glu 295	Arg	Glu	Thr	Leu	Gln 300	Trp	Leu	Glu	Arg
Leu 305	Ala	Pro	Val	Arg	Gly 310	Leu	Ile	Glu	Arg	Leu 315	Lys	Gln	Leu	Glu	Gln 320
Glu	Leu	Arg	His	Ser 325	Glu	Gln	Gln	Gln	Arg 330	Gln	Arg	Thr	Glu	Gln 335	Gln
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Ala	Arg	Glu 355	Arg	Gln	Ala	Gln	Ala 360	Asp	Asn	His	Leu	Arg 365	Gln	Ala	Gln
Ala	Pro 370	Leu	Arg	Glu	Ala	Phe 375	Gln	Leu	Glu	Ser	Glu 380	Ala	Arg	Arg	Leu
Glu 385	Arg	Thr	Leu	Ala	Glu 390	Arg	Gln	Glu	Leu	His 395	Arg	Gln	Ser	Asn	Gln 400
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Asp	Asp	Leu	Ala 500	Ala	Arg	Leu	Val	Glu 505	Leu	Arg	Arg	Gln	Thr 510	Asp	Ser
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Gln	Arg 530	Ala	Gly	Leu	Ala	Arg 535	Arg	Leu	Gly	Glu	Leu 540	Asp	Gln	Arg	Met
Val 545	Glu	Gln	Glu	Gln	Ala 550	Leu	Leu	Asp	Leu	Lys 555	Arg	Gln	Gly	Ser	Gln 560
CÀa	Ala	Glu	Glu	Val 565	ГЛа	Ala	Ala	Glu	Gln 570	Ala	Leu	Gln	Val	Thr 575	Arg
Glu	Leu	Leu	Gln 580	Arg	Gln	Arg	Leu	Ala 585	Arg	Ser	Ala	Ser	Val 590	Glu	Gln

Leu	Arg	Ala 595	Gly	Leu	Val	Asp	Gly 600	Glu	Ala	Сла	Pro	Val 605	Сув	Gly	Ser
Gln	Glu 610	His	Pro	Tyr	His	His 615	Ser	Glu	Gln	Leu	Leu 620	Ala	Ala	Leu	Gly
Glu 625	His	Asp	Asp	Gln	Glu 630	Gln	Val	Arg	Ala	Glu 635	Gln	Ser	Leu	Glu	Arg 640
Leu	Arg	Gln	Thr	Leu 645	Val	Gly	Leu	Arg	Glu 650	Gly	Tyr	Ser	Ser	Gln 655	Arg
Glu	Arg	Leu	Asn 660	Gln	Ser	Arg	Gln	Glu 665	Gln	Gln	Glu	Leu	Thr 670	Gly	Gln
Leu	Ala	Ala 675	Leu	Asp	Arg	Gln	Leu 680	Asp	Gln	Trp	Thr	Leu 685	Pro	Glu	Glu
Leu	Arg 690	Leu	Leu	Gln	Pro	Ser 695	Ala	Gln	Leu	Glu	Trp 700	Leu	Ala	Gln	Arg
Leu 705	Asp	Asp	Leu	Ala	Gly 710	Gln	Arg	Gln	Gln	Cys 715	Gln	Arg	Asp	Phe	Asp 720
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Arg	Ala	Ala	Glu 740	Thr	Ile	Leu	Gln	Gln 745	Arg	Gln	Gln	Ala	Leu 750	Thr	Glu
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Ser	Ser	Asn 35	Val	Ala	Leu .		Val. 40	Ala	Pro	Glu	Ser	7 Val 45	l Ala	a Gly	y Tyr
Ser	Lys 50	Ser	Gly	Ser .	_	Leu 55	Ile	Val	Gln	Leu	Lys 60	Th:	Gly	/ Glu	ı Ser
Val 65	. Arg	Ile	Ala		Phe 70	Tyr	Ala	Glu	Gly	Gln 75	Pro	Sei	s Sei	Glr	n Leu 80
Ph∈	e Leu	Ala		Lys . 85	Asp	Lys	Leu '		Ala 90	Val	Asp	Let	ı Pro	95	o Val
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Val	Tyr 2450	Thr	Phe	Gly	Ser	Thr 2455	Thr	Leu	Leu	Ile	Glu 2460	Asp	Asn	Thr

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Glu	Ala	Gly 355	Val	Glu	Pro	Asp	Glu 360	Arg	Arg	Asn	Ala	Arg 365	Gly	Asp	Leu
Glu	Leu 370	Arg	Ser	Gly	Thr	Leu 375	Arg	Asn	Ala	Gly	Ser 380	Leu	Val	Ala	Ser
Arg 385	Ala	Leu	Glu	Ala	390	Ala	Ser	Gln	Ala	Leu 395	Asp	Asn	Gln	Gly	Gly 400
Ser	Leu	Lys	Gly	Ala 405	Thr	Val	Arg	Val	Asp 410	Ala	Gly	His	Leu	Asp 415	Asn
Arg	Gly	Gly	Lys 420	Leu	Leu	Ala	Glu	Gly 425	Glu	Leu	Arg	Val	Glu 430	Ala	Ser
Ser	Leu	Asp 435	Asn	Arg	Gln	Asp	Gly 440	Leu	Leu	Gln	Ser	Arg 445	Asp	Arg	Ala
Val	Val 450	Lys	Thr	Arg	Gly	Asp 455	Leu	Asp	Asn	Arg	Gly 460	Gly	Gln	Val	Ile
Gly 465	Leu	Asn	Asp	Leu	Glu 470	Val	Gly	Ala	Ala	Thr 475	Leu	Asp	Asn	Gly	Gln 480
Gln	Gly	Leu	Leu	Gly 485	Ser	Gln	Gln	Ser	Thr 490	Arg	Val	Ser	Ala	Gln 495	Ala
Leu	Val	Asn	Arg 500	Gly	Aap	Gly	Glu	Val 505	Ser	Gly	Lys	Arg	Val 510	Glu	Ala
Arg	Val	Gly 515	Ser	Leu	Asp	Asn	Arg 520	Gly	Gly	Lys	Leu	Ile 525	Gly	Asp	Asp
Leu	Leu 530	Val	Val	Ala	Ser	Gly 535	Ala	Ile	Asp	Asn	Arg 540	Leu	Gly	Leu	Phe
Ser 545	Ala	Ala	Asn	Arg	Leu 550	Asp	Leu	Arg	Ala	Arg 555	Ser	Leu	Asp	Asn	Ser 560
Gly	Lys	Gly	Thr	Leu 565	Ser	Ser	Arg	Gly	Gly 570	Leu	Glu	Val	Ser	Leu 575	Gly
Gly	Leu	Leu	Asp 580	Asn	Arg	Asp	Glu	Gly 585	Asn	Leu	Leu	Ser	Gln 590	Gly	Ala
Gln	Arg	Val 595	Thr	Val	Gly	Gln	Leu 600	Asp	Asn	Arg	Ala	Gly 605	Gly	Leu	Leu
Ser	Ser 610	Arg	Ser	Glu	Leu	Asn 615	Val	His	Gly	Ala	Ser 620	Leu	Asp	Asn	Arg
Gly 625	Gly	Val	Leu	Val	Ala 630	Asp	Ala	Gly	Leu	Ser 635	Ala	Thr	Gly	Gly	Ala 640
Phe	Asp	Asn	Arg	Asp 645	Gly	Gly	Ser	Ala	Ser 650	Gly	ГÀа	Ala	Gly	Val 655	Arg
Val	Glu	Val	Ala 660	Ser	Leu	Arg	Asn	Asp 665	Gln	Gly	Gly	ГÀа	Leu 670	Leu	Ser
Asp	Gly	Arg 675	Leu	Asp	Leu	Ala	Ala 680	Asn	Ala	Val	Gly	Asn 685	Ala	Gly	Gly
Arg	Ile 690	Ala	Ala	Lys	Gly	Asp 695	Leu	Gln	Ala	Thr	Leu 700	Gly	Ser	Leu	Ala
Gln 705	Gln	Gly	Gly	Glu	Leu 710	Val	Ser	Glu	Lys	Thr 715	Leu	Lys	Val	Ala	Ala 720
Asp	Thr	Leu	Asp	Asn 725	Ser	Gln	Ser	Gly	Leu 730	Ile	Ala	Ala	Asn	Gly 735	Gly
Ile	Ala	Ile	Glu 740	Ala	Arg	Gln	Val	Asp 745	Asn	Arg	Ala	Gly	Glu 750	Ile	Ser

Ser	Thr	Ser 755	Lys	Val	Ala	Val	Asn 760	Ala	Arg	Glu	Gln	Leu 765		Asn	Arg
Gly	Gly 770	Lys	Val	Ile	Gly	Asp 775	Ser	Gly	Leu	Arg	Leu 780		Val	Gln	Arg
Leu 785	Leu	Asn	Gln	Ala	Lys 790	Gly	Val	Leu	Ala	Gly 795	Arg	Asp	Gly	Leu	Ser 800
Leu	Asp	Gly	Gly	Glu 805	Leu	Phe	Asn	Gly	Asp 810	Gly	Gly	Arg	Leu	Asp 815	Ser
Gln	Asn	Ser	Leu 820	Ser	Val	Ser	Leu	Gly 825	Gly	Val	Leu	Asp	Asn 830		Gly
Gly	Ala	Leu 835	Val	Ser	Glu	Gly	Ser 840	Leu	Thr	Ala	Arg	Ala 845	Ala	Arg	Leu
Asp	Asn 850	Arg	Gly	Gly	Thr	Phe 855	Ser	Ser	Ala	Gly	Ala 860		Ala	Leu	Thr
Ser 865	Gln	Ala	Ala	Leu	Asp 870	Asn	Gln	Gly	Gly	Arg 875	Leu	Leu	Ser	Asp	Ala 880
Gly	Val	Thr	Leu	Gln 885	Gly	Ala	Ser	Leu	Asp 890	Asn	Ser	Arg	Ser	Gly 895	
Ile	Ser	Ala	Dys 900	Gly	Ala	Val	Asp	Ile 905	Arg	Thr	Gly	Val	Leu 910		Asn
Ser	Arg	Asn 915	Gly	Gly	Ile	Gly	Ser 920	Asn	Ala	Gly	Ile	Thr 925		Val	Ala
Ala	Arg 930	Leu	Asp	Asn	Gly	Gln 935	Gln	Gly	Arg	Val	Ser 940		Lys	Gly	Leu
Leu 945	Asp	Ala	Asn	Leu	Lys 950	Gly	Leu	Asp	Gln	Arg 955	Gly	Gly	Gly	Val	Leu 960
Ile	Ser	Glu	Thr	Gly 965	Val	Thr	Leu	Asp	Leu 970	Asn	Gly	Gly	Thr	Leu 975	
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Gln	Leu	Gly 995	Ala	Val	Asp	Asn	Gly 1000		a Gl	y Gl	y Gl		e S 05	er S	er Asp
Arg	Ala 1010		e Thi	Let	ı Alá	a Ala 10:		la S	er L	eu A	_	sn 020	Arg	Gly	Gly
Arg	Leu 1025		e Gly	/ Ala	a Alá	a Ası 103		eu T	hr L	eu A	_	le 035	Ala	Gln	Ala
Leu	Asp 1040		ı Sei	. Let	ı Alá	a Gly 104		al I	le S	er G	-	la 050	Ala	Gly	Leu
Asp	Ile 1055		a Alá	a Ala	a Arç	J Let 106		sp A	sn S	er A		065 9	Gly	Thr	Leu
Ala	Ser 1070		g Ala	a Gly	/ Ile	e Ası 10'		eu A	rg V	al A		ly 080	Ala	Leu	Aap
Asn	His 1085		a Glu	ı Gl∑	7 Thi	109		er G	ly A	la A	_	eu 095	Thr	Leu	Ala
Ser	Ala 1100		: Let	ı Asp	) Ası	n Sei 110		ly L	ys G	ly L		eu 110	Ser	Gly	Asn
Ala	Gly 1115		ı Sei	· Val	L Ala	a Thi		ly A	la L	eu A	-	sn 125	Ala	Glu	Gly
Gly	Gln 1130		ı Ile	e Sei	Glr	n Gly		al L	eu A	ap V		er 140	Ser .	Ala	Asp
Leu	Asp	Asr	n Arg	g Gl	/ Gly	/ Ala	a Le	eu S	er G	ly L	ys G	ln	Ser	Leu	Arg

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		1145					1150					1155			
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G	Hy	Gly 1190	Glu	Ile	Ser	Ala	Arg 1195	Gly	Asp	Leu	Arg	Leu 1200	Thr	Val	Glu
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L	₋eu	Leu 1265	Ala	Arg	Arg	Ile	Asp 1270	Asn	Gly	Gln	Gln	Gly 1275		Ile	Ile
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G	ly	Ala 1295	Gly	Leu	Leu	Ser	Gly 1300	Trp		Gly		Thr 1305	Val	Thr	Gly
G	ly	Ser 1310	Leu		Asn		Ala 1315			Thr		Ser 1320	Ser	Lys	Asp
G	ly		Leu				Leu 1330		Gly	Ala			Asn	His	Gly
G	∃ln		Ala	Leu	Val	Ser	Lys 1345	Gly					Asp	Ala	Ala
S	Ser			Asn	Ala	Gln	Gly 1360	Ile	Val	Ser	Gly		Ser	Asp	Val
Т	hr			Ile	Ala	Gly	Lys 1375	Leu		Asn			Gly	Gly	Leu
V	/al	Ser	Ala				Leu	Ser				Asp		Thr	Leu
L	₋eu		Asn	Ala		Gly	1390 Arg	Ile						Leu	Leu
L	ıys	1400 Gly	Ala	Ser		Asp	1405 Asn	Ser		Gly		1410 Leu	Ile	Ser	Gln
		1415				Ī			_	Ī		1425			
		1430					1435					1440			
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G	lu	Ile 1475	Ser	Ala	Gly	Ser	Leu 1480	Asp	Asn	Ser	Ala	Ser 1485		Thr	Leu
A	Ala	Ser 1490		Ala	Gly	Met	Ser 1495	Leu	Arg	Leu	Gly	Gly 1500	_	Ala	Leu
A	Arg	Asn 1505	Gln	Gln	Asp	Gly	Leu 1510	Ile	Phe	Ser	Gln	Ala 1515	Gly	Ala	Leu
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Ala         Gly         Asp Asn Arg         Leu         Arg Ile Gly         Gly         Ala         Leu         Asp         Asp         Leu         Asp         Leu         Asp															
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Asp Phe 1670       Ser Leu Ala Gly Ala 1675       Leu Ala Asn Arg Phe 1680       Gly Gln 1680         Glu Ser 1685       Glu Ser Glu Leu His 1690       Leu Arg Ala Ala Ala Ala 1695       Ile Asp 1695         Ser Gly 1700       Gly Ser Leu Arg Ala Leu Gly Arg Ser Gly 1710       Leu Gly Arg Ser Gly 1710       Ser Thr 1710         Leu Val 1715       Ala Gly Gly Leu Asn Asn Ala Tyr Gly Val 1725       Leu Gly Arg Ser Leu Glu 1735       Leu Gly Ser Leu Glu 1735         Ala Asn 1730       Gln Asp Leu Asp Leu Gln Leu Gly Ser Leu 1740       Ala Asn 1740       Ala Asn 1740         Gly Gly 1745       Arg Ile Leu His Thr 1750       Gly Asn Gly Thr Phe 1755       Gly Leu 1745         Ser Gly 1760       Ala Arg Ala Gly Gly Glu Leu Thr 1770       Thr Asn 60         Ser Gly 1760       Ala Arg Ala Ser Glu Trp Thr Asn Ser Ser Val 1770         Leu Leu Leu Asp Ile Arg Ala Ser Glu Trp Thr Asn Ser Ser Val 1770         Gln Ala Glu Gly Arg Leu Asn Leu Asp Leu Asp Ile Gly Thr Phe 1800       Arg Glu 1780         Gly Asp Trp Ser Asn Asp Gly Leu Leu Ala Gln Ser Phe Thr 1815       Gly Arg Gly Arg 1825         Gly Asp Leu Ser Gly Gly Tyr Arg Gly Asn Gly Arg Ala 1840       1840         Ser Leu Gly Asp Phe Ala Leu Asn Asn Ala Ala Ser Leu Asp Leu Gly 1875         Asn Ala Ala Ser Leu Ala Gly 1870       Gly Asp Leu Cu Ala Gly 1875       Gly Asp Leu Gly Asp Phe Ala Leu Asn Ala Ala Ser Leu Ala Gly 1875         Asn Ala Ala Ser Leu	Ala		Gly	Leu	Leu	Ser		Asp	Gly	Gln	Arg		Leu	Asn	Gln
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1715	Ser	-	Gly	Ser	Leu	Arg		Leu	Gly	Arg	Ser	_	Ser	Thr	Arg
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Ser       Leu 1850       Gly Asp Phe Ala Leu 1855       Asn Ala Ala Ser Leu 1860       Leu 1860       Asp Leu 6 1860         Asn Ala Ala Ser Leu Ala Gly 1865       Asn Ala Asn Val Thr 1875       Leu Gly Asn 1887       Asn Ala Asn Val Thr 1875       Leu Gly Asn 1887         Gly Asn 1880       Leu Leu Val Asn Arg 1885       Gly Arg Ile Thr Ala 1890       Ala Gly Asn 1880         Leu Val Ala Ser Ala Ala Ser Leu Asn Asn Tyr Gly Thr Leu Gly	Gly		Trp	Ser	Asn	Asp		Leu	Leu	Ala	Ser		Gly	Ser	Phe
Asn Ala Ala Ser Leu Ala Gly 1865       Gly Ala Asn Val Thr 1875       Leu Gly Asn 1875         Gly Asn Leu Leu Val Asn Arg 1880       Gly Asn 1885       Leu Cu Val Asn Arg 1885         Leu Val Ala Ser Ala Ala Ser Leu Asn Asn Tyr Gly Thr Leu Cu Asn Tyr Gly Thr Leu Cu Asn Asn Tyr Gly Thr Leu Cu Asn Tyr Gly Thr Thr Leu Cu Asn Tyr Gly Thr	Arg		Asp	Leu	Ser	Gly		Tyr	Arg	Gly	Asn		Arg	Ala	Thr
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1880 1885 1890 Leu Val Ala Ser Ala Ala Ser Leu Asn Asn Tyr Gly Thr Leu G	Asn		Ala	Ser	Leu	Ala	_	Gly	Ala	Asn	Val		Leu	Gly	Ala
	Gly		Leu	Leu	Val	Asn	_	Gly	Arg	Ile	Thr		Ala	Gly	Asp
· · ·	Leu		Ala	Ser	Ala	Ala		Leu	Asn	Asn	Tyr	_	Thr	Leu	Gly

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Arg	Gly 1925	Leu	Leu	Phe	Ser	Gly 1930		Asp	Met	Thr	Leu 1935	Arg	Ala	Gly
Asp	Ile 1940	Thr	Asn	Leu	Tyr	Gly 1945	Asp	Val	Tyr	Ser	Leu 1950		Arg	Leu
Asp	Ile 1955	Ala	Arg	Asp	Asp	Ala 1960		Asn	Arg	Ala	Ala 1965	Ser	Leu	Arg
Asn	Leu 1970	Ser	Gly	Val	Ile	Glu 1975		Gly	Lys	Asp	Phe 1980		Leu	Arg
Ala	Ser 1985	Leu	Ile	Glu	Asn	Arg 1990	_	Ala	Val	Leu	Glu 1995	Ser	Lys	Ser
Gly	Leu 2000	Tyr	Thr	Ala	Lys	Met 2005		Gln	Thr	Ala	Cys 2010	Ile	Glu	Gly
Val	Asn 2015	Ala	Gly	Asp	Cys	Ser 2020		Lys	Arg	Asn	Ala 2025	Ile	Trp	Thr
Ile	Thr 2030	Gln	Arg	Asp	Lys	Thr 2035		Val	Thr	Ala	Ser 2040	Ser	Ala	Met
Gly	Gln 2045	Leu	Leu	Ala	Gly	Gly 2050		Phe	Ala	Ile	Asp 2055	Gly	Gly	Thr
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Gly	Val 2210		Val	Val	Val	Pro 2215		Thr	Ser	Gln	Leu 2220	Pro	Pro	Aap
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5	Ser	Val 2555		_	Tyr		Ser 2560				Gly	Arg 2565	Thr	Trp	Glu
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Thr	Leu 2855	Arg	Gln	Thr	Gln	Ile 2860	Val	Ala	Gln	Gly	Asn 2865	Leu	Ala	Ile
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Pro Thr Lys Ile Val Arg Ala Ile Gl 3470 3475	u Lys Lys Ser Asn Gln Ala 3480
Gly Gly Val Leu Val Gln Ala Asp Le 3485 3490	u Pro Ser Thr Asp Met Ser 3495
Ser Ile Ala Ala Arg Met Trp Gly Ly 3500 3505	s Thr Asn Ala Gln Ser Ile 3510
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Gly Val Pro Ile Val Asn Ile Ala Thr 50 55	Pro Asn Gly Ala Gly Leu Ser 60
Asn Asn His Phe Arg Asp Tyr Asn Val	Gly Ala Asn Gly Leu Ile Leu 75 80
Asn Asn Ala Thr Gly Lys Thr Gln Gly 85	Thr Gln Leu Gly Gly Ile Ile 90 95
Leu Gly Asn Pro Asn Leu Lys Gly Gln . 100 105	Ala Ala Gln Val Ile Leu Asn 110
Gln Val Thr Gly Gly Asn Arg Ser Thr	Leu Ala Gly Tyr Thr Glu Val 125
Ala Gly Gln Ser Ala Arg Val Ile Val . 130 135	Ala Asn Pro His Gly Ile Thr 140
Cys Gln Gly Cys Gly Phe Ile Asn Thr	Pro Arg Ala Thr Leu Thr Thr 155 160
Gly Lys Pro Ile Met Asp Gly Gln Arg	Leu Glu Arg Phe Gln Val Asp 170 175
Gly Gly Asp Ile Val Val Glu Gly Ala	Glu Leu Asn Val Gly Asn Leu 190
Glu Gln Phe Asp Leu Ile Thr Arg Ser .	Ala Lys Leu Asn Ala Lys Leu 205
Tyr Ala Lys Asn Leu Asn Ile Val Thr	Gly Arg Asn Asp Val Gln Ala
210 215  Asp Ser Leu Gln Ala Thr Pro Arg Ala	220 Ala Asp Gly Ser Glu Lys Pro
225 230	235 240

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Ile	Arg	Leu	Val 260	Gly	Thr	Glu	Gln	Gly 265	Val	Gly	Val	Lys	Leu 270	Ala	Gly
Asp	Met	Ala 275	Ala	Ser	Gly	Gly	Asp 280	Ile	Arg	Ile	Asp	Ala 285	Ser	Gly	Lys
Leu	Ser 290	Leu	Ala	Gln	Ala	Ser 295	Ser	Gln	Gly	Asp	Leu 300	ГÀа	Ile	Ala	Ala
Gln 305	Ala	Val	Glu	Leu	Asn 310	Gly	Lys	Thr	Tyr	Ala 315	Gly	Gly	Ser	Ala	Glu 320
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	Asp		500		_	_	-	505					510		
	Lys	515	_			_	520			_	Ī	525			
	530		-			535				-	540	J		•	-
Ile 545	Ser	Ser	Thr	Ser	Arg 550	Val	Val	Ala	Ser	Ala 555	Arg	Glu	Gln	Leu	Asp 560
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Pro	Arg	Met	Leu 580	Asn	Gln	Asp	Lys	Gly 585	Val	Leu	Ala	Ser	Arg 590	Asp	Gly
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Asn	Leu	Val 755	Ser	Asp	Thr	Gly	Ile 760	Thr	Leu	Asp	Leu	Asn 765	Lys	Gly	Ser
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Arg	Leu	Leu	Ser 820	Gly	Gly	Ala	Leu	Thr 825	Leu	Arg	Ile	Ala	Gln 830	Ala	Leu
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Ser	Ala	Tro	Lou	_										
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_														
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Gly	Ala 1985		Asp	Ala	Asn	Leu 1990		Gly	Leu	Asp	Gln 1995	Gln	Gly	Ser
Gly	Arg 2000		Val	Ser	Asp	Thr 2005	Ala	Ile	Ala	Leu	Asp 2010	Leu	Arg	Gly
Gly	Glu 2015		Val	Asn	Arg	Ala 2020	Gln	Gly	Leu	Ile	Ala 2025	Thr	Pro	Gly
Ala	Leu 2030		Leu	Arg	Gln	Leu 2035	_	Val	Val	Asp	Asn 2040	Ser	Gly	Gly
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Gly	Val 2195	Thr	Ala	Glu	Ala	Arg 2200		Ile	Asp	Asn	Arg 2205	Gly	Gly	Glu
Ile	Ser 2210	Ser	Val	Ala	ГÀв	Val 2215	Ala	Leu	Ala	Val	Arg 2220	Glu	Gln	Leu
Asp	Asn 2225	Arg	Gly	Gly	Lys	Val 2230	Ile	Gly	Asp	Ser	Glu 2235	Leu	Ser	Leu
Thr	Val 2240	Gln	Arg	Leu	Leu	Asn 2245	Gln	Ala	Lys	Gly	Val 2250	Leu	Ala	Ser
Arg	Asp 2255	Gly	Leu	His	Leu	Asp 2260	Gly	Ala	Glu	Leu	Leu 2265	Asn	Gly	Asp
Gly	Gly 2270	Leu	Leu	Ser	Ser	Gln 2275	Arg	Leu	Val	Asp	Val 2280	Thr	Leu	Ser
Gly	Ala 2285	Leu	Asp	Asn	Gln	Gly 2290	Ser	Gly	Ala	Leu	Val 2295	Ser	Glu	Glu
Ser	Leu 2300	Thr	Val	Lys	Ala	Asp 2305	Gln	Val	Asn	Asn	Gln 2310	Ala	Gly	Thr
Phe	Ser 2315	Ser	Ala	Gly	Ser	Leu 2320	Leu	Val	Thr	Ser	Arg 2325	Gly	Glu	Leu
Asn	Asn 2330	Gln	Gly	Gly	Arg	Leu 2335	Val	Thr	Asp	Ala	Gly 2340	Ala	Thr	Leu
Asn	Ser 2345	Thr	Gly	Phe	Asp	Asn 2350	Ser	Arg	Ala	Gly	Leu 2355	Val	Ser	Ala
ГÀв	Gly 2360	Ala	Val	Ala	Ile	Arg 2365	Thr	Gly	Ala	Leu	Asn 2370	Asn	Ser	Gln
Lys	Gly 2375	Ser	Ile	Gly	Gly	Asn 2380	Thr	Gly	Val	Thr	Leu 2385	Val	Ala	Gly
Leu	Val 2390	Asp	Asn	Gly	Arg	Glu 2395	Gly	Arg	Ile	Ser	Thr 2400	Lys	Gly	Thr
Leu	Asp 2405	Ala	Asn	Leu	Lys	Gly 2410	Leu	Leu	Gln	Gln	Gly 2415	Gly	Gly	Ser
Leu	Val 2420	Gly	Glu	Arg	Gly	Val 2425	Thr	Leu	Asp	Leu	Asn 2430	Gly	Gly	Thr
Leu	Asp 2435	Asn	His	Asp	Leu	Gly 2440	Leu	Val	Ser	Thr	Pro 2445	Gly	Ala	Leu
Leu	Leu 2450	Arg	Gln	Leu	Gly	Met 2455	Val	Asp	Asn	Ser	Val 2460	Gly	Gly	Glu
Ile	Ser 2465	Ser	Asp	Arg	Ala	Phe 2470	Thr	Leu	Ala	Ala	Asn 2475	Thr	Leu	Asn
Asn	Gln 2480	Gly	Gly	Arg	Leu	Ile 2485	Ser	Ser	Glu	Ala	Leu 2490	Thr	Leu	Arg
Ile	Ala 2495	Lys	Thr	Leu	Asp	Asn 2500	Ser	Leu	ГЛа	Gly	Gln 2505	Val	Leu	Ala
Thr	Asp 2510	Gly	Leu	Ala	Ile	Glu 2515	Ser	Gln	Val	Leu	Asp 2520	Asn	Arg	Ala
Gly	Thr 2525	Ile	Gly	Ser	Lys	Gly 2530	Asp	Ala	Arg	Ile	Ser 2535	Val	Thr	Ser
Leu	Asp 2540	Asn	Ala	Glu	Gln	Gly 2545	Ser	Leu	Val	Ser	Glu 2550	Gly	Arg	Leu
Glu	Leu 2555	Val	Ala	Asp	Gln	Val 2560	Ser	Asn	Gly	Asn	Gln 2565		Arg	Ile

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Ala	Ala 2570	Arg	Gly	Val	Leu	Glu 2575	Ala	Ala	Val	Gly	Thr 2580	Leu	Leu	Gln
Gln	Gly 2585	Gly	Glu	Leu	Val	Ser 2590	Gln	Gly	Ser	Leu	Asp 2595	Leu	Arg	Ala
Asp	Thr 2600	Leu	Asp	Asn	Ser	Gln 2605	Ser	Gly	Leu	Ile	Ala 2610	Ala	Asn	Gly
Gly	Ile 2615	Ala	Ile	Glu	Ala	Arg 2620	Gln	Val	Asp	Asn	Arg 2625	Ala	Gly	Glu
Ile	Ser 2630	Ser	Thr	Ser	Lys	Val 2635	Ala	Val	Asn	Ala	Arg 2640	Glu	Gln	Leu
Asp	Asn 2645	Arg	Gly	Gly	Lys	Val 2650	Ile	Gly	Asp	Ser	Gly 2655	Leu	Arg	Leu
Thr	Val 2660	Gln	Arg	Leu	Leu	Asn 2665	Gln	Ala	ГХа	Gly	Val 2670	Leu	Ala	Gly
Arg	Asp 2675	Gly	Leu	Ser	Leu	Asp 2680	Gly	Gly	Glu	Leu	Phe 2685	Asn	Gly	Asp
Gly	Gly 2690	Arg	Leu	Asp	Ser	Gln 2695	Asn	Ser	Leu	Ser	Val 2700	Ser	Leu	Gly
Gly	Val 2705	Leu	Asp	Asn	Gln	Gly 2710	Gly	Ala	Leu	Val	Ser 2715	Glu	Gly	Ser
Leu	Thr 2720	Ala	Arg	Ala	Ala	Arg 2725	Leu	Asp	Asn	Arg	Gly 2730	Gly	Thr	Phe
Ser	Ser 2735	Ala	Gly	Ala	Leu	Ala 2740	Leu	Thr	Ser	Gln	Ala 2745	Val	Leu	Asp
Asn	Gln 2750	Gly	Gly	Arg	Leu	Leu 2755	Ser	Asp	Ala	Gly	Val 2760	Thr	Leu	Lys
Gly	Ala 2765	Ser	Leu	Asp	Asn	Ser 2770	Arg	Ser	Gly	Val	Ile 2775	Ser	Ala	Lys
Gly	Ala 2780		Asp	Ile	Arg	Thr 2785	Gly	Val	Leu	Asp	Asn 2790	Ser	Arg	Asn
Gly	Gly 2795	Ile	Gly	Ser	Asn	Ala 2800	Gly	Ile	Thr	Leu	Val 2805	Ala	Ala	Arg
Leu	Asp 2810	Asn	Gly	Gln	Gln	Gly 2815	Arg	Val	Ser	Ala	Lys 2820	Gly	Leu	Leu
Asp	Ala 2825	Asn	Leu	Lys	Gly	Leu 2830	Asp	Gln	Arg	Gly	Gly 2835	Gly	Val	Leu
Val	Ser 2840		Thr	Gly	Val	Thr 2845	Leu	Asp	Leu	Asn	Gly 2850	Gly	Thr	Leu
Val	Asn 2855	Arg	Asp	Gly	Gly	Leu 2860		Ala	Thr	Pro	Gly 2865	Ala	Leu	Leu
Leu	Arg 2870		Leu	Gly	Ala	Val 2875	Asp	Asn	Gly	Ala	Gly 2880	Gly	Glu	Ile
Ser	Ser 2885	Asp	Arg	Ala	Phe	Thr 2890		Ala	Ala	Ala	Ser 2895	Leu	Asp	Asn
Arg	Gly 2900	Gly	Arg	Leu	Ile	Gly 2905	Ala	Asp	Ser	Leu	Thr 2910	Leu	Arg	Ile
Ala	Gln 2915	Ala	Leu	Asp	Asn	Ser 2920	Leu	Ala	Gly	Val	Ile 2925	Ser	Gly	Ala
Ala			Asp	Ile	Ala			Arg	Leu	Asp	Asn 2940		Ala	Lys
Gly			Ala	Ser	Arg			Ile	Asp	Leu	Arg		Asp	Gly
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		2945					2950					2955			
A	la.	Leu 2960	_	Asn	His	Ala	Glu 2965	_	Thr	Val	Ser	Gly 2970	Ala	Arg	Leu
T	hr	Leu 2975	Ala	Ser	Ala	Ser	Leu 2980	_	Asn	Ser	Gly	Lys 2985	_	Leu	Leu
S	er	Gly 2990		Ala	Gly	Leu	Ser 2995		Ala	Thr	Gly	Ala 3000	Leu	Asp	Asn
A	la.	Glu 3005	-	Gly	Gln	Leu	Ile 3010		Gln	Gly	Val	Leu 3015	Asp	Val	Ser
S	er	Ala 3020	_		_		Arg 3025					Ser 3030	Gly	Lys	Gln
s	er	Leu 3035	_			Ala	Ala 3040		Leu	Asp	Asn	Arg 3045	Gly	Gly	Leu
L	eu	Thr 3050		_	Gly		Leu 3055		Leu	Thr	Ala	Gly 3060	Arg	Val	Asp
S	er	Ala 3065	Asp	Gly	Gly	Glu	Ile 3070		Ala	Arg	Gly	Asp 3075	Leu	Arg	Leu
T	hr						Gln 3085	Arg	Gln	Gly	Arg		Ile	Gly	Glu
A	rg			Ser	Leu	Asp	Leu 3100	Arg					Asp	Asn	Gln
G	ly		Leu	Ile	Ser	Ala	Arg 3115	Gly	Pro	Leu			Glu	Arg	Leu
А	.sn		Leu	Asp	Asn	Arg	Gln 3130	Gly		Glu			Ser	Gln	Gln
G	ly			Leu	Leu	Ala	Arg 3145	Arg		Asp	Asn		Gln	Gln	Gly
А	rg	Ile	Ile	Ser	Ala	Gly	Lys	Leu	Arg	Leu	Asp	Ala	Asp	Ala	Leu
G	ly						3160 Leu	Leu		Gly	Trp		Gly	Leu	Thr
V	al		Gly	Gly		Leu	3175 Asp	Asn		Ala	Gly	-	Thr	Leu	Ser
s	er	3185 Lys				Leu	3190 Ala					3195 Gly	Ala	Leu	Asp
		3200	_	-			3205 Leu				_	3210			_
		3215	-		Ī		3220				Ī	3225		_	
A	.sp	Ala 3230		Ser	Leu	Asp	Asn 3235		Gln	Gly	Ile	Val 3240		Gly	Glu
S	er	Asp 3245	Val	Thr	Leu	Ser	Ile 3250		Gly	ГÀа	Leu	Asp 3255		Gly	Gln
G	ly	Gly 3260	Leu	Val	Ser	Ala	Gln 3265	_	Ala	Leu	Ser	Phe 3270	Glu	Arg	Asp
А	.ap	Thr 3275	Leu	Leu	Asn	Asn	Ala 3280	_	Gly	Arg	Ile	Asn 3285	Gly	Gly	Ser
L	eu	Leu 3290	Leu	Lys	Gly	Ala	Ser 3295		Asp	Asn	Ser	Asp 3300	Gly	Gln	Leu
I	le	Ser 3305	Gln	Gly	Arg	Leu	Asp 3310		Ile	Leu	Gly	Gly 3315	Ala	Leu	Val
A	.sn	Ala	Gly	Ala	Ala	Arg	Leu	Ala	Ser	Gly	Gly	Asp	Leu	Leu	Leu
		3320					3325					3330			

Arg	Ser 3335	Ala	Ser	Val	Asp	Asn 3340	Arg	Gly	Gly	Lys	Leu 3345	Val	Ser	Gln
Gly	Leu 3350	Leu	Glu	Ile	Ser	Ala 3355	Gly	Ser	Leu	Asp	Asn 3360	Ser	Ala	Ser
Gly	Thr 3365	Leu	Ala	Ser	Gln	Ala 3370	Asp	Met	Ser	Leu	Arg 3375	Leu	Gly	Gly
Gly	Ala 3380	Leu	Arg	Asn	Gln	Gln 3385	Asp	Gly	Leu	Ile	Phe 3390	Ser	Gln	Ala
Gly	Ala 3395	Leu	Glu	Val	Gln	Ala 3400	Gly	Ser	Leu	Asp	Asn 3405	Arg	Gln	Gly
Thr	Leu 3410	Gln	Ala	Gln	Gly	Asp 3415	Asn	Arg	Leu	Arg	Ile 3420	Gly	Gly	Ala
Leu	Asp 3425	Asn	Gln	Ala	Gly	Arg 3430	Leu	Asp	Ser	Arg	Ala 3435	Gly	Asn	Leu
Asp	Leu 3440	Gln	Ser	Gly	Ser	Leu 3445	Asp	Asn	Gly	Ala	Gly 3450	Gly	Val	Leu
Asn	Ser 3455	Ala	Lys	Gly	Trp	Leu 3460	Lys	Leu	Val	Thr	Gly 3465	Leu	Phe	Asp
Asn	Ser 3470	Ala	Gly	Val	Thr	Gln 3475	Ala	Gln	Ser	Leu	Glu 3480	Ile	Arg	Ala
Gly	Gln 3485	Gly	Val	Arg	Asn	Gln 3490	Gln	Gly	His	Leu	Ser 3495	Ala	Leu	Gly
Gly	Asp 3500	Asn	Arg	Ile	Val	Thr 3505	Ala	Asp	Phe	Asp	Asn 3510	Gln	Gly	Gly
Gly	Leu 3515	Tyr	Ala	Ser	Gly	Leu 3520	Leu	Ser	Leu	Asp	Gly 3525	Gln	Arg	Phe
Leu	Asn 3530	Gln	Gly	Ala	Ala	Ala 3535	Gly	Gln	Gly	Gly	Lys 3540	Val	Gly	Ala
Gly	Arg 3545	Ile	Asp	Phe	Ser	Leu 3550	Ala	Gly	Ala	Leu	Ala 3555	Asn	Arg	Phe
Gly	Gln 3560	Leu	Glu	Ser	Glu	Ser 3565	Glu	Leu	His	Leu	Arg 3570	Ala	Ala	Ala
Ile	Asp 3575	Asn	Ser	Gly	Gly	Ser 3580	Leu	Arg	Ala	Leu	Gly 3585	Arg	Ser	Gly
Ser	Thr 3590	Arg	Leu	Val	Ala	Gly 3595	Asp	Leu	Asn	Asn	Ala 3600	Tyr	Gly	Val
Leu	Glu 3605	Ser	Ala	Asn	Gln	Asp 3610	Leu	Asp	Leu	Gln	Leu 3615	Gly	Ser	Leu
Ala	Asn 3620	Ala	Gly	Gly	Arg	Ile 3625	Leu	His	Thr	Gly	Asn 3630	Gly	Thr	Phe
Gly	Leu 3635	Asp	Ser	Gly	Gln	Val 3640	Ile	Arg	Ala	Gly	Gly 3645	Glu	Leu	Thr
Thr	Asn 3650	Gly	Leu	Leu	Asp	Ile 3655	Arg	Ala	Ser	Glu	Trp 3660	Thr	Asn	Ser
Ser	Val 3665	Leu	Gln	Ala	Gly	Arg 3670	Leu	Asn	Leu	Asp	Ile 3675	Gly	Thr	Phe
Arg	Gln 3680	Thr	Ala	Glu	Gly	Lys 3685	Leu	Leu	Ala	Val	Gln 3690	Ser	Phe	Thr
Gly	Arg 3695	Gly	Gly	Asp	Trp	Ser 3700	Asn	Asp	Gly	Leu	Leu 3705	Ala	Ser	Asn

Gly	Ser 3710	Leu	Arg	Leu	Glu	Leu 3715	Ser	Gly	Gly	Tyr	Arg 3720		Asn	Gly
Arg	Ala 3725	Thr	Ser	Leu	Gly	Asp 3730		Ala	Leu	Asn	Ala 3735	Ala	Ser	Leu
Asp	Leu 3740	Gly	Asn	Ala	Ala	Ser 3745		Ala	Gly	Gly	Ala 3750		Val	Thr
Leu	Gly 3755	Ala	Gly	Asn	Leu	Leu 3760		Asn	Arg	Gly	Arg 3765		Thr	Ala
Ala	Gly 3770	Asp	Leu	Val	Ala	Ser 3775		Ala	Ser	Leu	Asn 3780		Tyr	Gly
Thr	Leu 3785	Gly	Gly	Gly	Gly	Asn 3790		Arg	Leu	Asn	Ala 3795		Ala	Leu
Leu	Asn 3800	Glu	Arg	Gly	Leu	Leu 3805		Ser	Gly	Ala	Asp 3810		Thr	Leu
Arg	Ala 3815		Asp	Ile	Thr	Asn 3820	Leu	Tyr	Gly	Asp	Val 3825		Ser	Leu
Gly	Arg 3830	Leu	Asp	Ile	Ala	Arg 3835		Asp	Ala	Gly	Gly 3840		Ala	Asn
Arg	Leu 3845		Asn	Ile	Ser	Gly 3850	Asn	Leu	Glu	Ser	Thr 3855		Asp	Met
Arg	Phe 3860	Ser	Val	Ser	Ser	Leu 3865	Leu	Asn	Arg	Arg	Glu 3870		Leu	Glu
Ile	Glu 3875		Asp	Leu	Gln	Asn 3880		Ala	Ile	Gly	Val 3885	Arg	CAa	Thr
Gly	Cys 3890	Gln	Leu	Ser	Glu	Arg 3895	Trp	Gly	Lys	Thr	Arg 3900		Ser	Ser
Glu	Leu 3905	Val	Trp	Ile	Arg	Glu 3910		Lys	Ser	Thr	Leu 3915		Asp	Ser
Ser	Ala 3920	Ala	Ala	Ser	Ile	Thr 3925	Ala	Gly	Arg	Asp	Leu 3930		Val	Val
Gly	Ala 3935	Ser	Leu	Gln	Asn	Ile 3940		Ser	Asn	Ile	Ser 3945	Ala	Val	Arg
Asp	Ala 3950	Thr	Leu	Ser	Leu	Ser 3955	Asn	Phe	Glu	Asn	1960 3960		Tyr	Ala
Leu	Gly 3965	Glu	Tyr	Ala	Val	Arg 3970	Gly	Val	Tyr	Ser	Pro 3975	Pro	Ser	Lys
Phe	Gly 3980	Glu	Glu	Leu	Leu	Met 3985	Arg	Ile	Leu	Ala	Tyr 3990	Asn	Ala	Val
Asn	Asp 3995		Ser	Tyr	Gly	Glu 4000	Gly	Tyr	Ala	Ser	Thr 4005	Gly	Gly	Arg
Leu	Pro 4010	Asn	Ile	His	Tyr	Phe 4015	Asp	Lys	Asn	Phe	Asn 4020	Glu	Lys	Val
Ser	Pro 4025	Leu	Glu	Val	Ile	His 4030	Gly	Asn	Gly	Lys	Asn 4035	Gly	Gly	Pro
Gly	Trp 4040	His	Leu	Tyr	Phe	Gly 4045	Thr	Leu	Asp	Val	Glu 4050		Pro	Asp
Thr	Asp 4055	Arg	Trp	Asn	Lys	Ala 4060	Ile	Gly	Arg	Ile	Pro 4065	Ala	Pro	Asn
Tyr	Ser 4070	Ser	Lys	Lys	Thr	Asp 4075	Ala	Ile	Pro	Asp	Leu 4080		Lys	Gly
Leu	Ala	Pro	Leu	Asp	Glu	Leu	Thr	Ile	Asn	Lys	Gly	Ala	Asn	Ser

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		4085					4090					4095			
Т	'hr	Val 4100	_	Ala	Val	Val	Gln 4105	Ala	Gly	Gly	_	Val 4110	Thr	Val	Asn
A	la	Ala 4115	Glu	Ser	Phe	Asn	Asn 4120		Val	Leu		Gly 4125	Phe	Gln	Ala
V	'al	Gln 4130	Glu	Thr	Gln	Leu	Pro 4135		Gln	Asp		Ala 4140	Val	Ser	Ser
Т	'hr	Thr 4145	Ser	Ala	Val	Val	Thr 4150		Lys	Ser		Leu 4155	Pro	Ala	Asp
L	eu	Ala 4160	_	Gln	Gln	Ile	Asn 4165		Leu	Thr		Pro 4170	Gly	Phe	Ser
L	eu	Pro 4175	Gln	Gly	Gln	Asn	Gly 4180		Phe	Arg		Ala 4185	Ser	Gln	Gly
A	la	Gln 4190		Asn	Gln	Ala	Ser 4195	_			_	Ser 4200	Ala	Ser	Asp
L	eu			Ser	Gly	His	Gly 4210	Val					Gln	Thr	Gly
S	er	Gly		Ser	Gly	Trp	Ser	Thr	Gln	Ala	_	Arg	Val	Gly	Asp
A	ap	_	Val	Thr	Ser	Leu	4225 Ala	Gly	Ser	Ala	Tyr		Gly	Arg	Val
A	la	4235 Glu		Ile	Asp	Ala	4240 Leu		Ala	Ser		4245 Pro	Ile	Ser	Gly
		4250			Ī		4255	Ī				4260			-
A	ap	Gly 4265		Asn	Thr		Arg 4270		Gln			Glu 4275	His	Gln	Ala
Т	'hr	Thr 4280	_			_	Leu 4285	Val		Gly		Ala 4290	Ser	Gly	His
S	er	Gly 4295		Gly	Val	Ile	Leu 4300	Ala	Asp	Leu		Gly 4305	Gly	Leu	Pro
S	er	Phe 4310		Ser	Leu		Ala 4315					Gln 4320	Gly	Thr	Val
P	ro	Gly 4325					Gly 4330		Ile	Leu		Asn 4335	Trp	Gln	Gly
A	la	Gln 4340					Ala 4345					Val 4350	Arg	Val	Glu
G	ly	Val	Val	Ser	Ser	Pro	Gly 4360	Gly	Asn	Gly	Ser	Ile	Leu	Ala	Asp
L	eu		Ala				Ser					Pro	Ser	Ala	Val
A	rg	4370 Ala		Gly	Ser	Leu	4375 Pro	Arg	Leu	Glu	Glu	4380 Arg	Ser	Ala	Leu
		4385					4390					4395			
ь	ieu	4400		PIO	Pro	vai	Gly 4405	GIN	Pro	AIA	ьeu	4410	ınr	ьeu	Pro
S	er	Val 4415	Ala	Arg	Val	Glu	Gly 4420	Val	Pro	Ser	Asn	Ala 4425	Thr	Pro	Ser
A	sn	Ser 4430	His	Lys	Tyr	Leu	Ile 4435	Glu	Thr	Asn	Pro	Ala 4440	Leu	Thr	Glu
L	eu	Lys 4445	Gln	Phe	Leu	Asn	Ser 4450	Asp	Tyr	Leu	Leu	Gly 4455	Gly	Leu	Gly
I	le	Asn	Pro	Asp	Asp	Ser	Lys		Arg	Leu	Gly	Asp	Gly	Leu	Tyr
		4460					4465					4470			

Glu	Gln 4475	Arg	Leu	Val	Arg	Glu 4480	Ala	Ile	Val	Gln	Arg 4485	Thr	Gly	Gln
Arg	Phe 4490	Ile	Ala	Gly	Leu	Asn 4495	Ser	Asp	Glu	Ala	Met 4500		Arg	Tyr
Leu	Met 4505	Asp	Asn	Ala	Ile	Ala 4510	Ser	Lys	Asp	Val	Leu 4515	Gly	Leu	Thr
Pro	Gly 4520	Val	Thr	Leu	Ser	Ala 4525	Ala	Gln	Val	Ala	Ala 4530	Leu	Thr	His
Asp	Ile 4535	Val	Trp	Leu	Glu	Glu 4540	Val	Glu	Val	Asn	Gly 4545	Glu	Lys	Val
Leu	Ala 4550	Pro	Val	Val	Tyr	Leu 4555	Ala	Gln	Ala	Glu	Gly 4560	Arg	Leu	Gly
Pro	Asn 4565	Gly	Ala	Leu	Ile	Gln 4570	Gly	Arg	Asp	Val	Asn 4575	Leu	Ile	Thr
Gly	Gly 4580	Asp	Leu	Arg	Asn	Ala 4585	Gly	Thr	Leu	Arg	Ala 4590	Gln	Asn	Asp
Leu	Ser 4595	Ala	Thr	Ala	Gly	Asn 4600	Ile	Asp	Asn	Ser	Gly 4605	Leu	Ile	Glu
Ala	Gly 4610	Asn	Arg	Leu	Asp	Leu 4615	Leu	Ala	Ser	Gly	Ser 4620	Ile	Arg	Asn
Asp	Gln 4625	Gly	Gly	Ile	Ile	Ala 4630	Gly	Arg	Glu	Val	Ser 4635	Leu	Ser	Ala
Leu	Thr 4640	Gly	Asp	Val	Ile	Asn 4645	Glu	Arg	Thr	Val	Thr 4650	Gln	His	Gln
Ser	Ser 4655	Tyr	Arg	Gly	Thr	Gly 4660	Thr	Thr	Glu	Ala	Phe 4665	Ala	Asp	Ser
Ala	Ala 4670	Arg	Ile	Glu	Ala	Ala 4675	Gln	Lys	Leu	Thr	Val 4680	Ser	Ala	Gly
Arg	Asp 4685	Val	Ala	Asn	Ile	Gly 4690	Gly	Val	Ile	Asp	Ser 4695	Lys	Gly	Asp
Leu	Ala 4700	Leu	Gln	Gly	Gly	Arg 4705	Asp	Val	Leu	Val	Ser 4710	Ala	Ala	Val
Ala	Glu 4715	Arg	Gly	Trp	Thr	Ala 4720	Gly	Ser	Gln	Ala	Tyr 4725	Gln	Thr	Gln
Thr	Thr 4730	Gln	Met	Gly	Ala	Glu 4735	Val	Val	Ala	Gly	Arg 4740	Asp	Ile	Ser
Val	Ser 4745	Ala	Gly	Arg	Asp	Ile 4750	Ser	Val	Val	Gly	Ser 4755	Arg	Ile	Asp
Ala	Arg 4760	Arg	Asp	Val	Thr	Phe 4765	Glu	Ala	Gly	Arg	Asp 4770	Val	Gly	Leu
Val	Ala 4775	Ala	Ala	Asn	Glu	Glu 4780	His	Ala	Tyr	Gly	Lys 4785	Thr	Lys	ГÀа
Val	Thr 4790	Phe	Gln	Asp	Asp	Lys 4795	Ile	Thr	Gln	Gln	Ala 4800	Thr	Arg	Val
Asp	Ala 4805	Gly	Gly	Asp	Leu	Ala 4810	Ile	Asn	Ala	Gly	Gln 4815	Asp	Leu	Arg
Leu	Val 4820	Ala	Ser	Gln	Ala	Ser 4825	Ala	Gly	Asp	Glu	Ala 4830	Tyr	Leu	Val
Ala	Gly 4835	Asp	Lys	Leu	Glu	Leu 4840	Leu	Ala	Ala	Asn	Asp 4845	Ser	Ser	Tyr

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Tyr	Leu 4850		Asp	ГÀа	ГÀа	Ser 4855		Gly	Ser	Phe	Gly 4860	Ser	ГÀа	Lys
Thr	Arg 4865	Arg	Asp	Glu	Ile	Thr 4870		Val	Thr	Ala	Val 4875	Gly	Ser	Gln
Ile	Ser 4880	Ser	Gly	Gly	Asp	Leu 4885	Thr	Leu	Leu	Ser	Gly 4890	Gly	Asp	Gln
Thr	Tyr 4895	Gln	Gly	Ala	Lys	Leu 4900		Ser	Gly	Asn	Asp 4905	Leu	Ala	Ile
Val	Ser 4910	Gly	Gly	Ala	Val	Thr 4915	Phe	Glu	Ala	Val	Lys 4920	Asp	Leu	His
Gln	Glu 4925	Ser	His	Glu	Lys	Ser 4930		Gly	Asp	Leu	Ala 4935	Trp	Gln	Ser
Ser	Lys 4940	Gly	Lys	Gly	Gln	Thr 4945	Asp	Glu	Thr	Val	Arg 4950	Gln	Ser	Gln
Ile	Val 4955	Ala	Gln	Gly	Asn	Leu 4960	Ala	Ile	Lys	Ala	Val 4965	Glu	Gly	Leu
ГÀа	Ile 4970	Asp	Leu	Lys	His	Ile 4975	Asp	Gln	Lys	Thr	Val 4980	Ser	Gln	Thr
Ile	Asp 4985	Ala	Met	Val	Gln	Ala 4990		Pro	Gln	Leu	Ala 4995	Trp	Leu	ГÀа
Gln	Met 5000	Glu	Gln	Arg	Gly	Asp 5005	Val	Asp	Trp	Arg	Arg 5010	Val	Gln	Glu
Leu	His 5015	Asp	Ser	Trp	ГÀа	Tyr 5020	Ser	Asn	Ser	Gly	Leu 5025	Gly	Val	Gly
Ala	Gln 5030		Ala	Ile	Ala	Ile 5035	Val	Val	Ala	Tyr	Phe 5040		Ala	Gly
Ala	Ala 5045	Ser	Ala	Ala	Leu	Gly 5050		Met	Ala	Gly	Val 5055	Gly	Ala	Gly
Ser	Gly 5060		Met	Met	Ala	Ala 5065	Ala	Gly	Ser	Thr	Ala 5070	Met	Val	Gln
Ala	Gly 5075	Thr	Ala	Val	Gly	Thr 5080	Ala	Ala	Ala	Gly	Trp 5085	Ala	Asn	Ala
Ala	Gly 5090		Ala	Val	Ala	Met 5095	Gly	Met	Ala	Ser	Asn 5100	Gly	Ala	Ile
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	Thr 5120	Ser	Ser	Asp	Ala	Leu 5125	_	Gly	Tyr		Val 5130		Gly	Thr
Thr	Ala 5135	Gly	Leu	Thr	Ala	Gly 5140		Tyr	Asp	Lys	Trp 5145	Thr	Ser	Thr
Gln	Thr 5150	-	Thr	Ser	Thr	Ala 5155	Leu	Pro	Asn	Thr	Gly 5160	Ala	Val	Ala
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Ser	Asn 5180	Gln	Leu	Leu	Gln	Asn 5185	Gly	Thr	Ser	Val	Leu 5190	Leu	Asp	Arg
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_														
	5225					5230					5235			
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Asp	Phe 5255		Thr	Gly	Ala	Leu 5260	Ala	Ala	Gly	Val	Asn 5265	Glu	Ala	Leu
Val	Asp 5270		Leu	Ala	Lys	Gln 5275		Ala	Ser	Leu	Pro 5280		Asp	Asp
Lys	Lys 5285	_	Leu	Leu	Ile	Met 5290	Ser	Ser	Gln	Leu	Ile 5295	Gly	Val	Leu
Ala	Ala 5300		Thr	Gln	Gly	Asp 5305	Ala	Asp	Ala	Lys	Ser 5310	Leu	Gln	Thr
Gly	Ala 5315	_	Val	Ala	Gly	Asn 5320	Ala	Thr	Gln	His	Asn 5325	_	Leu	Ser
His	Trp 5330		Glu	Glu	Lys	Lys 5335	_	Gln	Glu	Val	Asp 5340	_	Сув	Lys
Asp	Lys 5345	Gln		CÀa		Thr 5350		Ile	Glu	Ala	Lys		Ala	Ile
Ile	Ser 5360		Gln	Gln	Asp	Val 5365	Gly	Ile	Val	Val	Gly 5370	Val	Gly	Gly
Gly	Ile 5375		Leu	Ser	Thr	Ala 5380	Glu	Thr	Ala	Val	Gly 5385	Val	Tyr	Glu
Leu	Val 5390			Trp	_	Glu 5395		Tyr			Leu 5400	Glu	Gln	Leu
Ala	Thr 5405	Ser	Pro	Glu	Phe	Arg 5410					Asp 5415	Asn	Tyr	Leu
Lys	Gly 5420				Arg	Ala	Ala	Phe	Leu	Thr		Ala	Tyr	Glu
Asp	Ala 5435	Gly		Gln				Thr	Ala	Gly	Val	Glu	Gly	Gly
Arg	Phe 5450	Ala	Ala	Glu	Leu		Gly		Leu			Val	ГÀз	Gly
Gly	Ala 5465	Gln	Ile	Thr	Ala							Lys	Asn	Leu
Val	Asn 5480	Ala	Ile	Ala	Glu		Pro	Val	Ser	Gly		Met	Ser	Ser
Gln	Leu	Gly						Gly			Gly		Gly	Gly
Lys	5495 Gly	Tyr				Leu		His			Lys		His	Ile
Leu	5510 Tyr	Gly	Asp	Lys	Pro	_	Ser	Gly	Gly	His		_	Pro	Gly
Gln	5525 Ala	Gly	Lys	Thr	Val		Pro	Gln	Asn	Trp			Asp	Гла
Ile	5540 Val		Glu	Val	Gly	5545 Asp	Ile	Ala	Thr	Ser	5550 Pro	Ser	Thr	Lys
	5555				_	5560					5565			
Ī	Tyr 5570				Ī	5575	Ī				5580			_
Asp	Pro 5585	Ala	Lys	Trp	Val	Ala 5590	Tyr	Glu	Val	Arg	Asp 5595	Gly	Val	Arg
Met	Arg 5600	Val	Val	Tyr	Gln	Pro 5605	Ala	Thr	Gly	Lys	Val 5610	Ile	Thr	Ala

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agegeteegg etacteecee tgeegageee agegeeeegg egeegtegag egacacteeg 1	80
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aagggcaagc gcgaagcctc caaggccggt catgaaggca gctgcggtgc ggatcgcaag 2	40
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teegegaaga eeeeggeeaa ggeeggegee gagggeaagt geggggaggg caagtgegge 2	40
gacgcetect ttgcccgaac cgacaccgat cacgatggca aggtctcgcg cgccgagttc 3	00
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ttcatttccg aagccgaggc ctacgaacac ctgcgcaaga cctacgaggc caacggcaag	420
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gggcaggccg gcgagaccgt cgtggcggac aacccgccgc cgggaggcag gagcgtcacg	180
ccgatggccg agacgaagac gaaaaaggcg tccatcggcc ggaaaagcgt gccgctcgcg	240
gtgatcggag aaagagaaga tcgctgcggc agacgcctgg acgagaagga acgccgcaag	300
gcgatcgtgg agcagcggat aatggcggga atgacccgct ccgatgtgga gcgggcgctg	360
ggcaagccgg accgggtcag cgggaacaat gcggaggtgc gttatcagta caaggccgac	420
aagcgacggg gagcgagaag cgtgagcttc gatcaggagg gatgtgtgaa gggaagagaa	480
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accaccegeg eggaatacta ecegteetge taegageegg tgtegeacet gegeageace	180
gataacgcag tgcgcaattc ggccatcacc ggcgccatta ccggcggcct cctgggcggc	240
etggeeggeg geetggeeag egaegagaae egeggeegea atgeegeeet egetgeegea	300
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gatgacegeg egegeategg etectaeggt acegaegteg acegeageae egtegagate	420
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ggcgagaaca tcagcaacta cacccaggcc tacgagaaag acctgcagca ggtcggcgta	660
cegegegeeg aggtgaccaa ggtegeegag geegagaace gegeeageac tacgaaagge	720
ggcagcaagc ccaagaccgg cagcaatccc aaggtgccga aggaagcggt cgccaccgag	780
cagaccatce gcaaggeeca ggaegegeaa agegaaggea acaaggtgge eteccaggge	840
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aagctgttcg agaccttggt gaaagacggc gagaaggctg aaaaagaagc gaagtccgat	180
gtggacgcgc aggtcggtgc ggcgaaggct tccgcccgct ctgcgaagag caaggtcgac	240
gaggttcggg accgtgcgct cggcaagtgg agcgagctcg aggaagcttt cgacaagcgc	300
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agcaaggtcg atacgctgac caagcagatc gagaaactca ccggcgtcag cgtcaagccg	420
geggegaagg cageggecaa geetgeggeg aaaceggetg ccaagecege ggegaaaace	480
gcagoggoca agooggoago taaacoggoa gocaaggoog oogocaagoo tgoggogaaa	540
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gccaaaccga ctgcgaaggc cgcagcgaaa ccggcgacca agccggcagc caaggccgcg	660
gcgaagcctg ctgcgaaacc tgccgcagcc aagcctgccg cgaagccggc agccaagccg	720
geogotgoga cogoogocaa geoogoggog aaacotgoog ccaagooggo tgogaaaaag	780
cetgeggega agaageegge ageeaageee geegeggega aaceggeege teeegeegeg	840
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<211> LENGTH: 1866

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<sup>&</sup>lt;211> LENGTH: 2067

<sup>&</sup>lt;212> TYPE: DNA

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ccugcugcga aggeggeage caagecugeg gugaaaaeeg uageggegaa geeugeggee	480	

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gcgaagcccg	cagccaagcc	gacggcgaag	ccugcugcga	aaccggcggc	caagcccgcg	600	
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ccugcggcga	cucccagege	cccggcagcc	gccuccagcg	cugcuucggc	aacgccugcc	1020	
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ccgcccggcu	ggucgugguc	gggaacuacc	ugcgucaagg	ccccgaccga	ucccacggau	720	
ccaaccgacc	cgaccacgcc	gggcagugac	ggcggcggcg	auggcaaugg	cgguggaaac	780	
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600

660

				-contin		
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<211> LENGTH: 2067
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<213> ORGANISM: Pseudomonas aeruginosa

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<sup>&</sup>lt;212> TYPE: RNA <213> ORGANISM: Pseudomonas aeruginosa

<sup>&</sup>lt;400> SEQUENCE: 83

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<sup>&</sup>lt;213 > ORGANISM: Pseudomonas aeruginosa

<sup>&</sup>lt;400> SEQUENCE: 89

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ccaccuuaua agcccauuaa auag 16884

- 1. 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 or exactly 35 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), or
- d) an amino acid sequence having a sequence identity of at least 60% with the amino acid sequence of b), said polypeptide being antigenic in a mammal.
- 2. (canceled)
- 3. The polypeptide according to claim 1, wherein the sequence identity with the amino acid sequence of a) is 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%.
- 4. The polypeptide according to claim 1, wherein the sequence identity with the amino acid sequence of b) is at least 60%, 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 claim **1**, wherein the at least 35 contiguous amino acid residues have 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, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61 and 62 in any one of SEQ ID NOs: 1-30, or
  - corresponding to any one of amino acid residues 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73 and 74 in any one of SEQ ID NOs: 2-30, or
  - corresponding to any one of amino acid residues 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 and 100 in any one of SEQ ID NOs: 3-30, or corresponding to any one of amino acid residues 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150 and 151 in any one of SEQ ID NOs: 4-30, or
  - corresponding to any one of amino acid residues 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174 and 175 in any one of SEQ ID NOs: 5-30, or
  - corresponding to any one of amino acid residues 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188,

- 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 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, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 271, 272, 273, 274, 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 and 300 in any one of SEQ ID NOs: 6-30, or corresponding to any one of amino acid residues 301, 302, 303, 304 and 305 in any one of SEQ ID NOs: 7-30, or
- corresponding to any one of amino acid residues 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 and 336 in any one of SEQ ID NOs: 8-30, or
- corresponding to any one of amino acid residues 337, 338, 339, 340, 341, 342 and 343 in any one of SEQ ID NOs: 9-30, or
- corresponding to any one of amino acid residues 344, 345, 346, 347 and 348 in any one of SEQ ID NOs: 10-30, or
- corresponding to any one of amino acid residues 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, 386, 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 and 416 in any one of SEQ ID NOs: 11-30, or
- corresponding to any one of amino acid residues 417, 418, 419, 420, 421, 422 and 423 in any one of SEQ ID NOs: 12-30, or
- corresponding to amino acid residue 424 in any one of SEQ ID NOs: 13-30, or
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with the proviso that the selected amino acid residue satisfies the formula N≤L-n+1, where N is the number of the selected residue, L is the number of amino acid residues in the sequence from which the residue is selected, and n is the number of consecutive amino acid residues.

- 6. (canceled)
- 7. (canceled)
- 8. (canceled)
- 9. (canceled)
- 10. (canceled)
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- 31. (canceled)
- 32. (canceled)
- 33. (canceled)
- 34. (canceled)
- 35. (canceled)
- 36. (canceled)
- 37. The polypeptide according to claim 1, 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 claim 1, 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 Pseudomonas aeruginosa.
- 41. The polypeptide according to claim 39, which induces a humoral and/or a cellular immune response.
  - An isolated nucleic acid fragment, which comprises
  - i) a nucleotide sequence encoding a polypeptide according to claim 1, or

- ii) a nucleotide sequence consisting of the amino acid encoding part of any one of SEQ ID NOs: 31-90.
- 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, option i), wherein the nucleotide sequence consists of 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, at least 153, at least 154, at least 155, at least 156, at least 157, at least 158, at least 159, at least 160, at least 171, at least 172, at least 173, at least 174, at least 175, at least 176, at least 177, at least 178, at least 179, at least 180, at least 181, at least 182, at least 183, at least 184, at least 185, at least 186, at least 187, at least 188, at least 189, at least 190, at least 191, at least 192, at least 193, at least 194, at least 195, at least 196, at least 197, at least 198, at least 199, at least 200 and at least 201 consecutive nucleotides in the amino acid encoding part of any one of SEQ ID NOs: 30-90.
  - 45. (canceled)
  - 46. (canceled)
- 47. A vector comprising the nucleic acid according to claim 42 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**, option i), optionally a signal peptide coding sequence, a nucleotide sequence defined in claim **42**, option i), and optionally a terminator.
- **49**. The vector according to claim **47**, wherein the expression control region drives expression in a prokaryotic cell.
- **50**. The vector according to claim **47**, which is capable of autonomous replication.
- **51**. The vector according to claim **47**, which is capable of being integrated into the genome of a host cell.
- **52.** The vector according to claim **47**, which is incapable of being integrated into the genome of a mammalian host cell.
- **53**. The vector according to claim **47**, which is selected from the group consisting of a virus, a bacteriophage, a plasmid, a minichromosome, and a cosmid.
- **54.** A cell which is transformed to carry the vector according to claim **47**.
- **55.** The transformed cell according to claim **54**, which is capable of replicating the nucleic acid fragment defined in claim **42**, option i).
- **56**. The transformed cell according to claim **54**, which is capable of expressing the nucleic acid fragment defined in claim **42**, option i).
- **57**. The transformed cell according to claim **54**, which is selected from a prokaryotic cell or a eukaryotic cell.
- **58**. The transformed cell according to claim **54**, which is a bacterial cell selected from the group consisting of *Escherichia, Bacillus, Salmonella*, and *Mycobacterium*.

- **59.** The transformed cell according to claim **54,** which is stably transformed by having the nucleic acid defined in claim **42,** option i), stably integrated into its genome.
- **60**. The transformed cell according to claim **54**, which secretes or carries on its surface the polypeptide according to claim **1**
- **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 claim **54**.
- 63. A pharmaceutical composition comprising a polypeptide according to claim 1, a nucleic acid fragment according to claim 42, a vector according to claim 47, or a cell according to claim 54, 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 claim 1, a nucleic acid fragment according to claim 42, a vector according to claim 47, a cell according to claim 54, or a pharmaceutical composition according to claim 63 so as to induce adaptive immunity against *Pseudomonas aeruginosa* in the animal.
- 67. The method according to claim 66, wherein, when the polypeptide according to claim 1 or a composition comprising said polypeptide is administered, the animal receives between 0.5 and 5,000  $\mu$ g of the polypeptide according to claim 1 per administration.
- **68**. The method according to claim **66**, wherein the animal receives a priming administration and one or more booster administrations.
- $\mathbf{69}$ . The method according to claim  $\mathbf{66}$ , wherein the animal is a human being.
- **70**. The method according to claim **66**, wherein the administration is for the purpose of inducing protective immunity against *Pseudomonas aeruginosa*.
- 71. The method according to claim 70, wherein the protective immunity is effective in reducing the risk of attracting infection with *Pseudomonas aeruginosa* or is effective in treating or ameliorating infection with *Pseudomonas aeruginosa*.
- **72**. The method according to claim **66**, wherein the administration is for the purpose of inducing antibodies specific for *Pseudomonas aeruginosa* 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 *Pseudomonas aeruginosa* and wherein B-lymphocytes producing said antibodies are subsequently recovered from the animal and used for preparation of monoclonal antibodies.
  - 74. (canceled)
  - 75. (canceled)
  - 76. (canceled)
  - 77. (canceled)
  - 78. (canceled)
  - 79. (canceled)
  - **80**. (canceled) **81**. (canceled)

- 82. (canceled)83. (canceled)84. (canceled)
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- 86. (canceled)
- 87. (canceled)
- **88**. (canceled) **89**. (canceled)
- 90. (canceled)
- 91. (canceled)
- 92. (canceled) 93. (canceled)
- 94. The vector according to claim 47 wherein the vector is a cloning vector or an expression vector.
- 95. The transformed cell according to claim 58 wherein the bacterial cell is non-pathogenic.