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(54) **Title:** ENGINEERING RESISTANCE TO PIERCE'S DISEASE BY EXPRESSION OF A XYLELLA FASTIDIOSA HECA-LIKE HEMAGGLUTININ PROTEIN

(57) **Abstract:** *Xylella fastidiosa (Xj),* a Gram-negative, xylem-limited bacterium, is the causal agent of several economically important plant diseases, including Pierce's disease (PD) and Citrus Variegated Chlorosis (CVC). Identified is a HecA-like hemagglutinin gene in *Xylella fastidiosa* involved in the virulence of the pathogen.. In essence this protein is a "molecular glue" that specifically attaches to the surface of *Xylella fastidiosa*causing *Xylella fastidiosa* cells to form aggregrates. If this protein is expressed in transgenic plants, this protein could cause greater aggregation of *Xylella fastidiosa* cells in planta, thus slowing down the movement *of Xylellafastidiosa* and decreasing disease symptoms. The protein can also be introduced into the plant by inoculation with a plant endophyte which expresses and secretes a HecA-like hemagglutinin. Thus plants containing increased levels of *a Xylella fastidiosa* HecA-like hemagglutinin protein could have an increased level of field resistance to disease caused by *Xylella fastidiosa*

ENGINEERING RESISTANCE TO PIERCE'S DISEASE BY EXPRESSION OF A *XYLELLA FASTIDIOSA* HECA-LIKE HEMAGGLUTININ PROTEIN

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 USC §119(e) of U.S. Provisional Application 60/638,988, filed December 22, 2004.

GOVERNMENT RIGHTS

This invention was made with Government support from the California Department of Food and Agriculture (03-0287), USDA CSREES 2002-34442-12461 and UC Division of Agriculture and Natural Resources Pierce's Disease Research Grant (SA6627). The Government may have certain rights in this invention.

FIELD OF THE INVENTION

This invention is in the field of pest resistance. Specifically the invention relates to the resistance of plants against the bacterium *Xylella fastidiosa*, achieved by expression in plants of a gene encoding a bacterial HecA-like hemagglutinin.

BACKGROUND OF THE INVENTION

Xylella fastidiosa (*Xf*) is a Gram-negative, xylem-limited bacterium that is transmitted from plant to plant by several xylem-feeding insect vectors. (Hopkins, 1989) Strains of *Xylella fastidiosa* cause diseases in many economically important plants including grapevines (Pierce's Disease), citrus (Citrus Variegated Chlorosis), peach, plum, oleander, elm, sycamore, oak, maple, and coffee (De Lima et al., 1998; Purcell, 1997). The major symptoms of most *Xylella fastidiosa* diseases are associated with water-stress, due to reduced xylem flow, which is thought to result from occlusion of the xylem vessels by bacterial aggregates that likely contain EPS (da Silva et al., 2001), gums and tyloses (Hopkins 1989). The onset of disease is as follows: leaf margins progressively dry inward, scorched leaf blades abscise and fall, leaving the petiole attached to the cane (match stick symptom). The canes then lignify irregularly, which produces patches of green tissues surrounded by mature, brown tissue (green island symptom). Finally the whole plant dies. Thus there is a tremendous need to develop plants that are resistant to *Xylella fastidiosa* infection.

SUMMARY OF THE INVENTION

In one embodiment, the present invention meets these needs by providing transgenic plants or genetically engineered plant endophytes that express a HecA-like hemagglutinin, or a fragment thereof, which inhibits the growth and spread of *Xylella fastidiosa*, thereby providing resistance to Pierce's Disease and other diseases caused by *Xylella fastidiosa*. The HecA-like hemagglutinin proteins include the amino acid sequences NPNL (amino acids 114 through 117 of SEQ ID NO: 6) and NPYGI (amino acids 154 through 158 of SEQ ID NO: 6) and may be from *Xylella fastidiosa*. The HecA-like hemagglutinin may be expressed in various plants such as grapevines, citrus, peach, plum, oleander, elm, sycamore, oak, maple and coffee or in plant endophytes growing in such plants. In another embodiment, the present invention is further directed to seeds produced by the transgenic plants of the invention, or seeds produced by plants infected with a transgenic endophyte. In another embodiment the invention also provides for methods of generating such transgenic plants and plant endophytes.

In yet another embodiment, the invention is further directed to recombinant HecA-like hemagglutinins or fragments thereof which confer resistance to *Xylella fastidiosa* when expressed in plants or plant microbial endophytes which are present in plants. Two examples of these proteins are HxfA and HxfB.

In yet another embodiment, the invention is further directed to isolated nucleic acid sequences which encode recombinant *Xylella fastidiosa* HecA-like hemagglutinins or fragments thereof which confer resistance to *Xylella fastidiosa* when expressed in plants or plant endophytes present in plants.

In yet another embodiment, the invention is further directed to recombinant constructs containing such isolated nucleic acids. The recombinant constructs may further include a promoter. The promoter may be a constitutive promoter, inducible promoter, tissue- or cell-specific promoter, or a developmentally-regulated promoter. The promoters may be expressible in a plant, a bacteria and/or a plant endophyte. The recombinant constructs may further be in a vector. By way of example but not limitation, the vector may be a cloning, expression, transformation, or transfection vector.

In another embodiment, the invention is further directed to isolated nucleic acids encoding HecA-like hemagglutinins and paralogs, homologs and orthologs of the protein. The HecA-like hemagglutinin protein encoding nucleic acid sequence as defined herein refers

to any sequence that hybridizes to the nucleic acid molecule encoding the HecA-like hemagglutinin, or the complement thereof under at least low stringency, preferably moderate, high or very high stringency conditions, or is about 85%, 90%, 95% or 97% identical in the nucleic acid sequence, or encodes a polypeptide with Hec-A like hemagglutinin activity having at least about 85%, 90%, 95% or 97% sequence identity to the HecA-like hemagglutinin protein, and confer resistance to disease caused by *Xylella fastidiosa.*

Yet another aspect of the present invention is a host cell containing any of the above nucleic acids, vectors, or constructs. Such nucleic acids, vectors and construct may be introduced into a prokaryotic or eukaryotic host cell. Preferred host cells include bacterial cells such as *E. coli* and plant endophytes from such genera as Pseudomonas, Agrobacterium, Bacillus, and others, yeast cells, and plant cells. The nucleic acids, vectors and constructs may be introduced into the host cells so that the expression of the nucleic acid may be controlled or regulated. The introduction of the construct into the host cell may be transient or stable. The control or regulation may include tissue-specific promoters designed to express the isolated nucleic acids in given tissues. Such regulation may be directed to constitutive expression. The regulation may be responsive to various biotic, abiotic and artificial stimuli, relative to the native promoter. In yet another embodiment, the invention is further directed to plants which contain the host cells.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows Pierce's disease symptoms in grapevines. **A** shows mock inoculation of Chardonnay grapevines and **B** shows Chardonnay grapevines infected with the wild type strain Temecula showing a disease rating of 1, **C** shows a disease rating of 2, **D** shows a disease rating of 3, **E** shows a disease rating of 4, and **F** shows a disease rating of 5. Note the general health of the plants and the number of scorched leaves.

Figure 2 shows disease progression of various grapevine varieties inoculated with wild type or Tn5 mutants of *Xylella fastidiosa.* Disease severity was based on a visual disease scale, from 0 to 5 and was assessed 10, 14, 16, 18, 20 and 32 weeks after inoculations. The data is an average of two independent replications (6 plants total) for the inoculations in Chardonnay grapevines and one replication (3 plants total) for the inoculations in Chenin Blanc and Thompson seedless grapevines. PspB *Xylella fastidiosa* mutant was lost in storage

and was not inoculated in Chenin Blanc and Thompson seedless. HxfB was only inoculated in Chardonnay grapevines. (a) = disease severity was rated as 0 (healthy) 10 weeks after inoculation. (b) = water control was not showing symptom during the course of disease progression (disease severity was 0). * = mutant values were not significantly different from wild type values at the 95% confidence level ($p<0.05$).

Figure 3 shows an alignment of the N-terminal region of the hemagglutinin-like proteins from *X. fastidiosa* and the hemagglutinin protein, HecA from *E. chrysanthemi.* Letters and numbers on the left indicate the name of the *Xylella fastidiosa* genes as described in the *Xylella fastidiosa* PD genome web site (University of Campinas, Brazil, Institute of Computing, Library for Bioinformatics). HxfA and HxfB indicate the *Xylella fastidiosa* hemagglutinin proteins, PD2118 (SEQ ID NO: 5, GenBank accession number NP 780288) and PD1792 (SEQ ID NO: 3, GenBank accession number NP 779977), respectively. HecA indicates the name of the hemagglutinin protein from *E. chrysanthemi* (GenBank accession number AF501263). Numbers on the right indicate amino acid residues. The two conserved secretion domains NPNL (amino acids 114 through 117 of SEQ ID NO: 6) and NPYGI (amino acids 154 through 158 of SEQ ID NO: 6), of proteins secreted through the two-partner secretion (TPS) pathway are underlined (Schonherr et al., 1993). N, P, L, G and I indicate asparagine, proline, leucine, glycine and isoleucine, respectively. Several Tps proteins, including HecA, harbor a CXXC motif (SEQ ID NO: 33), which is absent in others. These cysteines (C) are not essential for secretion (Schonherr et al., 1993). An asterisk (*) indicates that Tps secretion domains were conserved in those amino acid sequences.

Figure 4 shows Lipopolysaccharide (LPS) profiles of strains of *Xylella fastidiosa* as revealed by SDS-PAGE and silver staining. In lane 1 is wild type strain and lane 2 is XF1542 mutant strain.

Figure 5 shows the growth of *Xylella fastidiosa* wild type and Tn5 mutants in liquid PD3 medium. Growth curves were determined based on OD_{600}. Data are average of two experiments with two repetitions each.

Figure 6 shows HxfA-dependent aggregation of *Xylella fastidiosa* cells *in vitro* and *in planta*. Panels **A**, **C**, **E** and **G** show *Xylella fastidiosa* wild type cells; Panels **B**, **D**, **F** and **H** show *Xylella fastidiosa hxf*A mutant cells. Panels **A** and **B** show wild type and *hxf*A mutant cells, respectively, inoculated into PD3 medium in a 125 ml flask and placed on a shaker. The degree of self-aggregation was visualized after 10 days of incubation. Panels **C** and **D** show wild type and *hxf*A mutant cells, respectively, plated onto PD3 medium plates. The colony morphology was examined after 10 days of incubation. Panels **E** and **F** show wild type and *hxf*A cells in xylem vessels. Note the lack of a three dimension array in the HxfA mutant compare to wild type. Panels **G** and **H** show higher magnification of wild type and *hxf*A cells in a biofilm. Note the wild type cells typically aggregated together side to side while the *hxf*A mutant cells did not aggregate in this manner. Scale bar equivalent to 5 microns in every panel.

Figure 7 shows a model of possible mechanisms involved in *X. fastidiosa* adhesion to xylem vessels of grapevines. Rods are *X. fastidiosa* cells. **A** shows how *Xylella fastidiosa* bacteria attach to the surface using most likely non-fimbrial adhesins, other than hemagglutinins (Tables 4; Feil et al., 2003); **B** shows how HxfA, HxfB and other adhesins mediate secondary contact between *Xylella fastidiosa* cells allowing in **C**, which shows microcolony formation. Based on the results, hemagglutinins appear to be important mediators for cell-cell aggregation; **D** shows bacterial cells finally aggregating to each other via hemagglutinins HxfA and HxfB, fimbriae and exopolysaccharides (EPS) to form matured biofilms within the xylem vessels (Tables 2 and 4, Figures 6; Feil et al., 2003).

BRIEF DESCRIPTION OF THE SEQUENCE LISTING

SEQ ID NO: 1 is the amino acid sequence of PD2116, a *Xylella fastidiosa* hemagglutinin-like protein.

SEQ ID NO: 2 is the amino acid sequence of PD2110, a *Xylella fastidiosa* hemagglutinin-like protein.

SEQ ID NO: 3 is the amino acid sequence of PD1792, a *Xylella fastidiosa* hemagglutinin-like protein, also referred to as HxfB.

SEQ ID NO: 4 is the amino acid sequence of PD1246, a *Xylella fastidiosa*

hemagglutinin-like protein.

SEQ ID NO: 5 is the amino acid sequence of PD2118, a *Xylella fastidiosa* hemagglutinin-like protein, also referred to as HxfA.

SEQ ID NO: 6 is the amino acid sequence of HecA, a hemagglutinin protein from *E. chrysanthemi*.

SEQ ID NO: 7 is the amino acid sequence of PD0988, a *Xylella fastidiosa* hemagglutinin-like protein.

SEQ ID NO: 8 is the amino acid sequence of PD0986, annotated as a *Xylella fastidiosa* hemagglutinin-like protein (Van Sluys et al. 2003).

SEQ ID NO: 9-32 are sequences of primers used herein.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the present invention provides transgenic plants or genetically engineered plant endophytes that are present in plants that express a HecA-like hemagglutinin, or a fragment thereof, which inhibits the growth and spread of *Xylella fastidiosa*, thereby providing resistance to Pierce's Disease and other diseases caused by *Xylella fastidiosa*. The HecA-like hemagglutinin may be isolated from *Xylella fastidiosa*

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of the components set forth in the following description. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

Throughout this disclosure, various publications, patents and published patent specifications are referenced. The disclosures of these publications, patents and published patent specifications are hereby incorporated by reference into the present disclosure to more fully describe the state of the art to which this invention pertains. The practice of the present invention will employ, unless otherwise indicated, conventional techniques of plant breeding, immunology, molecular biology, microbiology, cell biology and recombinant DNA, which are within the skill of the art. See, e.g., Sambrook, Fritsch and Maniatis, MOLECULAR CLONING: A LABORATORY MANUAL, 2nd edition (1989); CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (F. M. Ausubel, *et al.* eds., (1987); Plant Breeding: Principles

and Prospects (Plant Breeding, Vol 1) M.D. Hayward, N.O. Bosemark, I. Romagosa; Chapman & Hall, (1993.); Coligan, Dunn, Ploegh, Speicher and Wingfeld, eds. (1995) CURRENT PROTOCOLS IN PROTEIN SCIENCE (John Wiley & Sons, Inc.); the series METHODS IN ENZYMOLOGY (Academic Press, Inc.): PCR 2: A PRACTICAL APPROACH (M.J. MacPherson, B.D. Hames and G.R. Taylor eds. (1995), Harlow and Lane, eds. (1988) ANTIBODIES, A LABORATORY MANUAL, and ANIMAL CELL CULTURE R.I. Freshney, ed. (1987).

Unless otherwise noted, technical terms are used according to conventional usage. Definitions of common terms in molecular biology may be found in Lewin, Genes V, published by Oxford University Press, 1994 (SBN 0-19-854287-9); Kendrew *et al.* (eds.), The Encyclopedia of Molecular Biology, published by Blackwell Science Ltd., 1994 (SBN 0-632-02182-9); and Robert A. Meyers (ed.), Molecular Biology and Biotechnology, a Comprehensive Desk Reference, published by VCH Publishers, Inc., 1995 (ISBN 1-56081-569-8); Ausubel *et al.* (1987) Current Protocols in Molecular Biology, Green Publishing; Sambrook *et al.* (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor, New York. Definitions of common terms in plant biology may be found in Esau, Plant Anatomy, published by John Wiley & Sons (1977) (ISBN 0-471-24520-8); and Solomon *et al.*, Biology, published by Saunders College Publishing (1993).

Definitions

In order to facilitate review of the various embodiments of the invention, the following definitions are provided:

Promoter: A regulatory nucleic acid sequence, typically located upstream (5') of a gene or protein-coding sequence that, in conjunction with various cellular proteins, is responsible for regulating the expression of the gene or protein-coding sequence. The promoters suitable for use in the heterologous nucleic acids of this invention are functional in plants and in other host organisms used for expressing the inventive polynucleotides. Many plant promoters are publicly known. These include constitutive promoters, regulated promoters, inducible promoters, root-, tissue- and cell-specific promoters, and developmentally-regulated promoters. Exemplary promoters and fusion promoters are described, e.g., in WO 02/00894, which is herein incorporated by reference.

The promoters may be those normally associated with a transgene of interest, or heterologous promoters which are derived from genes of other plants, viruses, and plant pathogenic bacteria and fungi. Those skilled in the art will be able without undue experimentation to select promoters that are suitable for use in practicing the subject invention.

Regulated promoter: As used herein, this term refers to any promoter functional in a plant that provides differential expression levels in response to stimuli internal to the plant such as developmental signals. This includes both promoters that increase expression and promoters that decrease expression in response to stimuli or changed external conditions. Many promoters that are regulated promoters are also inducible promoters. For example, promoters that are responsive to auxin are both because they will change levels of expression in response to developmental changes in auxin levels and in response to externally supplied auxin.

Examples of regulated promoters under developmental control include promoters that initiate transcription only, or preferentially, in certain tissues, such as leaves, roots, fruit, seeds, or flowers. Exemplary promoters include the anther specific promoter 5126 (U.S. Pat. Nos. 5,689,049 and 5,689,051, both herein incorporated by reference), glob-1 promoter, and gamma-zein promoter. An exemplary promoter for leaf- and stalk-preferred expression is MS8-15 (see U.S. Pat. No. 5,986,174, herein incorporated by reference). Examples of seed-preferred promoters included, but are not limited to, 27 kDa gamma zein promoter and waxy promoter (Boronat et al. (1986); Reina et al. (1990); and Kloesgen et al. (1986)). Promoters that express in the embryo, pericarp, and endosperm are disclosed in U.S. applications Ser. No. 60/097,233 filed Aug. 20, 1998 and U.S. applications Ser. No. 60/098,230 filed Aug. 28, 1998 both of which are hereby incorporated by reference. The operation of a promoter may also vary depending on its location in the genome. Thus, a developmentally regulated promoter may become fully or partially constitutive in certain locations. A developmentally regulated promoter can also be modified, if necessary, for weak expression.

Tissue specific promoter: As used herein, this term refers to any promoter functional in a plant that provides differential expression levels in different tissues within the plant. Such promoters may provide tissue specific expression in one or several tissues. Many promoters that are tissue specific are also regulated promoters. For example, some promoters specifically express in plant seeds only during certain stages of the seeds growth cycle.

Examples of tissue specific promoters include those listed above that initiate transcription only, or preferentially, in certain tissues, such as leaves, roots, fruit, seeds, or flowers. Examples from above include anther specific promoters, leaf- and stalk-specific promoters, seed-specific promoters, embryo-specific promoters, pericarp-specific promoters, and endosperm-specific promoters. Additionally, as discussed above under localization, tissue specific expression occurs when there is on average a skewed expression in one or more tissues of a plant when compared to the average expression in the other tissues in such plant.

Sequence Identity: Sequences that show similarity to those described in this application can be identified by computer-based methods, using public domain sequence alignment algorithms and sequence similarity search tools to search sequence databases (public domain databases include Genbank, EMBL, Swiss-Prot, PIR and others).

Similarity searches retrieve and align sequences for comparison with a target sequence to be analyzed (i.e., a query sequence). The optimal alignment between local regions of the compared sequences is known as a local alignment. Sequence comparison algorithms use scoring matrices to assign an overall score to each of the alignments.

Polynucleotide and polypeptide sequences may be aligned, and percentage of identical residues in a specified region may be determined against other polynucleotide and polypeptide sequences, using computer algorithms that are publicly available. The percentage identity score is dependent on the length of the overlap region of the sequences being compared.

The similarity between two nucleic acid sequences, or two amino acid sequences may be expressed in terms of sequence identity (or, for proteins, also in terms of sequence similarity). Sequence identity is frequently measured in terms of percentage identity; the higher the percentage, the more similar the two sequences are. As described herein, homologs and variants of the HecA-like hemagglutinin-encoding nucleic acid molecules may be used in the present invention. Homologs and variants of these nucleic acid molecules will possess a relatively high degree of sequence identity when aligned using standard methods. Such homologs and variants will hybridize under high stringency conditions to one another.

Methods of alignment of sequences for comparison are well known in the art. Various programs and alignment algorithms are described in: Smith and Waterman (1981); Needleman and Wunsch (1970); Pearson and Lipman (1988); Higgins and Sharp (1988);

Higgins and Sharp (1989); Corpet *et al.* (1988); Huang *et al.* (1992); and Pearson *et al.* (1994). Altschul *et al.* (1994) presents a detailed consideration of sequence alignment methods and homology calculations.

The NCBI Basic Local Alignment Search Tool (BLAST) (Altschul *et al.*, 1990) is available from several sources, including the National Center for Biotechnology Information (NCBI, Bethesda, MD) and on the Internet, for use in connection with the sequence analysis programs blastp, blastn, blastx, tblastn and tblastx. It can be accessed at the NCBI Website. A description of how to determine sequence identity using this program is available at the NCBI website.

Homologs of the disclosed protein sequences are typically characterized by possession of at least 40% sequence identity counted over the full length alignment with the amino acid sequence of the disclosed sequence using the NCBI Blast 2.0, gapped blastp set to default parameters. The adjustable parameters are preferably set with the following values: overlap span 1, overlap fraction = 0.125, word threshold (T) = 11. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched; however, the values may be adjusted to increase sensitivity. Proteins with even greater similarity to the reference sequences will show increasing percentage identities when assessed by this method, such as at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90% or at least about 95% sequence identity.

Homologs of the disclosed nucleic acid sequences are typically characterized by possession of at least 40% sequence identity counted over the full length alignment with the amino acid sequence of the disclosed sequence using the NCBI Blast 2.0, gapped blastn set to default parameters. In addition, such sequences hybridize to homologous sequences under high stringency conditions. A preferred method utilizes the BLASTN module of WU-BLAST-2 (Altschul *et al.*, 1996); set to the default parameters, with overlap span and overlap fraction set to 1 and 0.125, respectively. Nucleic acid sequences with even greater similarity to the reference sequences will show increasing percentage identities when assessed by this method, such as at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90% or at least about 95% sequence identity.

The alignment may include the introduction of gaps in the sequences to be aligned. In addition, for sequences which contain either more or fewer amino acids than a HecA-like hemagglutinin from *Xylella fastidiosa*, it is understood that in one embodiment, the percentage of sequence identity will be determined based on the number of identical amino acids in relation to the total number of amino acids. Thus, for example, sequence identity of sequences shorter than that shown in the figures as discussed below, will be determined using the number of amino acids in the longer sequence, in one embodiment. In percent identity calculations relative weight is not assigned to various manifestations of sequence variation, such as, insertions, deletions, substitutions, *etc.*

In one embodiment, only identities are scored positively (+1) and all forms of sequence variation including gaps are assigned a value of "0", which obviates the need for a weighted scale or parameters as described herein for sequence similarity calculations. Percent sequence identity can be calculated, for example, by dividing the number of matching identical residues by the total number of residues of the "shorter" sequence in the aligned region and multiplying by 100. The "longer" sequence is the one having the most actual residues in the aligned region.

Proteins can be classified according to their sequence relatedness to other proteins in the same genome (paralogs) or a different genome (orthologs). Ortholog genes are genes that evolved by speciation from a common ancestral gene. These genes normally retain the same function as they evolve. Paralog genes are genes that are duplicated within a genome. These genes may acquire new specificities or modified functions which may be related to the original one. Phylogenetic analysis methods are well-known to those with ordinary skill in bioinformatics.

As will be appreciated by those skilled in the art, the sequences of the present invention may contain sequencing errors. That is, there may be incorrect amino acid sequences, nucleotides, frameshifts, unknown nucleotides, or other types of sequencing errors in any of the sequences; however, the correct sequences will fall within the homology and stringency definitions herein for nucleic acids, and the protein homology described for proteins or polypeptides.

Stringency: Stringency refers to hybridization conditions chosen to optimize binding of polynucleotide sequences with different degrees of complementarity. Stringency is affected by factors such as temperature, salt conditions, the presence of organic solvents in

the hybridization mixtures, and the lengths and base compositions of the sequences to be hybridized and the extent of base mismatching, and the combination of parameters is more important than the absolute measure of any one factor.

Very High Stringency: Very high stringency conditions refers to hybridization to filter-bound DNA in 5 X SSC, 2% sodium dodecyl sulfate (SDS), 100 μg/ml single stranded DNA at 55-65° C for 8 hours, and washing in 0.1 X SSC and 0.1% SDS at 60-65° C for thirty minutes.

High Stringency: High stringency conditions refers to hybridization to filter-bound DNA in 5 X SSC, 2% sodium dodecyl sulfate (SDS), 100 μg/ml single stranded DNA at 55-65° C for 8 hours, and washing in 0.2 X SSC and 0.2% SDS at 60-65° C for thirty minutes.

Moderate Stringency: Moderate stringency conditions refers to hybridization to filter-bound DNA in 5 X SSC, 2% sodium dodecyl sulfate (SDS), 100 μg/ml single stranded DNA at 55-65° C for 8 hours, and washing in 0.2 X SSC and 0.2% SDS at 50-55° C for thirty minutes.

Low Stringency: Low stringency conditions refers to hybridization to filter-bound DNA in 5 X SSC, 2% sodium dodecyl sulfate (SDS), 100 μg/ml single stranded DNA at 55-65° C for 8 hours, and washing in 2.0 X SSC and 0.2% SDS at 50-55° C for thirty minutes.

Construct: Unless otherwise stated, the term "construct" refers to a recombinant genetic molecule comprising one or more isolated polynucleotide sequences of the invention.

Genetic constructs used for transgene expression in a host organism comprise a gene promoter sequence operably linked to an open reading frame coding for at least a functional portion of a polypeptide of the present invention and optionally a gene termination sequence 3' downstream of the open reading frame. The open reading frame may be orientated in either a sense or anti-sense direction, depending upon the intended use of the gene sequence. The construct may also comprise selectable marker gene(s) and other regulatory elements for gene expression.

Operably linked: A first nucleic acid sequence is operably linked with a second nucleic acid sequence when the first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter controls the transcription or expression of the coding sequence. Generally, operably linked DNA sequences are contiguous and, where

necessary, join two protein-coding regions in the same reading frame. With respect to polypeptides, two polypeptide sequences may be operably linked by covalent linkage, such as through peptide bonds or disulfide bonds.

Vector: The term "vector" refers to a nucleic acid molecule which is used to introduce a polynucleotide sequence into a host cell, thereby producing a transformed host cell. A "vector" may comprise genetic material in addition to the above-described genetic construct, e.g., one or more nucleic acid sequences that permit it to replicate in one or more host cells, such as origin(s) of replication, selectable marker genes and other genetic elements known in the art (e.g., sequences for integrating the genetic material into the genome of the host cell, and so on).

Transformed: A transformed cell is a cell into which has been introduced a nucleic acid molecule by molecular biology techniques. As used herein, the term transformation encompasses all techniques by which a nucleic acid molecule might be introduced into such a cell, plant or animal cell, including transfection with viral vectors, transformation by *Agrobacterium*, with plasmid vectors, and introduction of naked DNA by electroporation, lipofection, and particle gun acceleration and includes transient as well as stable transformants.

Isolated: An "isolated" biological component (such as a nucleic acid or protein or organelle) has been substantially separated or purified away from other biological components in the cell or the organism in which the component naturally occurs, i.e., other chromosomal and extra-chromosomal DNA and RNA, proteins and organelles. Nucleic acids and proteins that have been "isolated" include nucleic acids and proteins purified by standard purification methods. The term embraces nucleic acids including chemically synthesized nucleic acids and also embraces proteins prepared by recombinant expression *in vitro* or in a host cell and recombinant nucleic acids as defined below. As an example, a gene in a large genomic DNA fragment such as a contig is not sufficiently purified away from other biological components to be considered isolated due to the relatively large amount of extra DNA found in the average contig. As outlined below "recombinant nucleic acids" and "recombinant proteins" also are "isolated" as described above

Recombinant: By "recombinant nucleic acid" herein is meant a nucleic acid that has a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two otherwise separated segments of sequence. This artificial combination is

often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of nucleic acids, e.g., by genetic engineering techniques, such as by the manipulation of at least one nucleic acid by a restriction enzyme, ligase, recombinase, and/or a polymerase. Once introduced into a host cell, a recombinant nucleic acid is replicated by the host cell; however, the recombinant nucleic acid once replicated in the cell remains a recombinant nucleic acid for purposes of this invention. By "recombinant protein" herein is meant a protein produced by a method employing a recombinant nucleic acid. As outlined above "recombinant nucleic acids" and "recombinant proteins" also are "isolated" as described above. A gene in a large fragment such as a contig would not be a "recombinant nucleic acid" given that such artificial combination does not relate to the gene. However, if sequences around or within a gene in a contig have been manipulated for purposes relating to that gene (i.e., not merely because the gene is near the end of the contig), then such a gene in a contig would constitute a "recombinant nucleic acid" due to the relative proximity of the recombinant portion of the nucleic acid to the gene in question.

Complementary DNA (cDNA): A piece of DNA that is synthesized in the laboratory by reverse transcription of an RNA, preferably an RNA extracted from cells. cDNA produced from mRNA may include 5' and/or 3' noncoding sequences (i.e., 5' UTR, 3' UTR) but typically lacks internal, non-coding segments (introns) and regulatory sequences, such as promoters, that determine transcription.

Open reading frame (ORF): A continuous coding sequence of a gene flanked by a start and stop codon. An ORF lacks internal termination codons and can usually be translated into an amino acid sequence.

Transgenic plant: As used herein, this term refers to a plant that contains recombinant genetic material not normally found in plants of this type, as well as recombinant genetic material normally found in such plants but in an abnormal position in the genome, and which has been introduced into the plant in question (or into progenitors of the plant) by human manipulation. Thus, a plant into which recombinant DNA is introduced by transformation is a transgenic plant, as are all offspring of that plant that contain the introduced transgene (whether produced sexually or asexually). It is understood that the term transgenic plant encompasses the entire plant and parts of the plant, for instance grains, seeds, flowers, leaves, roots, fruit, pollen, stems *etc*.

Standard molecular biology methods and plant transformation techniques can be used

to produce transgenic plants that produce plants having a recombinant gene or genes providing HecA-like hemagglutinin activity.

Ortholog: Two nucleotide or amino acid sequences are orthologs of each other if they share a common ancestral sequence and diverged when a species carrying that ancestral sequence split into two species, sub-species, or cultivars. Orthologous sequences are also homologous sequences. Orthologous sequences hybridize to one another under high-stringency conditions. The term "polynucleotide", "oligonucleotide", or "nucleic acid" refers to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. The terms "polynucleotide" and "nucleotide" as used herein are used interchangeably. Polynucleotides may have any three-dimensional structure, and may perform any function, known or unknown. The following are non-limiting examples of polynucleotides: a gene or gene fragment, exons, introns, messenger RNA (mRNA), transfer RNA, ribosomal RNA, ribozymes, cDNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, isolated DNA of any sequence, isolated RNA of any sequence, nucleic acid probes, and primers. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. If present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component. A "fragment" or "segment" of a nucleic acid is a small piece of that nucleic acid.

Gene: A "gene" refers to a polynucleotide containing at least one open reading frame that is capable of encoding a particular protein after being transcribed and translated.

Primer: The terms "primer" and "nucleic acid primer" are used interchangeably herein. A "primer" refers to a short polynucleotide, whether occurring naturally as in a purified restriction digest or produced synthetically, which is capable of acting as a point of initiation of synthesis when placed under conditions in which synthesis of a primer extension product, which is complementary to a nucleic acid strand, is induced, i.e., in the presence of nucleotides and an inducing agent such as a polymerase and at a suitable temperature and pH. The primer may be either single-stranded or double-stranded and must be sufficiently long to prime the synthesis of the desired extension product. The exact length of the primer will depend upon many factors, including temperature, source of primer and use of the method.

Polymerase chain reaction: A "polymerase chain reaction" ("PCR") is a reaction in

which replicate copies are made of a target polynucleotide using a "primer pair" or a "set of primers" consisting of an "forward" and a "reverse" primer, and a catalyst of polymerization, such as a DNA polymerase, and particularly a thermally stable polymerase enzyme. Methods for PCR are taught in U.S. Patent Nos. 4,683,195 (Mullis) and 4,683,202 (Mullis *et al.*). All processes of producing replicate copies of the same polynucleotide, such as PCR or gene cloning, are collectively referred to herein as "amplification" or "replication".

Characterization of HecA-like Hemagglutinins

A hemagglutinin-like gene has been identified in *Xylella fastidiosa* that has 80% amino acid homology with a hemagglutinin gene called HecA from *Erwinia chrysanthemi* (Rojas et al, 2002). HecA mediates surface attachment, cell aggregation and contributes to the virulence of *E. chrysanthemi*. Multiple pathogenicity testing of one *Xylella fastidiosa* HecA homolog, designated as HxfA, clearly shows the HxfA has an important role in *Xylella fastidiosa* virulence. As explained in detail below, the HxfA mutants no longer clump together in liquid culture, as do wild type *Xylella fastidiosa* cells. Scanning electron microscopic examination of cell masses that attach to the inside of a glass flask show the HxfA cells are largely disordered and not attached together by the length of their cell surface like wild type cells (Guilhabert and Kirkpatrick, 2005). This data indicates that HxfA is essentially a molecular "glue" that plays a very important role in cell-cell aggregation. Also identified is another HecA-like hemagglutinin in *Xylella fastidiosa*, designated HxfB, in which mutation also causes the phenotype above.

It is known that one of the virulence determinants of *Xylella fastidiosa* is its ability to systemically colonize susceptible Vitis genotypes and more resistant genotypes have the ability to slow the movement of *Xylella fastidiosa* by producing gums and tyloses (Fry and Mollenhauer, 1990). Following the teachings of one embodiment of this invention, a HecA-like hemagglutinin is introduced and expressed to reasonable levels in the xylem fluid of plants such as grapevines. The HecA-like hemagglutinin may be expressed by introducing the HecA-like hemagglutinin gene into the plant genome directly or by expressing the gene in a plant endophyte that has been introduced into the plant. This protein should act as an adhesive to cause *Xylella fastidiosa* cells to aggregate and reduce the number of planktonic cells that could circulate freely in xylem vessels and initiate new xylem vessel infections by degrading pit membranes that separate xylem elements. If the HecA-like hemagglutinin also

associated with the charged cellulose/pectin surfaces of the xylem secondary walls, it could further act as a cellular glue to immobilize and slow the systemic movement of *Xylella fastidiosa*. If this movement was slowed, *Xylella fastidiosa* may not have sufficient time to move back into permanent cordons and establish an overwintering systemic infection before a plant infected with a wild type *Xylella fastidiosa* cells was pruned off during the winter. The end result could be a plant that was far less likely to support overwintering, systemic infections of *Xylella fastidiosa* than a non-engineered plant.

In one embodiment, the present invention is directed to the observation, as more fully described in the examples below, that *Xylella fastidiosa* strains which lack expression of HxfA or HxfB are more virulent that wild type strains, due to increased motility (Guilhabert and Kirkpatrick, 2005). This suggests that expression of a HecA-like hemagglutinin (the product of the HxfA and HxfB genes) in plants would hinder *Xylella fastidiosa* movement and therefore inhibit infection. As such, in one embodiment, the present invention is directed to transgenic plants which express a HecA-like hemagglutinin, and are therefore more resistant to disease caused by *Xylella fastidiosa*. In another embodiment, the present invention is directed to plant endophytes which express a HecA-like hemagglutinin, and which can be introduced into plants to provide resistance to disease caused by *Xylella fastidiosa*.

Constructs

HecA like hemagglutinin The present invention includes various aspects of nucleic acid sequences encoding one or more proteins that provide HecA-like hemagglutinin activity. One structural feature of HecA-like hemagglutinin proteins is the presence of conserved TPS (two partner secretion) domains, illustrated in Figure 3. There are two conserved sequence domains, NPNL (amino acids 114 through 117 of SEQ ID NO: 6) and NPYGI (amino acids 154 through 158 of SEQ ID NO: 6), which are found in HecA-like hemagglutinins.

A preferred embodiment of the nucleic acid of the present invention is an isolated nucleic acid encoding a HecA-like hemagglutinin protein or fragment thereof having cell clumping activity. Such HecA-like hemagglutinin proteins include HxfA and HxfB. Examples of such nucleic acids include nucleic acids that hybridize to the HecA-like hemagglutinin encoding nucleic acid disclosed herein under low, moderate, high or very high stringency, nucleic acids with 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 97%

identity to the HecA-like hemagglutinin encoding nucleic acids disclosed herein, and nucleic acids encoding a protein with 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% identity to the HecA-like hemagglutinin proteins disclosed herein. In addition, the nucleic acids may include nucleic acids that encode proteins that share conserved regions with other HecA-like hemagglutinin proteins when aligned with HecA-like hemagglutinin protein families. Such conserved regions may share 70%, 75%, 80%, 85%, 90%, 95%, or 97% identity.

In addition, the present invention includes the above nucleic acid sequences operably linked to a promoter. The preferred promoter is a heterologous promoter. The choice of promoter will be dictated by the target cell, tissue, and/or development expression pattern in which the HecA-like hemagglutinin protein is to be expressed. Selection of an appropriate promoter functional in a desired target cell is routine in the art. One of skill in the art can use, for example, a constitutive promoter, an inducible promoter or a regulated promoter depending upon the desired pattern of expression. In addition to natural promoters, mutant promoters and artificial promoters created by splicing distinct regulatory elements may be used.

Another aspect of the present invention is vectors including the nucleic acids and promoter linked constructs described above. There are a wide range of vectors available to one of skill in the art. Such vectors can include, without limitation, expression vectors, cloning vectors, shuttle vectors, etc. which can include, but are not limited to, the following vectors or their derivatives: human, animal, or plant viruses such as vaccinia virus, adenovirus, cauliflower mosaic virus (CaMV), geminivirus, brome mosaic virus, and tobacco mosaic virus; insect viruses such as baculovirus; yeast vectors; bacteriophage vectors (e.g., lambda), and plasmid (e.g. the Ti plasmid of Agrobacterium tumefaciens) and cosmid DNA vectors, to name but a few. Selection of the appropriate vector will be dictated by the target cells, desired expression mode (e.g., transient expression versus permanent integration into the genome versus independently replicating vectors will cause one of skill in the art to select different vectors), and ease of recombinant manipulation. In some circumstances, one of skill in the art would use a shuttle vector that is functional in at least two organisms so that the nucleic acid may be manipulated in one organism and then transferred into the other.

For example, vectors can be engineered which allow for the production of transgenic plants which express a HecA-like hemagglutinin. Vectors can also be created which allow

for the expression of a HecA-like hemagglutinin in a plant endophyte.

Transgenic Plants

One approach described herein involves production of a transgenic plant that expresses anti-microbial peptides in hopes of eliminating or killing *Xylella fastidiosa* cells *en planta*. The hemagglutinin-mediated resistance described herein more specifically targets *Xylella fastidiosa* and offers a transgenic resistance approach that may be more acceptable to regulatory agencies and the public. For some plants, if the hemagglutinin gene is expressed at sufficient levels in rootstocks, such rootstocks may provide systemic protection to existing cultivars grafted on engineered rootstocks. One example of a plant which can be modified to express a HecA-like hemagglutinin is grapevines. Other examples of plants include but are not limited to: citrus, peach, plum, oleander, elm, sycamore, oak, maple, alfalfa, almond, pear, coffee, mulberry, sedges, periwinkle, and hemlock

Introduction of the selected construct into plants is typically achieved using standard transformation techniques. The basic approach is to: (a) clone the construct into a transformation vector, which (b) is then introduced into plant cells by one of a number of techniques (e.g., electroporation, microparticle bombardment, *Agrobacterium* infection); (c) identify the transformed plant cells and regenerate whole plants from the identified plant cells, and (d) select progeny plants containing the introduced construct.

Preferably all or part of the transformation vector will stably integrate into the genome of the plant cell. That part of the transformation vector which integrates into the plant cell and which contains the introduced recombinant sequence may be referred to as the recombinant expression cassette.

Selection of progeny plants containing the introduced transgene may be made based upon the detection of the recombinant HecA-like hemagglutinin encoding gene in transgenic plants, upon the detection of the recombinant HecA-like hemagglutinin protein-coding sequence or upon enhanced resistance to a chemical agent (such as an antibiotic) as a result of the inclusion of a selectable marker gene incorporated into the transformation vector.

Successful examples of the modification of plant characteristics by transformation with cloned nucleic acid sequences are replete in the technical and scientific literature. Selected examples, which serve to illustrate the knowledge in this field of technology

include: U.S. Patent No.5,571,706 ("Plant Virus Resistance Gene and Methods"); U.S. Patent No.5,677,175 ("Plant Pathogen Induced Proteins"); U.S. Patent No. 5,510,471 ("Chimeric Gene for the Transformation of Plants"); U.S. Patent No.5,750,386 ("Pathogen-Resistant Transgenic Plants"); U.S. Patent No.5,597,945 ("Plants Genetically Enhanced for Disease Resistance"); U.S. Patent No.5,589,615 ("Process for the Production of Transgenic Plants with Increased Nutritional Value Via the Expression of Modified 2S Storage Albumins"); U.S. Patent No.5,750,871 ("Transformation and Foreign Gene Expression in Brassica Species"); U.S. Patent No. 5,268,526 ("Overexpression of Phytochrome in Transgenic Plants"); U.S. Patent No. 5,780,708 ("Fertile Transgenic Corn Plants"); U.S. Patent No. 5,538,880 ("Method for Preparing Fertile Transgenic Corn Plants"); U.S. Patent No. 5,773,269 ("Fertile Transgenic Oat Plants"); U.S. Patent No. 5,736,369 ("Method for Producing Transgenic Cereal Plants"); U.S. Patent No. 5,610,049 ("Methods for Stable Transformation of Wheat"); U.S. Patent No. 6,235,529 ("Compositions and Methods for Plant Transformation and Regeneration"); Iocco et al. (2001); and Mezzetti et al. (2002) all of which are hereby incorporated by reference in their entirety. These examples include descriptions of transformation vector selection, transformation techniques and the construction of constructs designed to express an introduced transgene.

The transgene-expressing constructs of the present invention may be usefully expressed in a wide range of plants which are susceptible to diseases caused by *Xylella fastidiosa*.

Methods for the transformation and regeneration of monocotyledonous and dicotyledonous plant cells are known, and the appropriate transformation technique will be determined by the practitioner. The choice of method will vary with the type of plant to be transformed; those skilled in the art will recognize the suitability of particular methods for given plant types. Suitable methods may include, but are not limited to: electroporation of plant protoplasts; liposome-mediated transformation; polyethylene glycol (PEG-mediated transformation); transformation using viruses; micro-injection of plant cells; micro-projectile bombardment of plant cells; vacuum infiltration; and *Agrobacterium*-mediated transformation. Typical procedures for transforming and regenerating plants are described in the patent documents listed above.

Following transformation, transformants are preferably selected using a dominant selectable marker. Typically, such a marker will confer antibiotic or herbicide resistance on

the seedlings of transformed plants, and selection of transformants can be accomplished by exposing the seedlings to appropriate concentrations of the antibiotic or herbicide. Suitable markers include, without limitation, those genes coding for resistance to the antibiotic spectinomycin or streptomycin (e.g., the aada gene), the streptomycin phosphotransferase (SPT) gene coding for streptomycin resistance, the neomycin phosphotransferase (NPTII) gene encoding kanamycin or geneticin resistance, the hygromycin phosphotransferase (HPT) gene coding for hygromycin resistance. After transformed plants are selected and grown the plant can be assayed for expression of recombinant HecA-like hemagglutinin. Examples of plants which can be transformed to express a HecA-like hemagglutinin gene include but are not limited to grapevine, citrus, peach, plum, oleander, elm, sycamore, oak, maple, alfalfa, almond, pear, coffee, mulberry, sedges, periwinkle, and hemlock.

Transgenic Plant Endophytes

In another embodiment, levels of *Xylella fastidiosa* (Xf) hemagglutinin (HA) protein may be increased in xylem fluids of plants by introducing and expressing a cloned *Xylella fastidiosa* HecA-like hemagglutinin gene in a bacterial/fungal endophyte that colonizes plant tissues such as xylem tissues.

Endophytes There are a number of bacterial endophytes that can colonize and multiply to reasonably high populations in the xylem of plants. Some of these endophytes such as Pseudomonas and Agrobacterium species are well studied and transformation systems for introducing any gene into these species are numerous and well documented. Genetically engineered bacterial endophytes could introduce significant levels of HecA-like hemagglutinin directly into the xylem fluids where *Xylella fastidiosa* resides and causes disease and possibly slow their colonization as described for transgenic grapevines expressing a HecA-like hemagglutinin.

Another strategy for elevating levels of *Xylella fastidiosa* HecA-like hemagglutinin in xylem fluids would be to introduce and express a cloned *Xylella fastidiosa* HecA-like hemagglutinin gene in an avirulent strain of *Xylella fastidiosa*. Such engineered avirulent strains of *Xylella fastidiosa* could be introduced into plants such as grapevines. This strategy could slow or inhibit the initiation or progression of Pierce's disease by virulent stains of *Xylella fastidiosa*.

Also identified are other endophytes, such a Bacillus and a Cellulomonas spp. that

may be more difficult to genetically manipulate. However, these two endophytes are naturally antagonistic to *Xylella fastidiosa* and they have provided some level of protection against the development of Pierce's disease when they are inoculated into grapevines that are later exposed to *Xylella fastidiosa*-infectious insect vectors. (D. Darjean, Chemical and Biological strategies for the management of *Xylella fastidiosa*, the causal agent of Pierce's disease of grapes, Ph.D. dissertation, University of California, Davis.) If HecA-like hemagglutinin could be expressed by a xylem-colonizing, *Xylella fastidiosa*-antagonistic bacterial endophyte, the HecA-like hemagglutinin may aggregate and immobilize the *Xylella fastidiosa* cells and make them more susceptible to inhibitory substance(s) produced by these endophytic antagonists. It is also possible that endophyte expressed HecA-like hemagglutinin could act as an adhesion molecule that would associate *Xylella fastidiosa* cells and the antagonistic endophyte, thus potentially providing better suppression of *Xylella fastidiosa* populations in grapevines and possibly provide a control for diseases caused by *Xylella fastidiosa* such as Pierce's disease.

Any bacterial or fungal endophyte which can colonize plant tissues can be used. Examples of such fungal endophytes include *Eutypella aequlinearis* and *Diatrypella* spp.

Introduction of a HecA-like hemagglutinin into a plant endophyte Transformation of endophytes is well known in the art. Any endophyte which can be used to express a HecA-like hemagglutinin in a plant may be used. The following reference describes one method of genetic engineering of bacterial endophytes: Simon R, Priefer U, Pühler A. A broad host range mobilization system for in vivo genetic engineering: transposon mutagenesis in Gram negative bacteria. *Bio/Technology.* 1983;1:784–791, which is hereby incorporated by reference in its entirety.

One example of an endophyte which can be engineered to express a HecA-like hemagglutinin is Agrobacterium. Transformation of Agrobacterium is well known in the art. One transformation method which can be used is the freeze thaw method, in which a suspension containing a DNA construct and Agrobacterium cells grown in culture is frozen. After thawing, the transformed cells can be selected with the antibiotic whose resistance is carried in the DNA construct used. These transgenic endophytes can then be introduced into plants where they will express the HecA-like hemagglutinin, thereby conferring resistance to disease caused by *Xylella fastidiosa*.

Another endophyte which can be transformed with a HecA-like hemagglutinin is

Pseudomonas. Methods of transformation of Pseudomonas are well known in the art. One example of a method of transforming Pseudomonas is by electroporation.

Another endophyte which can be transformed with a HecA-like hemagglutinin is avirulent *Xylella fastidiosa*. Methods of transformation of Xylella are well known in the art. One example of a method of transforming Xylella is by electroporation.

Fungal endophytes can be transformed using a calcium chloride/polyethylene glycol (PEG) protocol as described in the following reference: Malardier L, Daboussi MJ, Julien J, Roussel F, Scazzocchio C, Brygoo Y., Cloning of the nitrate reductase gene (niaD) of Aspergillus nidulans and its use for transformation of Fusarium oxysporum. *Gene*. 1989 May 15; 78(1):147-56, which is hereby incorporated by reference in its entirety.

The following reference provides a review of genetic engineering of fungal endophytes: B. Chai and M.B. Sticklen, 1998. Applications of biotechnology in turfgrass genetic improvement. *Crop Science* 38: 1320-1338, which is hereby incorporated by reference in its entirety.

Introduction of endophyte expressing a HecA-like hemagglutinin into plants Any method which is capable of introducing endophytes expressing a HecA-like hemagglutinin into a plant may be used.

The transgenic endophyte-infected plants may be established initially by methods which involve directly incorporating transgenic endophytes into seedlings or other appropriate plant tissues of naturally occurring plants. Once the plant tissues are infected, they can be used for the development of plants having endophyte-enhanced performance characteristics, namely, the resistance to disease caused by *Xylella fastidiosa*. These plants can then be used in more traditional plant-breeding procedures for producing further improved varieties.

Selected plants can be infected with transgenic endophytes as seedlings, as callus tissue, as plantlets derived from single meristems or as somatic embryos, using methods known to those of skill in the art of plant tissue culture. Methods of culturing plant tissues are well known to modern plant biologists.

Plant tissues may be inoculated with transgenic endophytes by placing the endophyte into a direct wound or cut made in the plant tissue. Where the plant tissues to be inoculated

are plantlets from germinated seedlings or developed from plant meristems, the cut may be made directly into the stem of the plant. The inoculation can be carried out by placing a small amount of an endophyte directly on or into the cut. Likewise callus tissue may be cut and the endophyte applied directly to the wound.

Inoculated plant tissues are allowed to heal, and the tissues are allowed to develop into plants which can be further cultivated by methods appropriate for the tissue type initially inoculated. If plantlets have been inoculated, they can be grown in sterile culture for six to eight weeks before they are transferred to greenhouse and transplanted into soil.

If callus tissue has been inoculated with a transgenic endophyte, the tissue can be transferred into medium to allow the development of somatic embryos and plantlets.

Inoculated plants may be removed from the sterile growth medium using forceps and transferred into (non-sterile) greenhouse potting mixture. The plantlets may be grown in potting mix for 4 to 6 weeks until they are of sufficient size that a piece of the stem material can be excised and checked under the microscope for the presence of the endophyte.

Plants

In another embodiment, the present invention is directed to transgenic plants expressing a HecA-like hemagglutinin from *Xylella fastidiosa*, and plants containing transgenic endophytes which express a HecA-like hemagglutinin.

Plants which find use in the invention are those which are susceptible to infection by *Xylella fastidiosa*, for example grapevines, citrus, peach, plum, oleander, elm, sycamore, oak, maple, alfalfa, almond, pear and coffee. Also contemplated are other plants such as mulberry, sedges, periwinkle, and hemlock. Any plant which is discovered to be subject to disease caused by *Xylella fastidiosa* may be used in the invention. Both monocotyledonous and dicotyledonous plants may be used.

Uses

The transgenic plants expressing a HecA-like hemagglutinin and the plants harboring a plant endophyte expressing a HecA-like hemagglutinin will be more resistant to diseases caused by *Xylella fastidiosa* infection compared to wild type plants and plants not harboring

an endophyte expressing a HecA-like hegagglutinin. Recombinant HecA-like hemagglutinin is therefore useful for expresstion in plants that are susceptible to *Xylella fastidiosa* infection. Such plants will innately inhibit *Xylella fastidiosa* infection without addition of antibiotics or exogenously added chemicals.

In addition, nucleic acids of the invention will be useful in generating the transgenic plants of the present invention. The HecA-like hemagglutinin encoding genes (such as HxfA and HxfB) may be used to identify such genes in other species. In addition, the HecA-like hemagglutinin encoding nucleic acid will be useful in designing probes that may be used to detect HecA-like hemagglutinin encoding nucleic acid expression levels and specific variants of HecA-like hemagglutinin genes. Such probes may be useful in breeding plants with particular HecA-like hemagglutinin genes or expression patterns.

Transformation or transfection of prokaryotic or eukaryotic host cells with the nucleic acid of the HecA-like hemagglutinin gene will be useful in expressing, amplifying, modifying, and transforming the HecA-like hemagglutinin gene into plants. The primers and vectors of the invention will be useful for the same purposes. Modification of the HecA-like hemagglutinin encoding nucleic acid and the HecA-like hemagglutinin amino acid sequence may entail truncation, mutagenesis, deletions, additions, fusions, or other alterations of various parts of the gene or protein in order to change its activity, thereby altering or retaining the activity of the HecA-like hemagglutinin protein. Such mutations, deletions, substitutions, additions, and fusions of the HecA-like hemagglutinin encoding nucleic acid and protein are within the scope of the invention. HecA-like hemagglutinin encoding nucleic acid fusions may include the use of heterologous promoters to alter the regulation of the HecA-like hemagglutinin gene.

In addition, the nucleic acids of the invention will be useful in generating plant endophytes which express a HecA-like hemagglutinin.

The following examples are provided to illustrate further embodiments of the invention.

Example 1: Pathogenicity assays and identification of *Xylella fastidiosa* hypervirulent mutants.

Materials and Methods

Bacterial strains, growth conditions and primers. The PD *Xylella fastidiosa* strain Temecula was isolated and stored as previously described (Guilhabert et al., 2001). For all experiments, the wild type and Tn5 Temecula *Xylella fastidiosa* mutants were grown at 28°C in PD3 medium (Davis et al., 1981) with or without 5 □g/ml of kanamycin. For the growth, aggregation, adhesion and colony morphology assays, *Xylella fastidiosa* cells, previously seeded on PD3 plates, were harvested, transferred into two ml of PD3 liquid medium and adjusted to OD_{600}=0.25 (10^8cells ml^{-1}). The adjusted *Xylella fastidiosa* suspension was diluted 1:100 with fresh PD3 medium, and used for all growth kinetics, adhesion and colony morphology assays. Culture volumes did not exceed 20% of the capacity of the flasks or tubes to ensure adequate aeration of the culture. The cultures were established in duplicate. All the primers used in this study are presented in Table 1.

Random transposon mutagenesis

Electrocompetent *Xylella fastidiosa* Temecula cells were prepared as previously described (Guilhabert and Kirkpatrick, 2003). The *Xylella fastidiosa* Temecula strain was mutagenized using the transposome protocol described (Guilhabert et al., 2001). A random insertion library of 1,000 Tn5 *Xylella fastidiosa* mutants was generated.

Pathogenicity assays. Each Tn5 *Xylella fastidiosa* mutant was individually innoculated into Chardonnay, Chenin Blanc and Thompson seedless grapevines to assess pathogenicity. All 1,000 Tn5 *Xylella fastidiosa* mutants in Chardonnay were screened for altered symptom development. This screen identified 7 *Xylella fastidiosa* Tn5 mutants that showed a pronounced hypervirulence phenotype 21 weeks after inoculation (i.e. grapevines inoculated with these Tn5 mutants developed more severe disease symptoms than did vines inoculated with the wild type Temecula strain). In order to confirm their hypervirulence phenotype, the 7 mutants and wild type controls were retested in a similar matter for i) earlier symptom development ii) more severe symptom development during a period of 32 weeks and iii) earlier death of the inoculated grapevines. The disease progression of the 7 mutants and wild type controls was performed in three plants each of Chardonnay, Chenin Blanc and Thompson seedless grapevines (9 plants total for each mutant). The *Xylella fastidiosa* 1792 mutant strain was tested twice in a similar manner in three Chardonnay grapevines (6 plants total).

Results

In order to understand the mechanisms by which *Xylella fastidiosa* causes plant

disease, a random transposition approach was taken to disrupt genes potentially involved in *Xylella fastidiosa* virulence and/or movement in grapevine plants. Seven putative hypervirulent *Xylella fastidiosa* mutants (i.e. grapevines inoculated with these Tn5 mutants developed more severe disease symptoms than did the wild type Temecula strain 21 weeks after inoculation), out of 1,000 that were screened, were selected and retested by inoculating three additional Chardonnay as well as three Chenin Blanc and Thompson seedless grapevines. All of the 7 Tn5 *Xylella fastidiosa* hypervirulent mutants tested showed i) earlier symptom development, ii) higher disease score over a period of 32 weeks and iii) earlier death of the inoculated grapevines than the wild type cells when inoculated into all grapevines (Figure 2); thus demonstrating that the hypervirulence phenotype is correlated with earlier symptom development and earlier vine death in multiple *Vitis vinifera* cultivars.

Example 2: Identification of genes associated with the hypervirulent phenotype and sequence analyses.

Materials and Methods

Identification of mutated genes and sequence analysis. All the *Xylella fastidiosa* mutants are described in Table 1.

After assessing pathogenicity in greenhouse-grown grapevines (see below), the site of Tn5 insertion of the mutants with enhanced virulence (hypervirulent *Xylella fastidiosa* mutants) was identified by a two-step procedure. The chromosomal region flanking the Tn5 element was first amplified using an oligonucleotide, Poforw that binds specifically to the transposon sequence in combination with a degenerate primer, Arb1 that anneals to sequences flanking the Tn5 insertion. Then, following PCR amplification, direct sequencing was accomplished using a second oligonucleotide, kan-2 fp-1 that primes the PCR fragment downstream of Poforw near the right border of the transposon (Chun et al., 1997; Hermann et al., 2000). One colony of each Tn5 *Xylella fastidiosa* mutant was transferred into 10 µl of de-ionized water and 3 µl of the suspension was used as template in the PCR reaction. All PCR reactions were conducted with conditions described by Hermann et al., 2000, using a Taq DNA polymerase (Promega, Madison, WI) diluted in a TaqStar™ antibody (BD Biosciences Clontech, Palo Alto, CA). Only the first step of a modified two-step PCR protocol was used (Chun et al., 1997). Briefly, the first 12 cycles included an annealing step of 30 sec, initially at 36°C, then increasing 1°C per cycle; the last 25 cycles included a primer-annealing step of

30 sec at 65°C. After amplification, the PCR products were purified using the "Qiaquick PCR purification kit" (Qiagen, Valencia, CA) and were sequenced in a "2X" Big Dye Terminator sequencing reactions (Applied Biosystems, Foster City, CA), using the outward primer kan-2 fp-1 by the Division of Biological Sciences DNA sequencing facility at UC Davis.

An additional hemagglutinin-like mutant strain, Xf1246 was also identified by sequencing the insertion sites of the random mutants from the library described above.

Six of the Tn5 insertion sites were confirmed using as forward primers kan-2 fp-1 and kan-2 rp-1 that bind close to the right and left borders of the transposome, respectively, and reverse primers derived from the sequences obtained in the mutated ORF. The identity of the two putative hemagglutinin mutated genes, xf2118 and xf1246 was further confirmed by Southern Blot analysis (see below). All PCR reactions were conducted and cycled with standard conditions (Smart et al., 1996). The 35 cycles of PCR included an annealing step of 1 minute at 58°C. The resulting PCR products were sequenced to further confirm the location of the Tn5 insertion sites.

DNA sequences were analyzed with the program Bioedit version 5.0.6 (Tom Hall, North Carolina State University, Department of Microbiology) and database searches were performed with the BLAST program accessed through the National Center for Biotechnology Information (NCBI) website (Altschul et al., 1990). GenBank comparisons in the NCBI conserved domain were performed to identify conserved domains in hypothetical proteins. This was accomplished using tools available at the NCBI Structure group website on the Internet, which maintains the Molecular Modeling Database of macromolecular 3D structures. The protein alignments were performed using the CLUSTALW method, which is described in Thompson et al., 1994, and on the Internet at the website of the European Bioinformatics Institute.

Results

In order to determine the identity of the mutated gene, the transposon insertion sites of the mutants were identified using a combination of PCR and sequencing (Table 1). Six of the mutated genes corresponded to genes with assignable functions and one gave a significant match with a hypothetical conserved gene. Southern blot analysis of the hypervirulent *Xylella fastidiosa* mutants showed that the clones contained a single transposon insertion (data not shown). Regions flanking the Tn5 mutated gene sequences also were the same as the sequences of their respective regions in the wild type *Xylella fastidiosa* Temecula strain; thus

confirming the position of the Tn5 insertion in the hypervirulent mutants.

One hypervirulent Tn5 mutant was disrupted in PD2118, which putatively encodes a hemagglutinin-like secreted protein. A second mutant was disrupted in PD1542, which putatively encodes a dolichol-phosphate mannosyltransferase lipopolysaccharide, *dmt*, which might be involved in LPS biosynthesis by adding a sugar onto the O-polysaccharide chain. The five other Tn5 mutants were disrupted in PD1198, PD0218, PD0681, PD0875 and PD1244 genes, which putatively encode for a ferric enterobactin receptor *bfe* A, a serine protease, *psp* B, a glucose/galactose transporter, *glu* P, a coenzyme F390 synthetase, *paa* K and a hemagglutinin-like hypothetical protein, respectively (Table 1).

A number of large exoproteins, including hemagglutinins, are secreted by a two-partner secretion (TPS) pathway (Jacob-Dubuisson et al., 2001). Adhesins secreted through the TPS pathway (Tps proteins), share similar "secretion domains" despite their limited overall sequence similarities (Jacob-Dubuisson et al., 2001). The secretion domain includes a 110-amino acid (aa) conserved region in the N-proximal region (Schönherr et al., 1993). The Tsp secretion domains are conserved in HecA, a hemagglutinin protein in *E. chrysanthemi* (GenBank accession number AF501263; Rojas et al., 2002) The first 200-aa were analyzed in the N-proximal region of the seven gene products that were annotated as hemagglutinin-like proteins in the PD genome sequence (Van Sluys et al., 2003). The putative seven *Xylella fastidiosa* hemagglutinin proteins were aligned with the hemagglutinin HecA of *E. chrysanthemi* (Figure 3).

Although the three *Xylella fastidiosa* hemagglutinin-like products PD2116, PD2110 and PD0988 showed 34%, 35% and 26% amino acid identity, respectively with a putative hemagglutinin-related protein from *Ralstonia solanaceraum* (GenBank accession number Np_522632.1), comparison of their N-proximal 250 aa sequences did not reveal the previously described Tps secretion domains (Figure 3). The putative hemagglutinin-related protein from *Ralstonia solanaceraum* mentioned above did not contain the Tps secretion domains. The PD *Xylella fastidiosa* product PD0986, annotated as a hemagglutinin-like protein (Van Sluys et al., 2003), did not possess any homology with putative hemagglutinin or adhesin proteins from other bacteria.

Further amino acid sequence analyses revealed that the Tps secretion domains were only conserved in the last three *Xylella fastidiosa* hemagglutinin-like genes PD2118, PD1792 and PD1246 (Figure 3). Interestingly, PD gene PD1246 has a frameshift/point mutation in its

sequence (Van Sluys et al., 2003); thus PD1246 is most likely not functional in the Temecula strain. In addition to the presence of the Tps secretion domains in their sequence, PD2118 and PD1792 gene products also possess 27% and 37% amino acid identities, respectively with the HecA protein from *E. chrysanthemi*. Therefore, the PD2118 and PD1792 gene products were named HxfA and HxfB, respectively (H indicates hemagglutinin, xf, *Xylella fastidiosa*, A and B for the two first hemagglutinins described in *Xylella fastidiosa)*.

HxfB was cloned in E. coli, disrupted by Tn5 mutagenesis, and the disrupted gene introduced back into *X. fastidiosa.* The introduced construct replaced the wild type HxfB gene by homologous recombination (see Example 5).

GenBank comparisons of the hemagglutinin-like hypothetical PD1244 ORF, identified in the mutant study (see above), revealed homology only with genes in various *Xylella fastidiosa* genome sequences. The PD1244 product had 82% and 74% amino acid identity with the putative hemagglutinin-like products Xf2196 from the CVC and PD2116 from the PD strain of *Xylella fastidiosa*, respectively (Simpson et al., 2000 and Van Sluys et al., 2003). However, putative PD1244 gene predicts a 79-aa protein, whereas genes Xf2196 and PD2116 predict a 3442-aa and 439-aa protein, respectively. Therefore, the amino acid identity between gene products PD1244, Xf2196 and PD2116 is based only on a small region of the putative proteins. In contrast to Xf2196, the Tsp secretion domains noted in HecA were not identified in PD1244 or PD2116 products (Figure 3). No conserved domains were identified in PD1244 protein using the NCBI conserved domain database.

Example 3: Hypervirulent mutations altered *Xylella fastidiosa* growth rate and increased movement *in planta*.

Materials and Methods

***Xylella fastidiosa* growth curves and *en planta* bacterial population determinations.** Growth curve determinations were performed in 15 ml polystyrene tubes containing 3 ml of PD3 medium. A total of 14 tubes were prepared for the wild type and each Tn5 mutant, so as to allow destructive sampling of two tubes at every sampling time. Two independent growth curve determinations were performed. Due to the aggregate nature of *Xylella fastidiosa* liquid cultures, immediately after inoculation and after 2, 4, 6, 8, 12 and 16 days, the cultured cells were completely dispersed using a tissue homogenizer (Heidolph RzR 50) and the cell growth was monitored by measuring turbidity at OD_{600}nm. The doubling

time of the bacterial populations was calculated using a standard equation (Madigan et al., 1970).

The bacterial populations (number of cells per gram of petiole tissue) of the *Xylella fastidiosa* wild type and Tn5 mutants inoculated into Chardonnay vines were determined in the following manner: 14 weeks after inoculation, petiole tissues from each vine inoculated with either Tn5 mutant or wild-type *Xylella fastidiosa* cells were harvested at the point of inoculation and 25 centimeters above the point of inoculation. Petiole tissues were surface sterilized (1 min in 10% sodium hypochlorite and 1 min in 80% ethanol), rinsed three times in sterile de-ionized water and ground in 2 ml of sterile PBS buffer using a grinding machine (Biorega AG, Switzerland). Serial dilutions were prepared and 3 replicates of 10 µl were plated on PD3 agar medium with or without kanamycin. After incubating 7-10 days at 28°C, the number of bacteria was quantified.

Results

Growth curves of the Tn5 mutants and wild type *Xylella fastidiosa* strain showed that all the hypervirulent mutants reached the exponential and stationary phase in a manner similar to the wild type *Xylella fastidiosa* strain (Figure 5).

The doubling time of Tn5 mutants and wild type *Xylella fastidiosa* strain was also determined. The doubling time of the wild type *Xylella fastidiosa* strain was 0.5 day. In contrast, the doubling times of 4 of the Tn5 mutants were longer than the wild type strain, whereas the doubling time of *hxf*A (PD2118) and PD1244 mutants was faster than the wild type strain (Table 2). The doubling time of PD1198 *Xylella fastidiosa* mutant was not significantly different from the wild type strain.

In order to evaluate possible mechanisms that could explain the hypervirulence phenotype, bacterial populations and movement in infected grapevines was assessed for the seven mutants and wild type strain. The hypervirulent mutants moved faster in inoculated grapevines than the wild type at 25 cm above the point of inoculation 12 weeks post inoculation. In contrast, the population of the hypervirulent mutants was not significantly different than the wild type at the point of inoculation (Table 3). The data suggests that hypervirulent cells colonize more rapidly grapevine tissue than wild type cells.

Example 4: HxfA is involved in cell-cell aggregation *in vitro* and *in planta*-

Materials and Methods

Surface attachment, cell-cell aggregation and colony morphology assays. The Tn5 mutants or wild type *Xylella fastidiosa* cells were grown in 25 ml of PD3 broth medium in 125 ml glass Erlenmeyer flasks on an orbital shaker at 120 rpm to visualize the formation of bacterial cell clumps within the liquid medium and the formation of aggregated cells that attached to the inside of the flask (Marques et al., 2002).

Additional surface attachment and aggregation assays were performed in polystyrene (15 ml; Falcon 2051 tubes, Becton & Dickinson Labware), polypropylene (5 ml; Falcon 2063 tubes, Becton & Dickinson Labware) and borosilicate glass (10 ml) tubes containing PD3 medium. The cultures were incubated at 28^0C in a vertical position without shaking for 10 days. Attachment on the surface walls of the tubes was assessed by a crystal violet staining method (Espinosa-Urgel et al., 2000 and Leite et al., 2004). Briefly, after the incubation period, the PD3 medium was discarded and a 1% (wt/vol) solution of crystal violet was added to each tube and rinsed with de-ionized water. The remaining stain was eluted from the bacterial ring by ethanol. The absorbance of the ethanol-crystal violet solution was measured at 600 nm.

The cell-cell aggregation assay was performed as described by Burdman et al., (2000) and Leite et al., (2004). After 10 days of static incubation, the *Xylella fastidiosa* cultures were gently agitated and the aggregates allowed to settle for 20 min. The turbidity of the remaining upper culture medium, composed mostly of dispersed cells was measured using a spectrophotometer at 540 nm. The culture medium was returned to the original tube, the aggregate masses were dispersed using a tissue homogenizer (Heidolph RzR 50) for 1 min and the total cell culture was measured (ODt). Relative percentage of aggregated cells was estimated as follows: % aggregated cells= (ODt-ODs)/ODt x 100 (Burdman et al., 2000).

The colony morphology of the wild type or mutant cells was assessed by plating one hundred µl of a 10^8 cfu/ml solution onto 2 PD3 plates (4 plates total). Aberrant colony morphology of mutants was compared to wild type after 10 days growth on PD3 solid medium at 28^oC.

Scanning electron microscopy (SEM). The wild type and mutant cells of *Xylella fastidiosa* that were inoculated into grapevines or grown in PD3 broth were examined using scanning electron microscopy (SEM). Petiole samples were collected from symptomatic grapevines three months after inoculation. Petioles sections and bacterial aggregates,

harvested by centrifugation from *Xylella fastidiosa* liquid cultures grown in a glass Erlenmeyer flask, were fixed overnight in a 2.4% glutaraldehyde, 0.3% paraformaldehyde solution. Fixed samples were then dehydrated by increasing concentrations of ethanol, critically-point dried in a Tousimis Samdri-780A, placed on aluminum specimen mounts with carbon conductive tabs, and sputter-coated with gold using a Denton Vacuum Desk II cold sputter-etch unit. The morphology of the mutant or wild type *Xylella fastidiosa* aggregates grown in grapevines or grown in PD3 broth was observed at 5-12 khz with a Hitachi S-3500N SEM and images were recorded digitally.

Results

To evaluate whether the hypervirulence phenotype affected cell-cell attachment, the ability of each hypervirulent mutant to aggregate in culture was investigated. Cell-cell aggregation of each mutant was first visually assessed in 125 ml glass Erlenmeyer flasks placed on an orbital shaker. The wild type *Xylella fastidiosa* strain and 6 of the Tn5 mutants formed large aggregates when grown *in vitro* (Figure 6A, Table 2). In contrast, the *hxf*A mutant was impaired in its ability to form cell-cell aggregates in liquid culture (Figure 6B, Table 2).

The colony morphology of wild type, HxfA and HxfB cells were examined on solid medium. HxfA and HxfB mutants exhibited a homogenous distribution of cells, forming a continuous lawn of cells, whereas the wild type grew in separate clumps composed of small and medium-size individual colonies (Figure 6C and D); thus further confirming the inability of HxfA cells to self-aggregate.

An optical density assay (Burdman et al., 2000) was used to quantify the effect of the HxfA mutation on cell-cell aggregation. This assay further confirmed that cell-cell aggregation of HxfA mutant was decreased (Table 4).

The aggregates of wild type and *hxf*A mutant cells grown in PD3 medium and *in planta* were observed by scanning electron microscopy. Wild type cells, grown *in vitro* were aggregated together typically by cell-cell contact along the length of the cells (data not shown). The *hxf*A mutant cells did not appear to be aggregated in such a manner (data not shown). This result was further observed *in planta* (Figure 6). Figure 6F and H shows that HxfA cells did not form large clumps in the plants but rather *hxf*A cells typically formed a mono-layer of cells on the surface of the xylem vessels. In contrast, wild type cells formed a multiple-layer of cells that clearly aggregated to each others (Figure 6E and G).

Example 5: Cloning of the hemagglutinin gene, HxfB (PD1792). The PD1792 gene of a grapevine strain causing Pierce's disease (PD; *Xylella fastidiosa* Temecula isolate; Van Sluys et al., 2003) was amplified using the Expand Long Template PCR system (Roche, Mannhein, Germany) with primers PD1791 rev (5' GGAGCAAGACAGTCGCGGAT 3' (SEQ ID NO: 9)) and PD1793 forw (5' GATATCGTGAACGATTGCCGCCT 3' (SEQ ID NO: 10)), anneal to sequences that flank the ORF encoding the PD1792 gene. Briefly, the annealing temperature in both set of cycles was 58°C and the elongation times in the first and second set of cycle were 4' for 10 cycles and 4' + 20'' per cycle for 25 cycles, respectively. A PCR product of the expected 10,134 bp-size was obtained.

The PCR product was cloned into the pCR®-XL-TOPO® vector using the TOPO® XL PCR cloning kit (Invitrogen, Carlsbad, California) following the manufacturer recommendations. Cloning of the PD1792 gene was confirmed by sequencing the end of the cloned PCR product using primers, M13 forward and reverse (5' GTTTTCCCAGTCACGA 3'(SEQ ID NO: 11) and 5' CAGGAAACAGCTATGAC 3' (SEQ ID NO: 12), respectively; Invitrogen, Carlsbad, California). The sequencing was performed in a "2X" Big Dye Terminator sequencing reactions (Applied Biosystems, Foster City, CA) by the Division of Biological Sciences DNA sequencing facility at UC Davis. The sequences of the cloned PCR product perfectly matched the sequence of the PD1792 gene that is present in the PD genome sequence (Van Sluys et al., 2003).

Example 6: Site-directed mutagenesis of *hxf*B and confirmation of the observed *hxf*A phenotypes.

Materials and Methods

Site-directed mutagenesis. A 680 bp region of *Xylella fastidiosa* Temecula genome including a small coding sequence of the PD1792 gene was amplified using primers PD1792 rev and PD1792 forw and cloned into the pCR^{R}2.1-TOPO vector (Invitrogen, Carlsbad, California). The plasmid was then digested with *Eco*RI and the PD1792 insert was ligated into *Eco*RI-digested pUC18 plasmid creating pXF012. Plasmid pXF012 was linearized at the unique restriction site *Bst*BI of the cloned PCR-amplified PD1792 fragment. Two annealed *Bst*BI-adaptors carrying a *Mfe*I restriction site (5'CAATTGACGT 3' (SEQ OD NO: 13)) were ligated in *Bst*BI-digested pXF012. The Tn903 kanamycin resistance gene (Guilhabert et

al., 2001) was cloned into pXF012 cut with *Mfe*I to make pXF013. Insert and junction sequences of pXF013 were determined. Two μg of pXF013 plasmid DNA was electroporated into *Xylella fastidiosa,* and transformants were selected as described (Guilhabert et al., 2001). Disruption of the PD1792 locus was confirmed by using the Expand Long Template PCR system (Roche, Mannhein, Germany) with primers PD1791 rev and PD1793 forw, binding to the flanking ORFs of the mutated PD1792 gene. Briefly, the annealing temperature in both set of cycles was 58°C and the elongation times in the first and second set of cycle were 4' for 10 cycles and 4' + 20'' per cycle for 25 cycles, respectively. The identity of the PCR product was confirmed by using the restriction enzyme *Hind*III that cuts only once into the Tn903 kan-2 cassette.

Southern blot analysis of putative *X. fastidiosa* mutants. *Xylella fastidiosa* genomic DNAs were isolated from the mutant strains as described (Zang et al., 1998). Genomic DNAs from the transformants obtained by random mutagenesis were individually digested by the two restriction enzymes, *Eco*RI and *Eag*I. In order to confirm the identity of the two random hemagglutinin PD2118 and PD1246 mutant strains, their genomic DNAs were also digested with *Sal*I and *Xmn*I. All digested DNAs were electrophoresed, alkali-denatured, and transferred to a nitrocellulose membrane as previously described (Guilhabert et al., 2001). The Tn5 DNA, used as a probe in the hybridization analyses of restriction digested genomic DNAs from the *Xylella fastidiosa* mutants, was PCR amplified and purified (Guilhabert et al., 2001), and 25 ng was labeled with fluorescein dye using the "Gene Images™ random prime labeling module kit" (Amersham Biosciences, UK). Hybridizations and detection were carried out according to the recommendations of the "Gene Images™ CDP-Star™ detection module kit" (Amersham Biosciences, UK). Stringent post-hybridization wash conditions (15 min per wash) were once in 1X SSC-0.1% SDS at 60°C and once in 0.5X SSC-0.1% SDS at 68°C.

Results

To confirm that hemagglutinins are involved in *Xylella fastidiosa* virulence and cell-cell aggregation, a mutant in the second hemagglutinin identified above, HxfB (PD1792) was generated. The disruption of gene *hxf*B was confirmed by a long PCR procedure (data not shown). The mutant strain Xf1792 was inoculated twice in three Chardonnay grapevines and it consistently showed i) earlier symptom development, ii) higher disease score over a period of 32 weeks and iii) earlier death of the inoculated grapevines the wild type cells (Figure 2);

thus confirming that hemagglutinins are involved in attenuating *Xylella fastidiosa* pathogenicity. An optical density assay (Burdman et al., 2000) was used as described above to quantify the effects of the HxfB mutation on cell-cell aggregation. This assay further confirmed that hemagglutinins are involved in *Xylella fastidiosa* cell-cell aggregation (Table 4).

Example 7: Sequence analysis and subcloning of putative cell-cell binding domains of HxfA and HxfB.

Detailed sequence analysis of HxfA and B using revealed 7 (HxfA, PD2118) and 8 (HxfB, PD1792) domains in the N-terminal region of the proteins that likely represent the Hxf cell-cell binding domains. This analysis was performed by using the Biozon database, developed by researchers at Cornell University, and accessible through the World Wide Web. Three DNA fragments (AD1, AD2 and AD3, all 1.0 to 1.2kb in size) were identified in each protein that contained 3 or 4 putative binding domains. The AD2 fragment from HxfA and B were most similar in sequence to each other and therefore chosen as a likely marker for both Hxf proteins. AD2 was PCR-amplified, cloned and expressed in a protein fusion vector in E. coli and the AD2 fusion protein was purified by affinity chromatography. The fusion protein was injected into rabbits and antibodies against AD2 were produced. The AD2 antibodies are being used to determine the size and cellular location of native Hxf protein in X. fastidiosa and PD-affected grapevines. AD2 antibodies and purified AD2 proteins are being used to determine if the AD2 domain is mediating X. fastidiosa cell-cell aggregation.

Because the full-length Hxf genes (10.2kb) is larger than desirable to transform and be expressed in either plants or grapevine endophytes, a 3.5 kb fragment that contains all three putative binding domains (Ad1-AD3) from HxfA and HxfB were PCR-amplified and cloned in E. coli. These two 3.5kb fragments are being transformed into grapevine (V. vinifera), tobacco and Pseudomonas and Agrobacterium endophytes (D. Darjean-Jones, 2004) using appropriate technologies that have been previously discussed. Fusion protein derived from the 3.5kb fragments are being prepared and used as previously described for Hxf AD2. Using either individual Hxf AD domains or the 3.5kb to transform plant or endophytes will be more feasible than engineering the full-length Hxf gene and should confer the same desired resistance phenotype.

Tables and Figures

Table 1-PCR primers[1] and strains used in this study

			Source
Primers used to sequence the Tn5 insertion sites			
kan-2 fp-1	ACCTACAACAAAGCTCTCATCAACC (SEQ ID NO: 14)		Epicentre Technology
Arb1	GGCCACGCGTCGACTAGTACNNGATAT (SEQ ID NO: 15)		Caetano-Anoles, 1993
Poforw	CTGGCAGAGCATTACGCTGAC (SEQ ID NO: 16)		This study
Primers used to confirm the random Tn5 insertion sites		**Used to confirm putative mutated gene**	
kan-2 rp-1	GCAATGTAACATCAGAGATTTTGAG (SEQ ID NO: 17)		Epicentre Technology
kan-2 fp-1[2]	ACCTACAACAAAGCTCTCATCAACC (SEQ ID NO: 18)		Epicentre Technology
6191.2 forw	TGCAACCACGCTGAACA (SEQ ID NO: 19)	glucose/galactose transporter,*glu*P	This study
6211.2 rev	GGCATCGACCTCATT (SEQ ID NO: 20)	glucose/galactose transporter,*glu*P	This study
PD0219 forw	GCTGCACTCCAGATTGAACACTGT (SEQ ID NO: 21)	serine protease,*psp*B	This study
PD0217 forw	ACCTACACCTACACCACTGGA (SEQ ID NO: 22)	serine protease,*psp*B	This study
23531.2 forw	GATCTACCTGCTGTTGC (SEQ ID NO: 23)	hypothetical protein, PD1244	This study
23551.2 rev	GTGAGGATTATTACGGGTGGTG (SEQ ID NO: 24)	hypothetical protein, PD1244	This study
22281.2 forw	CGCGTGCTCGCTCTTCAAT (SEQ ID NO: 25)	coenzyme F390 synthetase,*paa*K	This study
22311.2 rev	TACCGAATGTGGCTTG (SEQ ID NO: 26)	coenzyme F390 synthetase,*paa*K	This study
11001.2 forw	ATTCACGCTCCATACG (SEQ ID NO: 27)	iron receptor,*bfe*A	This study
11021.2 rev	ATGTCGAGTCCTGTTGTG (SEQ ID NO: 28)	iron receptor,*bfe*A	This study
13991.2 rev	AACAGAGTGCTAGTCACC (SEQ ID NO: 29)	mannosyltransferase,*dmt*	This study
24521.2 forw	ACGACTTGCATAGCAGTAGC (SEQ ID NO: 30)	mannosyltransferase,*dmt*	This study
Primers used for the site-directed mutagenesis			
PD1792 rev	TTGTCCTGACGGTCG (SEQ ID NO: 31)		This study
PD1792 forw	CCACCATTGACAACC (SEQ ID NO: 32)		This study
PD1791 rev	GGAGCAAGACAGTCGCGGAT (SEQ ID NO: 9)		This study
PD1793 forw	GATATCGTGAACGATTGCCGCCT (SEQ ID NO: 10)		This study

Xf mutants	Relevant characteristics	Putative gene function[3]	
Xf2118	PD2118[4]::EZ::TN™<Kan-2>Tnp[5]	hemagglutinin-like secreted protein, HxfA	This study
Xf1542	PD1542::EZ::TN™<Kan-2>Tnp	mannosyltransferase (lps biosynthesis), Dmt	This study
Xf1198	PD1198::EZ::TN™<Kan-2>Tnp	ferric enterobacyin receptor, BfeA	This study
Xf0218	PD0218::EZ::TN™<Kan-2>Tnp	serine protease, PspB	This study
Xf0681	PD0681::EZ::TN™<Kan-2>Tnp	glucose/galactose transporter, GluP	This study
Xf0875	PD0875::EZ::TN™<Kan-2>Tnp	coenzyme F390 synthetase, PaaK	This study
Xf1244	PD1244::EZ::TN™<Kan-2>Tnp	hypothetical protein (hemagglutinin-like)	This study
Xf1792	PD1792::Tn903 kan-2[6]	hemagglutinin-like secreted protein, HxfB	This study
Xf1246	PD1246::EZ::TN™<Kan-2>Tnp	hemagglutinin-like secreted protein	This study

[1]: primer sequences are presented 5' to 3'.

[2]: primer kan-2 fp-1 was used to sequence and to confirm the Tn5 insertion sites

[3]: putative function of ORF based on homology between regions flanking the Tn5 insertion and other *Xf* gene sequences

[4]: identification number of open reading frame (ORF) in PD strain of *Xf*.

[5]: Tn5 derivative (Epicentre Technologies, Madison, WI).

[6]: Tn903 kan-2= kanamycin resistance cassette from EZ::TN™<Kan-2>Tnp (Epicentre Technologies, Madison, WI).

Table 2- Physiological properties of the *Xf* Tn5 mutants and wild type strain

	Phenotypes		
	Doubling time (in days):[a, b]	Attachment assay:[c]	
		Cell/cell aggregation	Surface attachment
Genotype:			
Wild type	0.50+/-0.018	+++	+++
HxfA	**0.45+/-0.005**	-	++
Dmt	**0.93+/-0.01**	+++	+++
BfeA	0.48+/-0.003	+++	+++
PspB	**ND[d]**	+++	+++
GluP	**0.88+/-0.13**	+++	+++
PaaK	**1.14+/-0.224**	+++	+++
hypothetical	**0.24+/-0.003**	+++	+++

[a]: doubling time calculated as described by Madigan et al., 1970.

[b]: significant difference indicated in bold; significance defined as $p<0.01$

[c]: frequency of attachment: -, absent; +, low; ++, moderate; +++, high.

[d]: Not determined (PspB mutant lost in storage)

Table 3- Bacterial populations of Thompson seedless grapevines 12 weeks after inoculation with wild-type or Tn5 *Xf* cells

	Xf bacterial populations (cfu/g of tissue)	
	At the point	25 cm above the point
Genotype:	of inoculation	of inoculation[a]
Wild type	10.6 (+/- 15) x 10^6	0
HxfA	6 (+/- 7) x 10^6	**5.3 (+/- 8) x 10^5**
Dmt	36.6 (+/-5.2) x 10^6	**3.6 (+/- 1.8) x 10^5**
BfeA	4.3 (+/- 4.6) x 10^6	**4.6 (+/- 4.4) x 10^4**
Gluc	2.8 (+/-2.6) x 10^6	**1.4 (+/-0.9) x 10^7**
PaaK	25 (+/-10) x 10^6	**1.8 (+/-0.1) x 10^7**
hypothetical	6.3 (+/- 4.5) x 10^6	**2.4 (+/- 16) x 10^4**

[a]: significance indicated in bold type; significance defined as $p<0.01$

Table 4- Cell-cell aggregation and cell-surface attachment of *Xf* wild type, *hxf*A and *hxf*B Tn5 mutants

	Cell-cell aggregation[a]	Cell-surface attachment[b] on:		
Genotype:		Glass surface	Polystyrene surface	Polypropylene surface
Wild type	36.2+/-8.9	0.9+/-0.7	0.07+/-0.020	.25+/-0.04
HxfA	**8.9+/-6.5**[c]	0.5+/-0.3	0.06+/-0.010	.20+/-0.03
HxfB	**9.2+/-1.0**	ND[d]	ND	ND

[a]: percentage of cell-cell aggregation was assessed as described in Burdman et al., 2000

[b]: cell-surface attachment was assessed by the crystal violet staining method as in Espinosa-Urgel et al., 2000

[c]: numbers in bold type are significantly different than wild type. Significance was defined as $p<0.01$

[d]: not determined

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We claim:

1. A construct comprising a nucleic acid molecule encoding a recombinant HecA-like hemagglutinin or fragment thereof which confers resistance to *Xylella fastidiosa* infection when expressed in plants.

2. The construct of claim 1 wherein the nucleic acid molecule encodes a polypeptide with at least about 85% identity to HxfA.

3. The construct of claim 1 wherein the nucleic acid molecule encodes a polypeptide with at least about 85% identity to HxfB.

4. The construct of claim 1 wherein the nucleic acid molecule encodes a polypeptide with at least about 90% identity to HxfA.

5. The construct of claim 1 wherein the nucleic acid molecule encodes a polypeptide with at least about 90% identity to HxfB.

6. The construct of claim 1 wherein the nucleic acid molecule encodes a polypeptide with at least about 95% identity to HxfA.

7. The construct of claim 1 wherein the nucleic acid molecule encodes a polypeptide with at least about 95% identity to HxfB.

8. The construct of claim 1 wherein the nucleic acid molecule encodes a polypeptide with at least about 97% identity to HxfA.

9. The construct of claim 1 wherein the nucleic acid molecule encodes a polypeptide with at least about 97% identity to HxfB.

10. The construct of claim 1 where the nucleic acid molecule encodes HxfA.

11. The construct of claim 1 where the nucleic acid molecule encodes HxfB.

12. The construct of claim 1 wherein the nucleic acid molecule hybridizes under high stringency conditions to the nucleic acid molecule of claim 10.

13. The construct of claim 1 wherein the nucleic acid molecule hybridizes under high stringency conditions to the nucleic acid molecule of claim 11.

14. The construct of claim 1 wherein said nucleic acid molecule is operably linked to a promoter.

15. The construct of claim 14 wherein the promoter is selected from the group consisting of constitutive promoters, inducible promoters, tissue- and cell-specific promoters, and developmentally-regulated promoters.

16. A host cell expressing a construct comprising a nucleic acid molecule encoding a recombinant HecA-like hemagglutinin or fragment thereof which confers resistance to *Xylella fastidiosa* infection when expressed in plants.

17. The host cell of claim 16, wherein said host cell is selected from the group consisting of Pseudomonas, Agrobacterium, and avirulent *Xylella fastidiosa.*

18. A plant containing the host cell of claim 16.

19. A transgenic plant expressing a recombinant HecA-like hemagglutinin or fragment thereof wherein said transgenic plant is more resistant to *Xylella fastidiosa* infection

as compared to a corresponding plant not expressing said recombinant HecA-like hemagglutinin or fragment thereof.

20. The transgenic plant of claim 19 wherein the plant is selected from the group consisting of grapevines, citrus, peach, plum, oleander, elm, sycamore, oak, maple and coffee.

21. The transgenic plant of claim 20 where the plant is a grapevine.

22. A seed produced by the transgenic plant of claim 19.

Figure 1

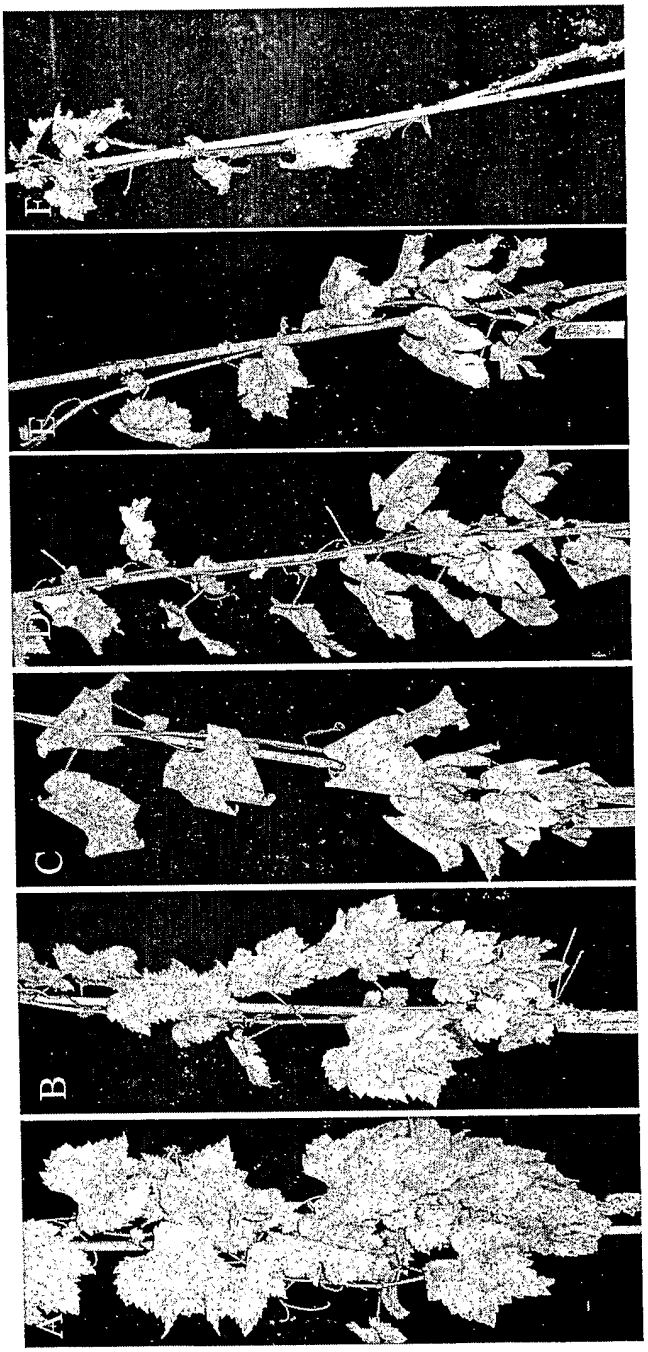


Figure 2

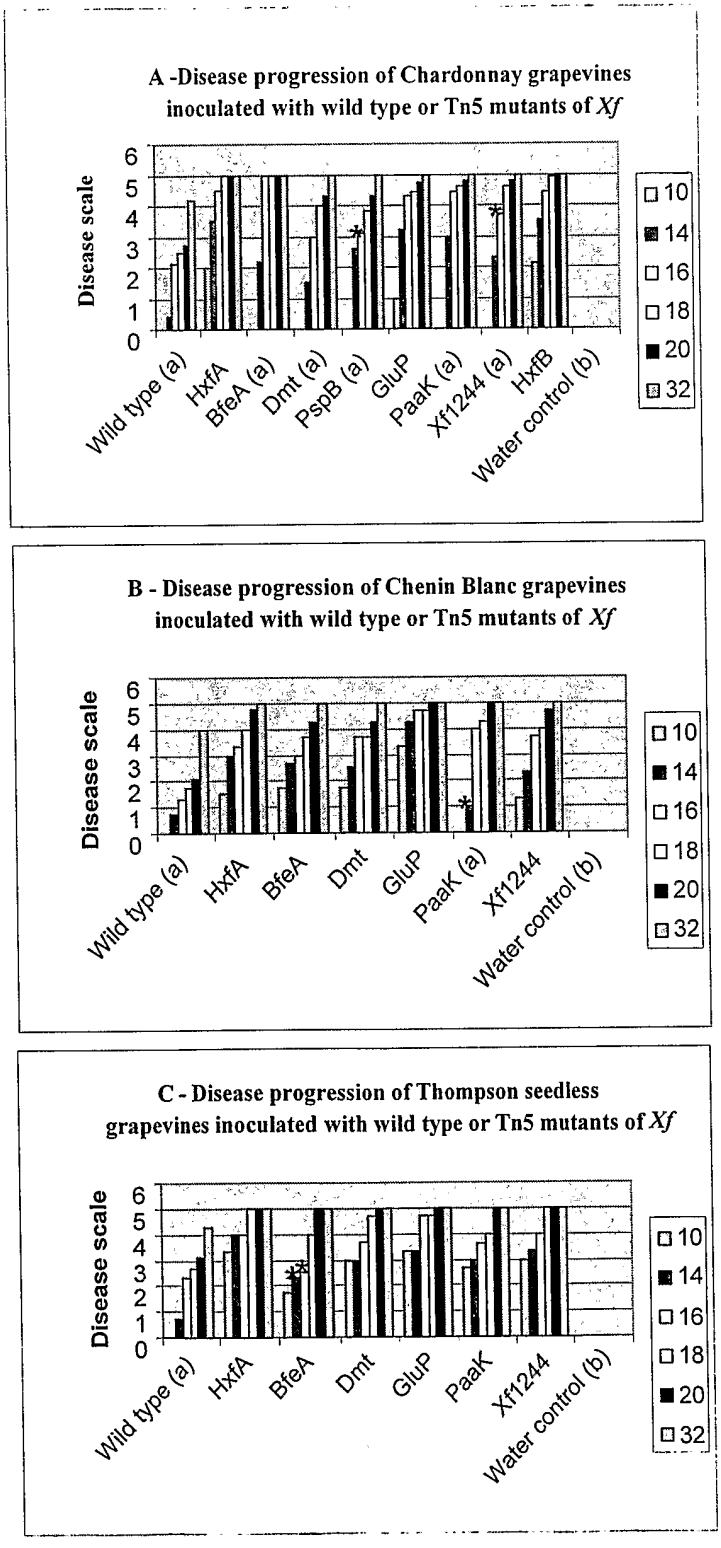

A -Disease progression of Chardonnay grapevines inoculated with wild type or Tn5 mutants of Xf
Disease scale
0
1
2
3
4
5
6
10
14
16
18
20
32
Wild type (a)
HxfA
BfeA (a)
Dmt (a)
PspB (a)
GluP
PaaK (a)
Xf1244 (a)
HxfB
Water control (b)
B - Disease progression of Chenin Blanc grapevines inoculated with wild type or Tn5 mutants of Xf
Disease scale
Wild type (a)
HxfA
BfeA
Dmt
GluP
PaaK (a)
Xf1244
Water control (b)
C - Disease progression of Thompson seedless grapevines inoculated with wild type or Tn5 mutants of Xf
Disease scale
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HxfA
BfeA
Dmt
GluP
PaaK
Xf1244
Water control (b)

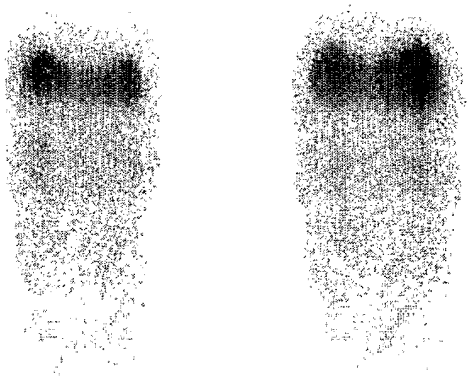
Figure 3

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*HxfB (PD1792) LTLGWVTITGIATAQVVADPHAPGQQRPTVLAAPNG---------TPLINIQTPSPAGVSR 105
      *PD1246 LSLGWVSITGMATAQVVADPHAPGQQRPTILTAPNG---------APLINIQTPSPAGVSR 105
*HxfA (PD2118) LTLGWVTITGIATAQVVADPHAPGQQRPTVLAAPNG---------TPLINIQTPSPAGVSR  87
   *HecA ALVWLTGLQPVLPAWAAGVTVASGN--TALEAAGNG---------VPVVNIATPDASGLSH  80
      PD0988 ALDHYRVQGGAIQIDGLGLDSHSTDYTALIARTVQLN---------AGLWAHTLQTTTGPAT  97
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                PD2110 GRLEEEKVRAKWREISAR-QDKLTADGLLKGLKESGISNINGLEHLILHPVDVFHELEKI 179
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      *PD1246 NTYQQFDITPQGAILNN--ARTPTQT-HLAGTVQGNPWLAAGTAKIILNEVNS--------- 155
*HxfA (PD2118) NTYQQFDITPQGAILNN--ARTPTQT-HLAGTVQGNPWLAAGTAKIILNEVNS--------- 137
   *HecA NRYHDFNVDNRGLILNNG-TARLTPS-QLGGLIQNNPNLNGRAAAAILNEVVS--------- 131
      PD0988 VALDGHPTASLPAPPGDR-PTVALDVSALGGMYAGKITLIGTEHGLGVRNAGQLSATS-- 154
      PD0986 LEVLAYNPAAEGNRLNTTYQAYTKPTHQLGELVTAGIEKLLEITKIASPASRLKAAAAKE 176

                                                  NPYGI CXXC
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                PD2110 LTHPKLLVQLGERAFQELLNKVSRMSEALIVGG--DQHAKQFGEDLGSVIADVGFALAAA 237 (SEQ ID NO: 2)
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      *PD1246 ----------PTSTQLHGTMEVAG--ARAQLIIANPSGITCNGCGVINAHQ 194 (SEQ ID NO: 4)
*HxfA (PD2118) ----------STPSQLHGSMEVAG--ARAQLIIANPSGITCNGCGVINAHQ 176 (SEQ ID NO: 5)
   *HecA ----------PNRSRLAGYLEVAG--QAANVVVANPYGITCSGCGFLNTPR 170 (SEQ ID NO: 6)
      PD0988 ----------APLTVTVDGLLENTGRLQSATDTQLNATAEVNNSGLISAAQT 196 (SEQ ID NO: 7)
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Figure 4



1 2

Figure 5

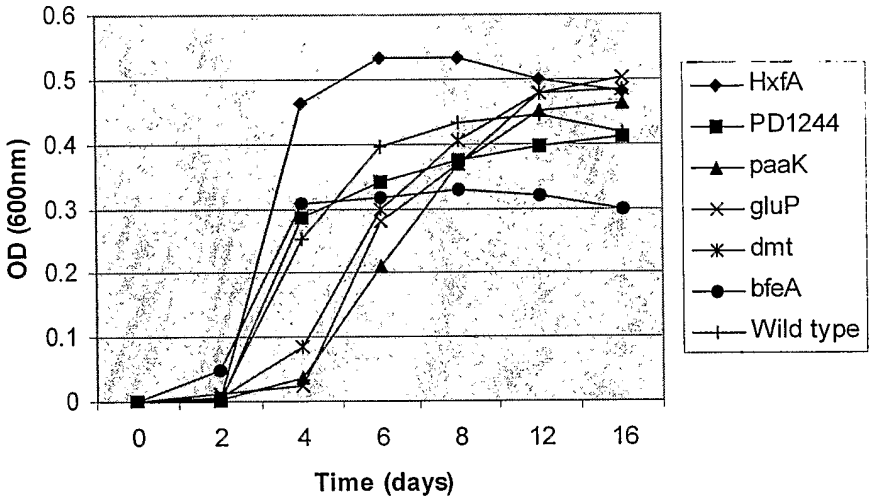

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0.4
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0.1
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OD (600nm)
0
2
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16
Time (days)
HxfA
PD1244
paaK
gluP
dmt
bfeA
Wild type

Figure 6

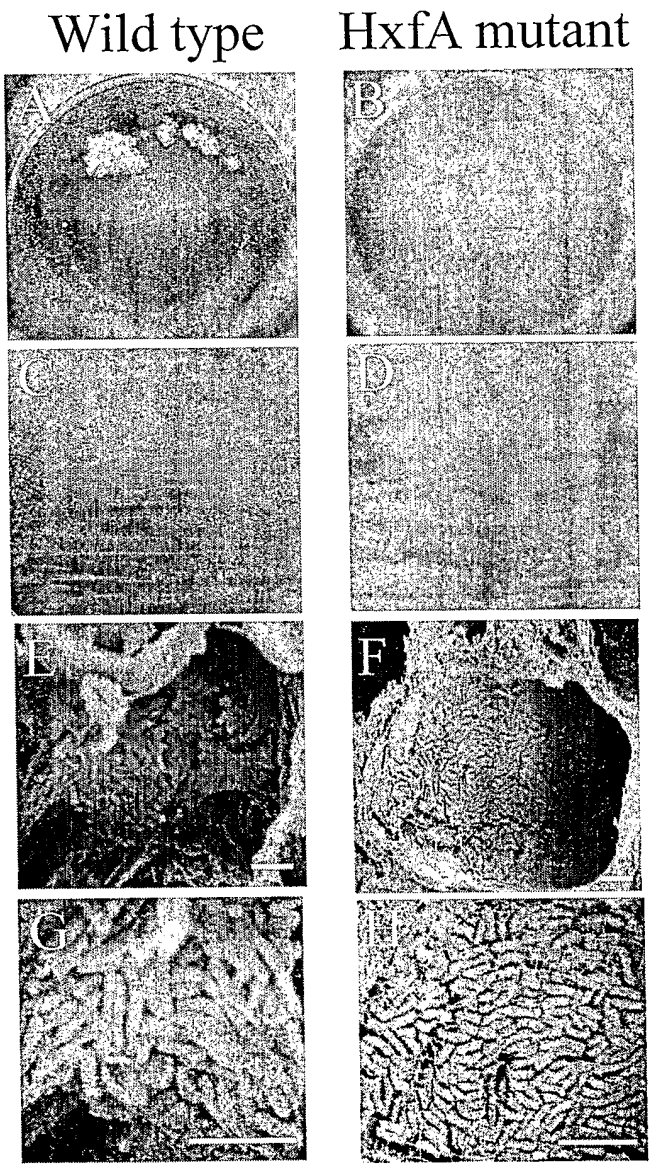
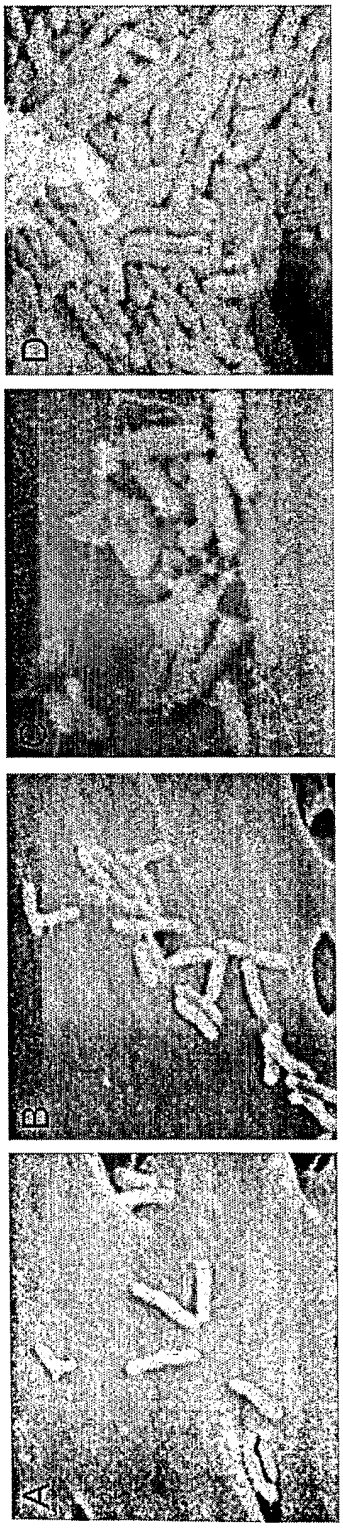


Figure 7



SEQUENCE LISTING

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        35                  40                  45
Phe Ser Asp Pro Arg Pro Glu Asp Thr Ala Gln Asp Arg Glu Ala Lys
    50                  55                  60
Arg Asn Leu Ile Thr Ser Ile Val Thr Gly Ile Ala Ser Thr Thr His
65                  70                  75                  80
Thr Asp Ala Ala Thr Ala Thr His Ala Ala Ile Ala Ala Val Asp Asn
                85                  90                  95
Asn Trp Leu Ala Ala Lys Gln Tyr Val Gln Met Val Ser Glu Glu Leu
            100                 105                 110
Glu Ala Ala Thr Glu Lys Asp Lys Gly Arg Leu Glu Glu Glu Lys Val
        115                 120                 125
Arg Ala Lys Trp Arg Glu Ile Ser Ala Arg Gln Asp Lys Leu Thr Ala
    130                 135                 140
Asp Gly Leu Leu Lys Gly Leu Lys Glu Ser Gly Ile Ser Asn Ile Asn
145                 150                 155                 160
Gly Leu Glu His Leu Ile Leu His Pro Val Asp Val Phe His Glu Leu
                165                 170                 175
Glu Lys Ile Leu Thr His Pro Lys Leu Leu Val Gln Leu Gly Glu Arg
            180                 185                 190
Ala Val Gln Asp Leu Leu Asn Lys Val Ser Arg Met Ala Glu Ala Leu
        195                 200                 205
Tyr Val Gly Gly Asp Gln His Ala Lys Gln Phe Gly Glu Asp Leu Gly
    210                 215                 220
Ser Val Ile Ala Asp Val Gly Phe Ala Leu Ala Ala Ala Gly Thr Val
225                 230                 235                 240
Lys Ala Gly Glu Ile Leu Ala Glu Ala Gly Ile Asn Leu Ser Lys Asp
                245                 250                 255
Val Leu Glu Gly Met Ala Thr Ser Lys Ala Asn Lys Leu Ser Asn Val
            260                 265                 270
Asp Asp Ile Val Ser Ala Glu Gln Glu Ala Leu Thr Arg Ile Gly Asn
        275                 280                 285
```

```
His Pro Asn Gly Pro Asp Leu Thr Gln Lys Pro Pro Gly Gln Phe Ile
    290                 295                 300
Ala Leu Gln Gln Glu Lys Arg Ile Glu Asp Val Lys Ser Val Val Gly
305                 310                 315                 320
Arg Arg Ser Pro Lys Asn Glu Leu Val Val Asp Arg Ile Lys Ile Glu
                325                 330                 335
Tyr Ile Pro Tyr Asp Pro Leu Val Lys Gly Gly Ser Asn Lys Ala Gly
            340                 345                 350
Asn Val Arg Val Phe Lys Ser Glu Ala Leu Thr Asp Lys Gln Ile Met
        355                 360                 365
Asn Tyr Ala Gln Gln Leu Ala Gly Asp Val Pro Leu Lys Glu Thr Ser
    370                 375                 380
Lys Lys Gly Val Tyr Leu Ala Glu Leu Ser Asp Gly Thr Lys Val Thr
385                 390                 395                 400
Leu Arg Ser Val Ser Ser Ser Asp Gln Val Thr Lys Ala Arg Trp Thr
                405                 410                 415
Ile Asp Ile Ala Asn Asn Pro Ser Leu Arg Glu Ile Thr Lys Glu Lys
            420                 425                 430
Val Glu Leu Lys Phe Arg
        435
```

<210> 2
<211> 436
<212> PRT
<213> Xylella fastidiosa

<400> 2

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Met Ala Thr Gly Gln Leu Thr Glu Gly Ser Pro Leu His Ala Ala Leu
 1               5                  10                  15
His Ala Leu Leu Ala Cys Ala Gly Ala Gly Ala Ser Gln Gln Arg Cys
            20                  25                  30
Ser Ser Gly Ala Gln Gly Ala Ala Ala Ser Ser Val Leu Thr Gly Leu
        35                  40                  45
Phe Ser Asp Pro Arg Pro Glu Asp Thr Ala Gln Asp Arg Glu Ala Lys
    50                  55                  60
Arg Asn Leu Ile Thr Ser Ile Val Thr Gly Ile Ala Ser Thr Thr His
65                  70                  75                  80
Thr Asp Ala Ala Thr Ala Thr His Ala Ala Ile Ala Ala Val Asp Asn
                85                  90                  95
Asn Trp Leu Ala Ala Lys Gln Tyr Val Gln Met Val Ser Glu Glu Leu
            100                 105                 110
Glu Ala Ala Thr Glu Lys Asp Lys Gly Arg Leu Glu Glu Glu Lys Val
        115                 120                 125
Arg Ala Lys Trp Arg Glu Ile Ser Ala Arg Gln Asp Lys Leu Thr Ala
    130                 135                 140
Asp Gly Leu Leu Lys Gly Leu Lys Glu Ser Gly Ile Ser Asn Ile Asn
145                 150                 155                 160
Gly Leu Glu His Leu Ile Leu His Pro Val Asp Val Phe His Glu Leu
                165                 170                 175
Glu Lys Ile Leu Thr His Pro Lys Leu Leu Val Gln Leu Gly Glu Arg
            180                 185                 190
Ala Phe Gln Glu Leu Leu Asn Lys Val Ser Arg Met Ser Glu Ala Leu
        195                 200                 205
Ile Val Gly Gly Asp Gln His Ala Lys Gln Phe Gly Glu Asp Leu Gly
    210                 215                 220
Ser Val Ile Ala Asp Val Gly Phe Ala Leu Ala Ala Ala Gly Thr Val
225                 230                 235                 240
Lys Ala Gly Glu Ile Leu Ala Glu Ala Gly Ile Asn Leu Ser Lys Asp
                245                 250                 255
Val Leu Glu Gly Met Ala Thr Ser Lys Ala Asn Lys Leu Ser Asn Val
```

```
            260                 265                 270
Asp Asp Ile Val Ser Ala Glu Gln Glu Ala Leu Thr Arg Ile Gly Asn
        275                 280                 285
His Pro Asn Gly Pro Asp Val Thr Gln Lys Pro Pro Gly Gln Tyr Ile
    290                 295                 300
Ala Leu Gln Gln Gly Ala Phe Asn Lys Ala Ile Ala Leu Val Asp Lys
305                 310                 315                 320
Ser Asn Ser Ser Ser Glu Phe Val Phe Ser Gly Leu Lys Ala Lys Val
                325                 330                 335
Thr Pro Arg Gly Ser Val Gly Gly Ser Asn Lys Ala Gly Asn Val Lys
            340                 345                 350
Val Leu Glu Ser Glu Ala Phe Ser Asp Gln Lys Ile Arg Glu Phe Ala
        355                 360                 365
Gln Gln Leu Ala Gly Asp Val Pro Leu Lys Glu Thr Arg Thr Pro Gly
    370                 375                 380
Val Tyr Ala Ala Lys Leu Ser Asp Gly Ser Trp Val Arg Leu Arg Ser
385                 390                 395                 400
Val Ser Ser Ser Asn Asn Glu Thr Lys Ala Arg Trp Thr Ile Asp Ile
                405                 410                 415
Glu Lys Asn Pro Thr Leu Met Glu Leu Thr Lys Thr Glu Lys Phe Glu
            420                 425                 430
Ile Lys Phe Arg
        435
```

<210> 3
<211> 3377
<212> PRT
<213> Xylella fastidiosa

<400> 3

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Met Asn Lys Asp Leu Tyr Arg Leu Ile Tyr Asn Arg Ala Leu Arg Leu
 1               5                  10                  15
Trp Gln Val Ala Ser Glu Arg Thr Thr Ala Pro Gly Gly Thr Ser Asp
            20                  25                  30
Pro Ser Pro Thr Ala Gln Pro Pro Ala Arg Ala Cys Leu His Pro Ile
        35                  40                  45
Pro Phe Ala Leu Trp Leu Thr Leu Gly Trp Val Thr Ile Thr Gly Ile
    50                  55                  60
Ala Thr Ala Gln Val Val Ala Asp Pro His Ala Pro Gly Gln Gln Arg
65                  70                  75                  80
Pro Thr Val Leu Ala Ala Pro Asn Gly Thr Pro Leu Ile Asn Ile Gln
                85                  90                  95
Thr Pro Ser Pro Ala Gly Val Ser Arg Asn Thr Tyr Gln Gln Phe Asp
            100                 105                 110
Ile Thr Pro Gln Gly Ala Ile Leu Asn Asn Ala Arg Thr Pro Thr Gln
        115                 120                 125
Thr His Leu Ala Gly Thr Val Gln Gly Asn Pro Trp Leu Ala Ala Gly
    130                 135                 140
Thr Ala Lys Ile Ile Leu Asn Glu Val Asn Ser Pro Thr Ser Thr Gln
145                 150                 155                 160
Leu His Gly Thr Met Glu Val Ala Gly Ala Arg Ala Gln Leu Ile Ile
                165                 170                 175
Ala Asn Pro Ser Gly Ile Thr Cys Asn Gly Cys Gly Val Ile Asn Ala
            180                 185                 190
His Gln Leu Thr Leu Thr Thr Gly Thr Pro Ile Phe Asn Ala Arg Gly
        195                 200                 205
Ala Leu Asp His Tyr Arg Val Gln Gly Gly Ala Ile Gln Ile Asp Gly
    210                 215                 220
Leu Gly Leu Asp Ser His Ser Thr Asp Tyr Thr Ala Leu Ile Ala Arg
225                 230                 235                 240
```

```
Thr Val Gln Leu Asn Ala Gly Leu Trp Ala His Thr Leu Gln Thr Thr
                245                 250                 255
Thr Gly Pro Ala Thr Val Ala Leu Asp Gly His Pro Thr Ala Ser Leu
            260                 265                 270
Pro Ala Pro Pro Gly Asp Arg Pro Thr Val Ala Leu Asp Val Ser Ala
        275                 280                 285
Leu Gly Gly Met Tyr Ala Gly Lys Ile Thr Leu Ile Gly Thr Glu His
    290                 295                 300
Gly Leu Gly Val Arg Asn Ala Gly Gln Leu Ser Ala Thr Ser Ala Pro
305                 310                 315                 320
Leu Thr Val Thr Val Asp Gly Leu Leu Glu Asn Thr Gly Arg Leu Gln
                325                 330                 335
Ser Ala Thr Asp Thr Gln Leu Asn Ala Thr Ala Gln Val Thr Asn Ser
            340                 345                 350
Gly Leu Ile Ser Ala Ala Gln Thr Leu Thr Leu His Thr Pro Thr Thr
        355                 360                 365
Ile Asp Asn Arg Ser Gly Thr Leu Asn Ala Ala Arg Leu Asp Ile Thr
    370                 375                 380
Gly Thr Arg Leu Asp Asn Arg Gly Gly His Ile Gln Gln Thr Gly Leu
385                 390                 395                 400
Gln Pro Leu Thr Leu Gln Thr Gln His Leu Asp Asn Gln Asp Gln Gly
                405                 410                 415
Arg Leu Gly Val Leu Asp Thr Pro Ala Pro Ala Thr Pro Ala Thr Pro
            420                 425                 430
Thr Val Thr Ala Pro Ile Ser Asn Ala Pro Pro Thr Val Thr Ala Pro
        435                 440                 445
Pro Ala Thr Asp Pro Thr Thr Ser Pro Val Ala Pro Thr Val Pro His
    450                 455                 460
Leu Ala His Gly Thr Leu Thr Leu Thr Gln Thr Ile Asp Asn Arg Gly
465                 470                 475                 480
Gly His Ile Thr Ala Gly Gly Pro Ile Asp Ala Ile Leu Thr Asp Leu
                485                 490                 495
Asp Asn Arg Asp Gly Thr Ala Ala Leu Asn Arg Leu Thr Leu Gln Gly
            500                 505                 510
Gln Arg Leu Asp Asn Gln His Gly Ile Leu Thr Leu Ala Thr Asp Ala
        515                 520                 525
Thr Ile His Thr His Thr Leu Asn Asn Thr Ala Gly Gln Leu His Ala
    530                 535                 540
Asn Gly Thr Leu Asp Leu Thr Ala Gln Arg Phe Ser Asn Gln Asn Gly
545                 550                 555                 560
Gln Leu Leu His Thr Gly Ser Gln Asn Ala Thr Leu Thr Ile Thr Asp
                565                 570                 575
Leu Leu Asp Asn Gln His Gly Leu Val Ala Ser Ala Ala Asn Ala Leu
            580                 585                 590
Thr Leu His Thr Asp His Leu Asn Asn Asp Ala Gly Gln Phe Gln Thr
        595                 600                 605
Asn Gly Ala Leu Asp Leu Thr Ala Gln Arg Phe Ser Asn Gln His Gly
    610                 615                 620
Gln Phe Leu His Asn Ser Pro Gln Ser Ala His Leu Arg Ile Asp Gly
625                 630                 635                 640
Gln Leu Asp Asn Gln Gln Gly Val Leu Ala Ser Asn Ala Ala Glu Leu
                645                 650                 655
Thr Leu Glu Thr Gly Gln Phe Asn Asn Asp Ser Gly Thr Leu Gln Gln
            660                 665                 670
Ser Gly Gln Gly Thr Leu His Ile Asp Ala Ala Thr Leu Thr Gly His
        675                 680                 685
Gly Gly Thr Leu Thr Ser Gln Gly Ala Leu Thr Leu Thr Gly Thr His
    690                 695                 700
Thr Asp Leu Ser His Ala Thr Thr Thr Ala Gln His Ile Thr Ile His
705                 710                 715                 720
Thr Asp Asp Leu Thr Thr Ala Gly Gly His Leu Thr Ala Tyr Gly Glu
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                725                 730                 735
His Thr Leu Gln Leu Asn Ala Arg Thr Arg Ile Asp Asn Thr Ala Gly
            740                 745                 750
Thr Ile Ala Thr Asn Gly Ser Leu Asp Leu His Thr Ala Ala Leu Asp
        755                 760                 765
Asn Thr Gly Gly Thr Leu His Ser Thr Ala Thr Gly Pro Asn Arg Leu
    770                 775                 780
Asp Ile Thr His Thr Leu Thr Asn Thr Ala Gly His Leu Leu Leu Asn
785                 790                 795                 800
Gly Pro Thr Thr Leu Thr Thr Gly Thr Trp Thr Asn Thr Gly Gly Gln
                805                 810                 815
Leu Gln Ile Thr Gly Pro Ala Thr Leu His Ala Thr Thr Leu Asp Asn
            820                 825                 830
Arg Gly Gly Ile Leu His Thr Ala Thr Gly Pro Leu Asp Leu Arg Val
        835                 840                 845
Thr Gly Thr Ile Asn Asn Gln Asp Asn Gly Ile Leu Ser Ser Thr Ala
    850                 855                 860
Ala Leu Thr Leu Thr Ala Ala Ser Leu His Asn Gln His Gly Thr Leu
865                 870                 875                 880
Asp Ala Ala Gly Pro Ala His Leu Thr Leu Thr Gly Leu Leu Asp Asn
                885                 890                 895
Thr Ala Gly Leu Leu Gln Thr Ala His Thr Leu Trp Leu Thr Ser Ala
            900                 905                 910
Gly Leu Thr Asn Arg Ser Gly Thr Leu Thr Ala Ala Ala Leu Thr Leu
        915                 920                 925
Asp Thr Gln Ala His Thr Leu Asp Asn Thr Ser Gly Arg Leu Gly Thr
    930                 935                 940
Thr Thr Gly Asn Leu Thr Leu His Thr Gly Leu Leu Asp Asn Thr Ala
945                 950                 955                 960
Gly Leu Leu Gln Thr Ala Ala Thr Leu Thr Ile Asp Thr Gly Ala Ala
                965                 970                 975
Pro Leu Thr Asn Arg Asp Gly Gly Thr Leu Leu Ala Ala Asp Thr Leu
            980                 985                 990
Asp Leu His Thr Thr Thr Leu Asp Asn Arg Gly Gly Thr Ile Asp Ser
        995                 1000                1005
Gln Thr Ala Thr His Leu His Thr Thr Thr Ile Asp Asn Thr Thr Ala
    1010                1015                1020
Gly His Ile Ser Ser Asn Gly Thr Leu Gln Ile Asp Gly Thr Thr Leu
1025                1030                1035                1040
Thr Asn Thr Gly Gly Arg Leu His Ser Gly Gly Asp Thr Arg Leu His
                1045                1050                1055
Leu Gln Asp Thr Leu Asn Asn His Asp Gly Arg Ile Thr Ala Ala Gly
            1060                1065                1070
Thr Leu Asp Ile Thr Thr Thr Thr Leu Asp Asn His Ser Thr Pro Leu
        1075                1080                1085
Thr Ala Pro Pro Ala Thr Gln Thr Arg Ala Pro Thr Gly Ala Pro Asp
    1090                1095                1100
Asn Gly Leu Tyr Ala Thr His Ile Gln Ile Ala Ser Thr Thr Leu Asp
1105                1110                1115                1120
Asn Thr Ala Gly Thr Leu Ser Ala Ala Gln Asn Leu Thr Leu Thr Leu
                1125                1130                1135
Ser Asp Thr Leu Thr Asn Thr Ala Gly His Leu Ser Ala Gly Ala Thr
            1140                1145                1150
Leu Asp Leu Thr Ala Asp His Leu Ser Asn His Thr Gly Thr Leu Leu
        1155                1160                1165
Ser Gly Ala Ser Gln Thr Leu His Leu His Arg Leu Thr Gly Asp Gly
    1170                1175                1180
Arg Leu His Ala Gly Asn Ala Leu Thr Leu Thr Leu Gln Asp Ser Leu
1185                1190                1195                1200
Asp Thr Ala Gly Thr Leu Ser Ala Thr Gly Leu Leu Thr Leu Thr Thr
                1205                1210                1215
```

Ala Gly Asp Leu Thr Asn Arg Gly Leu Ile Gln Ala Ala Asp Leu Thr
1220 1225 1230
Ala Arg Ala Arg Asp Ile Thr Thr Thr Ala Thr Gly Gln Leu Leu Ala
1235 1240 1245
Thr Gly His Thr Gln Leu Thr Ala Thr Gly Thr Leu Asn Asn Ser Gly
1250 1255 1260
His Leu Gln Ala Ala Asp Leu Thr Ala Gln Ala Arg Asp Ile Thr Thr
1265 1270 1275 1280
Thr Ala Thr Gly Gln Leu Leu Thr Thr Gly His Thr His Leu Thr Ala
1285 1290 1295
Thr Gly Thr Leu Thr Asn Ser Gly Leu Leu Gln Ala Pro Asp Leu Thr
1300 1305 1310
Ala Gln Ala Asn Thr Ile Thr Thr Thr Ala Thr Gly Arg Leu Leu Thr
1315 1320 1325
Ser Gly His Ala Gln Leu Thr Ala Thr Asp Thr Leu Thr Asn Ser Gly
1330 1335 1340
Leu Ala Gln Ala Gly Asp Leu Thr Val His Ala Arg Asp Ile Thr Asn
1345 1350 1355 1360
Thr Ala Thr Gly Gln Leu Ile Ala Asn Asn Leu Ala His Leu Thr Ala
1365 1370 1375
Thr Gly Thr Leu Thr Asn Arg Gly Leu Ile Asp Ala Phe Thr Thr His
1380 1385 1390
Leu Ser Ala Ala Thr Ile Asp Asn Leu Gly Thr Gly Arg Leu Tyr Gly
1395 1400 1405
Asp His Ile Ala Leu Gln Ala Gln Thr Leu Thr Asn Arg Asp Glu Thr
1410 1415 1420
Ser Asp Gly His Thr His Thr Ala Thr Ile Ala Ala Arg Gln Arg Leu
1425 1430 1435 1440
Asp Ile Gly Ala Asp Thr Leu Arg Asn Thr Ala Asn Ala Met Ile Leu
1445 1450 1455
Ser Asp Gly Asp Ala Ala Ile Gly Ala Thr Leu Asp Asn Ala Leu His
1460 1465 1470
Ala Thr Gly Ile Ala Ala Leu Leu Asp Asn Arg Ser Ala Thr Ile Asp
1475 1480 1485
Ile Thr Gly Asn Leu Asn Ile Thr Thr Thr Thr Leu Asn Asn Ile Arg
1490 1495 1500
Glu Asn Val His Ile Ala His Ala Pro Asp Val Val Thr Glu Ala Arg
1505 1510 1515 1520
Leu Glu Gln Pro His Trp Arg Lys Asn Gln Pro Asn Gly Gly Ser Gly
1525 1530 1535
Asp Phe Arg Leu Ser Ser Asn Tyr Asp Ala His Glu Ile Tyr Tyr Leu
1540 1545 1550
Asn Pro Ala Asp Ile Leu Lys Asp Glu Pro Tyr Ile Thr Pro Asp Gly
1555 1560 1565
Gln Gln Ile Arg Arg Ala Ile Val Arg Leu Thr Pro Gln Thr Ser Ala
1570 1575 1580
Tyr Phe Tyr Ala Arg Gly Gly Leu Tyr Ala Ser Gln Ala Glu Arg Arg
1585 1590 1595 1600
Arg Met Asp Leu Thr Ala Arg Thr Gly Asp Ser Val Leu Leu Tyr Tyr
1605 1610 1615
Thr Asp Arg Gln Asp Lys Gln Pro Asn Pro Asp His Ser Ala Ala Ala
1620 1625 1630
Ala Thr Asn Asp Ser Ala Phe Ile Gly Leu Asp Thr Pro Gln Gln Asn
1635 1640 1645
Glu Arg Leu Gln Thr Val Pro Ile Thr Tyr Ala Pro Gly Asp Asp Arg
1650 1655 1660
Leu Thr Tyr Asp Pro Thr Tyr Gly Thr Cys Thr Asp Asp Cys Val Arg
1665 1670 1675 1680
Leu Val Thr Trp His Asp Tyr Thr Asp Pro Asp Arg Thr Leu Ile Asp
1685 1690 1695
Met His Arg Gly Pro Asn Asp Val Arg Asp Asn Glu Arg Tyr Arg Gln

1700 1705 1710

Ala Thr Lys Thr Thr Gln Gln Glu Ile Leu Asn Pro Asp Ala Gly Ala
1715 1720 1725
Ala Thr Leu Ile Gln Ser Gly Gly Thr Met Met Ile Gln Ala Ala Thr
1730 1735 1740
Leu Arg Asn His Tyr Ala Asp Leu Leu Ala Gly Gly Asp Gln Thr Ile
1745 1750 1755 1760
Val Gly Leu Pro Pro His Pro Pro Lys Asp Asn Pro Glu Asp Glu Gln
1765 1770 1775
Lys Tyr Thr Pro Ala Leu Leu Ile Asp Asn Arg Ala Leu Gln Leu Ser
1780 1785 1790
Arg Thr Asp Thr Phe Gln Asn Ile Ser Thr Thr Tyr Arg Gly Asp Thr
1795 1800 1805
His Thr Trp Ser Asn Glu Ser Arg Thr Thr Pro Thr Ala Leu Ile Gly
1810 1815 1820
Gly Arg Ile Thr Ser Gly Gly His Gln His Ile Ala Ala Gln Lys Val
1825 1830 1835 1840
Asn Asn Val Thr Asp Ser Thr His Thr Pro Glu Pro Ile Gln His Leu
1845 1850 1855
Thr Tyr Asn Pro Ser Thr Gln Thr Leu Ser Val Val Asn Gly Val Ile
1860 1865 1870
Thr Ile Thr Asp Asn Ser Pro Ser Leu His Thr Val Ser Leu Ala Asp
1875 1880 1885
Asn Gly Phe Ser His Gly Gln Glu Leu Thr Tyr Ile Pro Asp Gln Ser
1890 1895 1900
Ile Thr Thr Pro Asn Ala Pro Ile Arg Asp Pro Ala Ala Pro Pro Ala
1905 1910 1915 1920
Val Thr Val Thr Pro Thr Gly Pro Leu Thr Leu Pro Asn Asn Ser Leu
1925 1930 1935
Phe Thr Ile His Pro Asp Thr Thr Thr Leu Ile Thr Thr Asp Pro His
1940 1945 1950
Phe Thr Leu Gly Arg Pro Tyr Thr Ser Ala Asp Ser Gln Leu His Ala
1955 1960 1965
Leu Gly Asp His Asp Thr Leu His Lys Arg Leu Gly Asp Gly Tyr Tyr
1970 1975 1980
Glu Gln Arg Leu Ile Arg Glu Gln Ile Ala Gln Leu Thr Gly Arg Arg
1985 1990 1995 2000
Arg Leu Asp Gly Tyr Thr Asp Asp Asp His Gln Tyr Arg Ala Leu Leu
2005 2010 2015
Asp Ala Gly Val Thr Val Thr Lys His Tyr Gly Leu Arg Pro Gly Ile
2020 2025 2030
Ala Leu Ser Ala Asp Gln Leu Ala Gln Leu Thr Ser Asp Ile Val Trp
2035 2040 2045
Leu Val Gln Gln Asn Val Gln Leu Pro Asp Gly Thr Thr Thr Arg Ala
2050 2055 2060
Leu Val Pro Arg Leu Tyr Leu Arg Pro Arg Thr Gly Asp Leu Thr Gln
2065 2070 2075 2080
Asp Gly Ala Leu Met Ala Ala Ala Ser Thr Thr Ile Asn Ala His Thr
2085 2090 2095
Leu Thr Asn Thr Gly Thr Ile Glu Ala Arg His Leu Ile Asp Ile Asn
2100 2105 2110
Ala His Ile Met Asp Gln Gln Gly Gly Arg Leu Thr Ala Asp Ala Ile
2115 2120 2125
Asp Ile His Thr Thr Gly Asp Phe Thr Thr Leu Gly Gly Gln Phe Lys
2130 2135 2140
Ala Arg Asp Tyr Leu Asn Ile His Ala Gln Gly Asn Phe Val Ala Ser
2145 2150 2155 2160
Ser Thr Leu Arg Gln Ala Thr Thr Gln Gly Thr Arg His His Ser Leu
2165 2170 2175

Thr Ala Leu Asp Gln Gln Ala Ser Phe Glu Val Thr Gly Pro Asp Ala
2180 2185 2190
Thr Leu Gly Leu Ser Thr Asn Gln Ala Met Thr Gln Gln Ala Val Ala
2195 2200 2205
Ile Ser Asn Thr Gly Thr Asp Gly Tyr Thr Ser Leu Lys Ala Thr Gly
2210 2215 2220
Pro Leu His Leu Gly Thr Leu Asn Thr His Arg Ser Asp Thr Thr Gln
2225 2230 2235 2240
Trp Asp Pro Arg Asn Ser Arg His Ser Arg Ile Asp Thr Glu His Gly
2245 2250 2255
Thr Ser Ile Arg Thr Ala Gly Asp Ile Ser Ile Ser Ala Asp Ala Gly
2260 2265 2270
Ile Thr Gly Arg Ala Val Thr Leu Asp Ser Ser Ala Gly Asp Leu Thr
2275 2280 2285
Leu Thr Ser Arg His Gly Ala Val Thr Leu Leu Ala Gly Glu Ala Arg
2290 2295 2300
Leu Ser Asp Gln Gln Glu Arg Thr Ser Arg Arg Ser Gly Leu Leu Arg
2305 2310 2315 2320
Ser Ser Ser Ser His Ser Thr Ser Ser Ser Thr Asp Thr Val Ala Leu
2325 2330 2335
Ser Ser Val Leu Gly Gly Lys Asn Ile Thr Ile Ala Ala Ala Asp Thr
2340 2345 2350
Val His Ser Val Gly Thr Gln Phe Ile Ala Asp Gln Asp Val Thr Leu
2355 2360 2365
Phe Gly Thr Lys Gly Val Arg Leu Glu Ser Ala Gln Asn Thr His Ser
2370 2375 2380
Ser His Tyr Thr Leu Gln Gln Arg Asn Ser Gly Phe Ser Arg Ala Gly
2385 2390 2395 2400
Leu Gly Ile Ser Ile Gly Ser Ser Arg Ser Ser Glu Gln Gly Asp Thr
2405 2410 2415
Gln Ala Thr Ser Ser Val Ala Asn Thr Val Ala Ala Leu Asn Gly Asn
2420 2425 2430
Ile Thr Ile His Ser Ser Gln Gly Asn Val Asp Ala Ala Gly Ser Glu
2435 2440 2445
Leu Leu Ala Ala Gly Asn Leu Ser Ala Ser Gly Val Asn Val Asp Leu
2450 2455 2460
Gly Glu Val Tyr Asp Thr Leu Ser Thr His Glu Gln Gln Ser Ser Lys
2465 2470 2475 2480
Gln Ser Gly Leu Thr Ile Gly Phe Asn Ser Ala Leu Thr Ser Thr Ala
2485 2490 2495
Gln Gly Val Ser Ala Asp Leu Lys Asn Arg Arg Asn Ala Pro Thr Gly
2500 2505 2510
Arg Leu Ser Ser Leu Tyr Gly Trp Arg Ala Leu Ser Thr Ala Ala Ser
2515 2520 2525
Ala Gly Tyr Gln Ala Tyr Gly Glu Ile Asp Thr Leu Arg Lys Thr Ser
2530 2535 2540
Ser Leu Pro Ser Thr Phe Gln Ile Gly Val Ser Val Gly Thr Ser Ser
2545 2550 2555 2560
Ser Gln Ser Gln Ser Ser Met Ser Ala Arg Thr Ala Arg Gly Thr Gln
2565 2570 2575
Leu Arg Ala Gly Gly Asp Ile Ser Ile Thr Ala Phe Gly Val Tyr Glu
2580 2585 2590
Leu Asp Glu Lys Gly Asn Pro Thr Leu Lys Ala Gly Thr Gly Asn Ile
2595 2600 2605
Asn Ala Thr Ala Ala Gln Phe Ser Ser His Asn Leu Asn Leu Thr Ala
2610 2615 2620
Ala Gly Asn Leu Asp Ala His Ser Ala Gln Ser Thr Gln Glu Gln Thr
2625 2630 2635 2640
Ser Ser Gln Arg His Arg Ser Ala Ser Leu Gly Ala Lys Ile Gly Val
2645 2650 2655
Thr Gly Gly Gly Thr Ser Val Ser Ala Asp Val Ala Arg Gly Arg Gly

2660 2665 2670
Ser Ser Arg Gln Gln Ser Val Thr Gln Val Asp Thr Val Phe Thr Val
2675 2680 2685
Ala Asn His Ala Thr Ile Ser Val Gly Gly Asp Ala Thr Met Lys Gly
2690 2695 2700
Ala His Leu Asn Ala His Ser Ile Lys Ala Thr Ile Ala Gly Asn Leu
2705 2710 2715 2720
Asp Ile Thr Ser Leu Gln Asp Thr Leu Gln Ala Ser Ala Gln Gln Arg
2725 2730 2735
Gln Ser Ser Ile Gly Gly Thr Trp Val Ile Asn Gly Ala Gly Ser Thr
2740 2745 2750
Ala Thr Phe Ser Arg Asn Arg Gln Asp Ala Thr Gln Asp Tyr Ala Ser
2755 2760 2765
Val Arg Asn Gln Ser Gly Leu Phe Ala Gly Ala Gly Gly Tyr Asp Ile
2770 2775 2780
Thr Val Gly Gly His Ser Gln Phe Asn Gly Gly Ala Leu Thr Ser Thr
2785 2790 2795 2800
Ala Pro Gln Ala Leu Gln Ala Phe Ser Thr Asn Thr Ile Gly Tyr Thr
2805 2810 2815
Asp Ile His Asn His Asn Ser Ala Asn Ala Ser Ala Ser Gly Ile Thr
2820 2825 2830
Ile Gly Ser Asp Leu Val Ser Gly Leu Ser Lys Asn Asn Pro Asn Gly
2835 2840 2845
Thr Ala Asn Leu Gly Leu Ser Ile Tyr Ser Gly Leu Arg Ser Gly Ala
2850 2855 2860
Gly Gln Trp Met Ala Asn Ala Asp Arg Ser Val Asn Gln His Ser Thr
2865 2870 2875 2880
Thr Ala Ala Val Val Ser Ala Thr Asn Ile Gln Val Ser Asp Pro Gly
2885 2890 2895
Ser Ser Gly Ala Leu Ala Thr Leu Arg Arg Asp Pro Ile Gly Ala His
2900 2905 2910
Gln Ala Leu Ser Pro Thr Asp Leu Gly Ala Leu Gln Thr Asp Val Gln
2915 2920 2925
Gln Arg Ser Gln Gly Gly Ala Leu Leu Ala Asp Ile Gly Arg Thr Met
2930 2935 2940
Val Asp Gln Ser Ile Ser Asn Met Leu Thr Pro Thr Leu Asn Arg Val
2945 2950 2955 2960
Phe Cys Ile Gln Gln Pro Cys Thr Asn Asp His Val Ala Asn Asp Ala
2965 2970 2975
Leu Val Lys Glu Arg Thr Glu Ala Leu Arg Gln Ala His Pro Gly Trp
2980 2985 2990
Ser Asp Arg Lys Leu Arg Gln His Ala Val Ala Glu Leu Ala Leu Thr
2995 3000 3005
Asp His Asn Ala Asn Arg Val Leu Asp Gln Asp Lys Val Lys Glu Met
3010 3015 3020
Ile Ala Asn Lys Gly Glu Gly His Tyr Ser Leu Gln His Asp Leu Leu
3025 3030 3035 3040
Ala Ser Gly Arg Trp Gly Ile Ser Arg Gly Ile Gly Asn Val Gln Val
3045 3050 3055
Leu Pro Val Ser Leu Ala Asp Leu Ser Arg Leu Ser Asp Glu Glu Lys
3060 3065 3070
Lys His Val Thr Leu Tyr Gly Asn Gly Ile Ser Asn Asp Ile His Arg
3075 3080 3085
Ala Gly Glu Leu Ala Leu Gln Met Thr Pro Lys Asn Asp Asn Arg Gly
3090 3095 3100
Asp Ile Ala Asn Ser Gly Glu Thr Tyr Gln Asn Thr Thr Tyr Gln Ala
3105 3110 3115 3120
Tyr Thr Lys Pro Thr His Gln Leu Gly Glu Leu Val Thr Ala Gly Ile
3125 3130 3135
Glu Lys Leu Leu Glu Ile Thr Lys Ile Ala Ser Pro Ala Ser Arg Leu
3140 3145 3150

Lys Ala Ala Ala Ala Lys Glu Leu Met Tyr Asn Ala Glu Asp Lys Lys
3155 3160 3165
Tyr Thr Asn Pro Ile Tyr Leu Glu Gly His Ser Arg Gly Thr Met Lys
3170 3175 3180
Leu Ser Asn Ala Leu Arg Val Leu Ala Ala Asp His Val Phe Ser Asp
3185 3190 3195 3200
Thr Leu Glu Ile Arg Ala Tyr Asn Pro Ala Ala Glu Gly Asn Arg Leu
3205 3210 3215
Ala Glu Ala Ala Ala Leu Val Thr Lys Lys Pro Val Lys Thr Trp Ala
3220 3225 3230
Pro Pro Lys Asp Phe Val Ala Asn Lys Ile Gly Gly Tyr Ala Gly Asn
3235 3240 3245
Ala Thr Phe His Asp Leu Trp Glu Ile Phe Gln Thr Asn Tyr Ser Val
3250 3255 3260
His Ser Ser Gly Gly Thr Ala Ala Leu Gly Ser Asp Ser Asn His Val
3265 3270 3275 3280
Asn Ala Pro Glu Leu Phe Ser Tyr Glu Gly Leu Asp Ile Lys Asp Met
3285 3290 3295
Asn Ala Lys Arg Gln Gly Arg Thr Ile Gly Leu Leu Gln Gln Trp Gln
3300 3305 3310
Lys Thr Pro Ser Pro Glu Asn Pro Val Ala Thr Gln Leu Thr Gln Leu
3315 3320 3325
Gln Arg Leu Leu Trp Gln Ser Gly Gln Trp Gln Gln Gln Leu Asp Asn
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Thr Pro Gly Leu Leu Thr Arg Pro Thr Pro Thr Thr Pro Asp Ala Pro
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Tyr

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<212> PRT
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35 40 45
Pro Phe Ala Leu Trp Leu Ser Leu Gly Trp Val Ser Ile Thr Gly Met
50 55 60
Ala Thr Ala Gln Val Val Ala Asp Pro His Ala Pro Gly Gln Gln Arg
65 70 75 80
Pro Thr Ile Leu Thr Ala Pro Asn Gly Ala Pro Leu Ile Asn Ile Gln
85 90 95
Thr Pro Ser Pro Ala Gly Val Ser Arg Asn Thr Tyr Gln Gln Phe Asp
100 105 110
Ile Thr Pro Gln Gly Ala Ile Leu Asn Asn Ala Arg Thr Pro Thr Gln
115 120 125
Thr His Leu Ala Gly Thr Val Gln Gly Asn Pro Trp Leu Ala Ala Gly
130 135 140
Thr Ala Lys Ile Ile Leu Asn Glu Val Asn Ser Pro Thr Ser Thr Gln
145 150 155 160
Leu His Gly Thr Met Glu Val Ala Gly Ala Arg Ala Gln Leu Ile Ile
165 170 175
Ala Asn Pro Ser Gly Ile Thr Cys Asn Gly Cys Gly Val Ile Asn Ala

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            180                 185                 190
His Gln Leu Thr Leu Thr Thr Gly Thr Pro Ile Phe Asn Ala Arg Gly
        195                 200                 205
Ala Leu Asp His Tyr Arg Val Gln Gly Gly Ala Ile Gln Ile Asp Gly
    210                 215                 220
Leu Gly Leu Asp Ser His Ser Thr Asp Tyr Thr Ala Leu Ile Ala Arg
225                 230                 235                 240
Thr Val Gln Leu Asn Ala Gly Leu Trp Ala His Thr Leu Gln Thr Thr
                245                 250                 255
Thr Gly Pro Ala Thr Val Ala Leu Asp Gly His Pro Thr Ala Ser Leu
            260                 265                 270
Pro Ala Pro Pro Gly Asp Arg Pro Thr Val Ala Leu Asp Val Ser Ala
        275                 280                 285
Leu Gly Gly Met Tyr Ala Gly Lys Ile Thr Leu Ile Gly Thr Glu His
    290                 295                 300
Gly Leu Gly Val Arg Asn Ala Gly Gln Leu Ser Ala Thr Ser Ala Pro
305                 310                 315                 320
Leu Thr Val Thr Val Asp Gly Leu Leu Glu Asn Thr Gly Arg Leu Gln
                325                 330                 335
Ser Ala Thr Asp Thr Gln Leu Asn Ala Thr Ala Glu Val Asn Asn Ser
            340                 345                 350
Gly Leu Ile Ser Ala Ala Gln Thr Leu Thr Leu His Thr Pro Thr Thr
        355                 360                 365
Ile Asp Asn Arg Ser Gly Thr Leu Asn Ala Ala Arg Leu Asp Ile Thr
    370                 375                 380
Gly Ala Arg Leu Asp Asn Arg Gly Gly His Ile Gln Gln Thr Gly Leu
385                 390                 395                 400
Gln Pro Leu Thr Leu Gln Thr Gln His Leu Asp Asn Gln Asp Gln Gly
                405                 410                 415
Arg Leu Gly Val Leu Asp Thr Pro Ala Pro Ala Ser Pro Ala Thr Pro
            420                 425                 430
Thr Val Thr Ala Pro Ile Ser Asn Ala Pro Pro Thr Val Thr Ala Pro
        435                 440                 445
Pro Ala Thr Asp Pro Thr Thr Ser Pro Val Ala Pro Thr Val Pro His
    450                 455                 460
Leu Ala His Gly Thr Leu Thr Leu Thr Gln Thr Ile Asp Asn Arg Gly
465                 470                 475                 480
Gly His Ile Thr Ala Gly Gly Ala Ile Asp Ala Ile Leu Thr Asp Leu
                485                 490                 495
Asp Asn Arg Asp Gly Thr Ala Ala Leu Asn Arg Leu Thr Leu Gln Gly
            500                 505                 510
Gln Arg Leu Asp Asn Gln His Gly Ile Leu Thr Leu Ala Thr Asp Ala
        515                 520                 525
Thr Ile His Thr His Thr Leu Asn Asn Ala Ala Gly Gln Leu His Ala
    530                 535                 540
Asn Gly Thr Leu Asp Leu Thr Ala Asp Thr Phe Ser Asn Gln Asn Gly
545                 550                 555                 560
Gln Leu Leu His Thr Gly Ser Gln Asn Ala Thr Leu Thr Ile Thr Asp
                565                 570                 575
Leu Leu Asp Asn Gln His Gly Ile Ile Ala Ser Ala Ala Asn Leu Leu
            580                 585                 590
Thr Leu Lys Thr Asp His Leu Asn Asn Ala Ala Gly Gln Leu His Ala
        595                 600                 605
Asn Gly Ala Leu Asp Leu Thr Ala Gln Arg Phe Ser Asn Gln Asn Gly
    610                 615                 620
Gln Leu Leu His Thr Gly Ser Gln Asn Ala Thr Leu Thr Ile Ala Asn
625                 630                 635                 640
Leu Leu Asp Asn Gln His Gly Leu Val Ala Ser Ala Ala Asn Ala Leu
                645                 650                 655
Thr Leu His Thr Gly His Leu Asn Asn Asp Ala Gly Gln Phe Gln Thr
            660                 665                 670
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Asn Gly Ala Leu Asp Leu Thr Ala Gln Arg Phe Ser Asn Gln His Gly
675 680 685
Gln Phe Leu His Asn Ser Pro Gln Ser Ala His Leu Arg Ile Asp Gly
690 695 700
Gln Leu Asp Asn Gln Gln Gly Val Leu Ala Ser Asn Ala Ala Glu Leu
705 710 715 720
Thr Leu Glu Thr Gly Gln Phe Asn Asn Asp Ser Gly Thr Leu Gln Gln
725 730 735
Ser Gly Gln Gly Thr Leu His Ile Asp Ala Ala Thr Leu Thr Gly His
740 745 750
Gly Gly Thr Leu Thr Ser Gln Gly Ala Leu Thr Leu Thr Gly Thr His
755 760 765
Thr Asp Leu Ser His Ala Thr Thr Thr Ala Gln His Ile Thr Ile His
770 775 780
Thr Asp Asp Leu Thr Thr Ala Gly Gly His Leu Thr Ala Tyr Gly Glu
785 790 795 800
His Thr Leu Gln Leu Asn Ala Arg Thr Arg Ile Asp Asn Thr Ala Gly
805 810 815
Thr Ile Ala Thr Asn Gly Ser Leu Asp Leu His Thr Ala Ala Leu Asp
820 825 830
Asn Thr Gly Gly Thr Leu His Ser Thr Ala Thr Gly Pro Asn Arg Leu
835 840 845
Asp Ile Thr His Thr Leu Thr Asn Thr Ala Gly His Leu Leu Leu Asn
850 855 860
Gly Pro Thr Thr Leu Thr Thr Gly Thr Trp Thr Asn Thr Gly Gly Gln
865 870 875 880
Leu Gln Ile Thr Gly Pro Ala Thr Leu His Ala Thr Thr Leu Asp Asn
885 890 895
Arg Gly Gly Ile Leu His Thr Ala Thr Gly Pro Leu Asp Leu Arg Val
900 905 910
Thr Gly Thr Ile Asn Asn Gln Asp Asn Gly Ile Leu Ser Ser Thr Ala
915 920 925
Ala Leu Thr Leu Thr Ala Ala Ser Leu His Asn Gln His Gly Thr Leu
930 935 940
Asp Ala Ala Gly Pro Ala His Leu Thr Leu Thr Gly Leu Leu Asp Asn
945 950 955 960
Thr Ala Gly Leu Leu Gln Thr Ala His Thr Leu Trp Leu Thr Ser Ala
965 970 975
Gly Leu Thr Asn Arg Ser Gly Thr Leu Thr Ala Ala Ala Leu Thr Leu
980 985 990
Asp Thr Gln Ala His Thr Leu Asp Asn Thr Ser Gly Arg Leu Gly Thr
995 1000 1005
Thr Thr Gly Asn Leu Thr Leu His Thr Gly Leu Leu Asp Asn Thr Ala
1010 1015 1020
Gly Leu Leu Gln Thr Ala Ala Thr Leu Thr Ile Asp Thr Gly Ala Ala
1025 1030 1035 1040
Pro Leu Thr Asn Arg Asp Gly Gly Thr Leu Leu Ala Ala Asp Thr Leu
1045 1050 1055
Asp Leu His Thr Thr Thr Leu Asp Asn Arg Gly Gly Thr Ile Asp Ser
1060 1065 1070
Gln Thr Ala Thr His Leu His Thr Thr Thr Ile Asp Asn Thr Thr Ala
1075 1080 1085
Gly His Ile Ser Ser Asn Gly Thr Leu Gln Ile Asp Gly Thr Thr Leu
1090 1095 1100
Thr Asn Thr Gly Gly Arg Leu His Ser Gly Gly Asp Thr Arg Leu His
1105 1110 1115 1120
Leu Gln Asp Thr Leu Asn Asn His Asp Gly Arg Ile Thr Ala Ala Gly
1125 1130 1135
Thr Leu Asp Ile Thr Thr Thr Thr Leu Asp Asn His Ser Thr Pro Leu
1140 1145 1150
Thr Ala Pro Pro Ala Thr Gln Thr Arg Ala Pro Thr Gly Ala Pro Asp

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        1155                1160                1165
Asn Gly Leu Tyr Ala Thr His Ile Gln Ile Ala Ser Thr Thr Leu Asp
    1170                1175                1180
Asn Thr Ala Gly Thr Leu Ser Ala Ala Gln Asn Leu Thr Leu Thr Leu
1185                1190                1195                1200
Ser Asp Thr Leu Thr Asn Thr Ala Gly His Leu Ser Ala Gly Ala Thr
                1205                1210                1215
Leu Asp Leu Thr Ala Asp His Leu Ser Asn His Thr Gly Thr Leu Leu
            1220                1225                1230
Ser Gly Ala Ser Gln Thr Leu His Leu His Arg Leu Thr Gly Asp Gly
        1235                1240                1245
Arg Leu His Ala Gly Asn Ala Leu Thr Leu Thr Leu Gln Asp Ser Leu
    1250                1255                1260
Asp Thr Ala Gly Thr Leu Ser Ala Thr Gly Leu Leu Thr Leu Thr Thr
1265                1270                1275                1280
Ala Gly Asp Leu Thr Asn Arg Gly Leu Ile Gln Ala Ala Asp Leu Thr
                1285                1290                1295
Ala Gln Ala Arg Asp Ile Thr Thr Thr Ala Thr Gly Gln Leu Leu Thr
            1300                1305                1310
Thr Gly His Thr His Leu Thr Ala Thr Gly Thr Leu Asn Asn Ser Gly
        1315                1320                1325
His Leu Gln Ala Ala Asp Leu Thr Ala Gln Ala His Asp Ile Thr Thr
    1330                1335                1340
Thr Ala Thr Gly Gln Leu Leu Thr Thr Gly His Thr His Leu Thr Ala
1345                1350                1355                1360
Thr Gly Thr Leu Asn Asn Ser Gly His Leu Gln Ala Ala Asp Leu Thr
                1365                1370                1375
Ala Gln Ala Asn Thr Ile Thr Asn Thr Gly Thr Phe Leu Ala Thr Ser
            1380                1385                1390
His Ala Thr Leu Thr Ala Thr Asp Thr Leu Thr Asn Ser Gly Leu Leu
        1395                1400                1405
Gln Ala Ala Asp Leu Thr Ala Gln Ala Asn Thr Ile Thr Asn Thr Ala
    1410                1415                1420
Thr Gly Arg Leu Leu Thr Thr Ala His Thr Gln Leu Thr Ala Thr Asp
1425                1430                1435                1440
Thr Leu Thr Asn Ser Gly Leu Val His Ala Gly Asp Leu Thr Val His
                1445                1450                1455
Ala Arg Asp Ile Thr Asn Thr Ala Thr Gly Gln Leu Ile Ala Ser Asn
            1460                1465                1470
Leu Ala Gln Leu Thr Ala Thr Ala Thr Leu Thr Asn Arg Gly Leu Ile
        1475                1480                1485
Asp Ala Phe Thr Thr His Leu Ser Ala Pro Thr Ile Asp Asn Leu Gly
    1490                1495                1500
Thr Gly Arg Leu Tyr Gly Asp His Ile Ala Leu Gln Ala His Thr Leu
1505                1510                1515                1520
Thr Asn Arg Asp Glu Thr Ser Asp Gly His Thr His Thr Ala Thr Ile
                1525                1530                1535
Ala Ala Arg Glu Arg Leu Asp Ile Gly Ala Asp Thr Leu Arg Asn Thr
            1540                1545                1550
Ala Asn Ala Met Ile Leu Ser Asp Gly Asp Ala Ala Ile Gly Ala Thr
        1555                1560                1565
Leu Asp Asn Thr Leu His Ala Thr Gly Ile Ala Thr Leu Ile Asp Asn
    1570                1575                1580
Arg Ser Ala Thr Ile Asp Ile Thr Gly Thr Leu Asn Ile Thr Thr Thr
1585                1590                1595                1600
Thr Leu Asn Asn Ile Arg Glu Asn Val His Ile Ala His Ala Pro Asp
                1605                1610                1615
Val Val Thr Glu Thr Pro Met Tyr Gln Pro His Trp Arg Lys Asn Lys
            1620                1625                1630
Pro Asn Gly Gly Ser Gly Asp Phe Arg Leu Ser Ser Asn Tyr Asp Ala
        1635                1640                1645
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His Asp Ile Tyr Tyr Leu Asn Pro Ala Asp Ile Leu Glu Asp Thr Pro
1650 1655 1660
Tyr Ile Thr Pro Asp Gly Gln Lys Ile His Arg Ala Ile Val Arg Leu
1665 1670 1675 1680
Thr Pro Gln Thr Ser Ala Tyr Phe Tyr Ala Arg Gly Gly Leu His Ala
1685 1690 1695
Ser Gln Ala Glu Arg Arg Arg Leu Asp Leu Thr Ala Arg Thr Gly Asp
1700 1705 1710
Ser Val Val Leu Tyr Tyr Thr Asp Arg Gln Asp Lys Gln Pro Asn Pro
1715 1720 1725
Asp His Val Ala Ala Ala Ala Thr Asn Asp Ser Ala Phe Ile Gly Leu
1730 1735 1740
Asp Ala Pro Gln Gln Asn Glu Arg Leu Lys Ile Val Pro Ile Thr Tyr
1745 1750 1755 1760
Ala Pro Gly Asp Asp Arg Leu Thr Tyr Asp Pro Thr Tyr Gly Thr Cys
1765 1770 1775
Thr Asp Asp Cys Val Arg Leu Val Thr Trp His Asp Tyr Thr Asp Pro
1780 1785 1790
Asp His Thr Leu Ile Asp Met Arg Arg Gly Pro Asn Asp Val Asp Asp
1795 1800 1805
Asn Glu Arg Glu Arg His Ala Thr Arg Thr Thr Gln Gln Glu Ile Leu
1810 1815 1820
Asn Pro Asp Ala Gly Ala Pro Ala Leu Ile Gln Ser Gly Gly Thr Met
1825 1830 1835 1840
Arg Ile Asp Val Gly Tyr Leu Tyr Asn His Tyr Ala Asp Leu Leu Ala
1845 1850 1855
Gly Gly Asp Gln Thr Ile Val Gly Leu Pro Pro His Pro Thr Lys Glu
1860 1865 1870
Thr Ala Asp Asp Glu His Lys Tyr Asn Arg Ala Leu Leu Ile Asp Asn
1875 1880 1885
Arg Ala Leu Gln Leu Ser Arg Thr Asp Arg Phe Gln Asn Ile Ser Thr
1890 1895 1900
Thr Tyr Arg Gly Lys Asp Ser Ala Pro Trp Ser Asn Glu Ser Arg Thr
1905 1910 1915 1920
Thr Pro Thr Thr Gln Ile Gly Gly Arg Ile Thr Ser Gly Gly His Gln
1925 1930 1935
His Ile Ala Ala Gln Thr Phe Asn Asn Val Thr Asp Ser Thr His Ala
1940 1945 1950
Pro Glu Pro Ile Gln His Val Thr Tyr Asn Pro Ser Thr Gln Thr Leu
1955 1960 1965
Thr Ile Ala Asp Gly His Ile Thr Val Thr Asp Thr Pro Pro Ser Leu
1970 1975 1980

His Thr Val Ser Leu Ala Asp Asn Gly Phe Ser His Gly Gln Glu Leu
1985 1990 1995 2000
Thr Tyr Ile Pro Glu Lys Ser Ile Thr Thr Pro Asn Ala Pro Ile Arg
2005 2010 2015
Asp Pro Ala Ala Pro Pro Arg Arg His Arg His Pro His Arg Pro Pro
2020 2025 2030
His Pro Ala Gln Gln Gln Pro Leu His His Ser Pro Arg His Arg His
2035 2040 2045
Pro His His His Arg Pro Pro Leu Tyr Pro Arg Pro Pro Leu His Gln
2050 2055 2060
Arg Arg Gln Pro Thr Pro Arg Pro Gly Arg Pro Arg His Pro Pro Gln
2065 2070 2075 2080
Thr Pro Arg Arg Arg Leu Leu Arg Thr Thr Pro His Pro Arg Thr Asn
2085 2090 2095
Arg Pro Thr His Arg Pro Pro Pro Pro Gly Arg Leu His Arg Arg Arg
2100 2105 2110
Pro Pro Ile Pro Arg Pro Pro Gly Arg Arg Pro His Arg Arg Gln Thr
2115 2120 2125

Ala Pro Thr Ala Pro Arg His Cys Pro Gln Cys Arg Pro Asn Gly Pro
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Thr His Gln Arg His Arg Leu Ala Arg Pro Thr Arg Arg Pro Pro Ala
2145 2150 2155 2160
Arg Arg His His His Arg Arg Pro Arg Pro Pro Pro Leu Pro Ala Pro
2165 2170 2175
Pro His Arg Arg Pro His Pro Arg Arg Arg Pro Pro Gly Gly Arg Gln
2180 2185 2190
His His His Gln Arg Pro His Pro His Gln His Arg His His Arg Pro
2195 2200 2205
Arg Pro His Gln His Gln His Pro His His Gly Pro Thr Arg Arg Pro
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Pro Tyr Arg Arg Arg His Gln His Pro His His Arg Arg Leu His Gln
2225 2230 2235 2240
Pro Gly Arg Thr Ile His Arg Arg Arg Leu Pro Gln Ser Pro Cys Pro
2245 2250 2255
Arg Gln Leu Pro Cys Gln His Pro Pro Arg Arg His His Pro Arg His
2260 2265 2270
Pro Pro Pro Gln Arg Asp Arg Thr Gly Pro Thr Gly Arg Leu His Arg
2275 2280 2285
His Arg Pro Arg Cys Leu Pro Trp Leu Glu His Arg Pro Ser His Asp
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Pro Thr Ser Arg Cys His Gln Gln His Arg His Arg Leu His Leu Pro
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Gln Ser His Arg Pro Pro Thr Pro Arg His Pro Gln His Pro Pro Gln
2325 2330 2335
Arg His His Pro Val Gly Pro Pro Gln Gln Pro Pro Gln Pro His Arg
2340 2345 2350
His Arg Thr Arg His Gln His Pro Gln Arg Arg Arg His Pro Thr Gln
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Gln Arg Pro Arg His Gln Pro Ala Cys Arg His Pro Pro Gln His Pro
2370 2375 2380
Arg His Arg Gln Arg Pro Gly His Arg Gln Arg His His Tyr Ala Arg
2385 2390 2395 2400
Gly His Pro Pro Ile His Gln Pro Arg Pro Gln Gln Thr Gln Arg Pro
2405 2410 2415
Pro Gln Gln Pro His His His His Pro Arg Arg Pro Thr Thr Asp Pro
2420 2425 2430
Gly His Glu Gln His Pro Gln Arg His Ser Pro Arg Gln Arg Gln Gln
2435 2440 2445
His His Arg His Arg Gln Pro Pro Pro Phe Arg Cys Arg His Leu His
2450 2455 2460
Ala Gly Gln Arg Arg Pro His Pro Pro Ser Arg His Gln His His Pro
2465 2470 2475 2480
Ile His Leu Leu Arg Thr His Gln Thr Lys Trp Pro His Pro Gln Arg
2485 2490 2495
Arg Arg Leu Pro His Pro Gly Gln Pro Lys Pro Ala His Arg Gln His
2500 2505 2510
His His Ser His His His His Arg Leu Pro His Arg Arg His Gln Arg
2515 2520 2525
Gln Cys Asp Pro Ala Gly Gly Arg Pro Leu Pro Thr Asp Arg Gln Arg
2530 2535 2540
Arg Pro Val Pro Arg Arg His Arg His Pro Arg Gln Lys Ser Arg His
2545 2550 2555 2560
His Pro Ser Pro Pro His Gln Pro His His Pro Thr His Arg His Pro
2565 2570 2575
Pro Lys Arg Pro His Arg Arg Pro Gln His Pro Pro Asp Cys Arg Cys
2580 2585 2590
Pro Asp Arg Pro Ala Asn Ala Thr Arg Arg Arg Ser Gln Arg Arg Pro
2595 2600 2605

Pro Pro Pro Arg Pro Gly Arg Pro His His Arg Pro Gly Arg Gln Lys
2610 2615 2620
His His Cys Arg Ala Pro Arg Pro Pro Arg Pro Gly Arg Pro Gln Arg
2625 2630 2635 2640
Leu Pro His Pro Trp Pro Gln His Thr Arg Gln His His His Asp His
2645 2650 2655
His His His Arg Arg Arg Leu Gln Arg Gln Arg Arg Arg Arg Pro His
2660 2665 2670
Gln Arg His Arg Arg Arg Ser Leu His Pro His His Pro Arg Gln Pro
2675 2680 2685
Arg Pro Arg Arg Gln His Asp Leu Pro Gln Ser Arg Trp Arg His Arg
2690 2695 2700
Pro Thr Gly Arg Arg Gln His His His Gln Arg Pro Ser Lys Pro Arg
2705 2710 2715 2720
Pro Gln Arg Arg Cys Arg Arg Gly Arg Glu Pro Arg Leu Gln Arg His
2725 2730 2735
Gln Cys Arg Pro His Arg Pro Arg Gln His Leu His Arg Gln Arg Pro
2740 2745 2750
Val Tyr Arg Pro His Leu Asp Gln Gln Pro Arg Arg Arg Arg Gln Pro
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Thr Asp His Ser Arg Arg Arg Pro Pro His Glu Arg Arg His Trp His
2770 2775 2780
Arg Gln Thr Arg His Cys Arg His Cys Trp Gln Pro His His Pro Lys
2785 2790 2795 2800
Pro Pro Arg His Pro Pro Leu Pro Gln Gln Arg Pro Gln Pro Trp Arg
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Gln Pro His Arg Arg Arg Arg Arg Gln Arg Gln Arg Gln Pro Gln Gln
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Pro Asn His Pro Gln Arg Leu Arg Gln Arg His Arg Thr Lys Arg Pro
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Val Tyr Trp Arg Trp Arg Leu His His Arg Trp Arg Pro Asp Pro Pro
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Tyr Arg Arg Arg His His Leu Gln Gln His Arg His Pro Gln Arg Pro
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Glu His Pro Gly His Arg His Pro Asp Pro Ala Arg His Lys Pro Arg
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His Leu His Arg His Pro Ser Gln Pro Gly Arg Arg Leu Gln Pro Gln
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2930 2935 2940
Pro Ser Trp Arg His Asp Arg Gln Arg Gln Gln Pro Gln His His Leu
2945 2950 2955 2960
Gln Arg His Gln Pro Arg Arg Pro His His Pro Arg Pro Arg Arg Pro
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Thr Arg Pro His Arg Pro His Arg Arg Pro Asp His Arg Arg Pro Gln
2980 2985 2990
Pro Arg His Pro His Arg His Arg His Gln Gln Arg Pro His Pro His
2995 3000 3005
Leu Arg Thr Thr His Gln Arg Arg Leu His Arg His Arg Pro Thr Thr
3010 3015 3020
Gly Asn Arg His Leu His Gln Gln Pro Cys Arg Arg Ser Arg Ser Gln
3025 3030 3035 3040
Asn Pro Pro Ser His Arg Arg Arg Pro Ser Arg Thr Arg Pro His Gln
3045 3050 3055
Arg Ile Gln Pro Thr Ala Ala Asn Ile Thr Pro Ser His His Pro His
3060 3065 3070
Gln Arg Ser Pro Gly His Gln Arg Arg Leu Gly Thr Gly Arg His Leu
3075 3080 3085
Pro Pro Asn His His Arg Leu Ser Arg Arg Cys Gln Arg Gln Arg Gln

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Arg Cys Gln Gln Arg Pro Cys Gln Thr His Asp Arg Gln Leu Arg Pro
3105                3110                3115                3120
Thr Thr Arg Arg His Arg His Trp Pro Leu Gly Gly His Arg Pro Thr
                3125                3130                3135
Asp Arg Arg Gln Pro Pro Thr Arg Arg Pro Pro Cys Pro Ala Gly Leu
            3140                3145                3150
Arg Arg Cys Cys Gly Gln Pro Thr Thr Leu Gln Gln Trp Arg Pro Arg
        3155                3160                3165
Arg Arg Arg Leu Gln Arg Pro His Gly Ile Ile Arg Pro Pro Pro Arg
    3170                3175                3180
Arg His Arg Pro Arg Pro Arg Ser Gln Thr Gln Pro His Tyr Leu His
3185                3190                3195                3200
Arg His Arg His Arg Gln His His Ala His Arg Cys Gly His Arg His
                3205                3210                3215
Pro Cys Arg His Arg Cys Arg Gly Gln Leu Val Gly Gly Gln Thr Ile
            3220                3225                3230
Arg Ser Asn Gly Lys Arg Gly Ala Gly Arg Tyr Gly Glu Arg Gln Arg
        3235                3240                3245
Ser Leu Gly Arg Gly Glu Ser Lys Ser Glu Val Ala Asp Gln Cys Pro
    3250                3255                3260
Pro Arg Thr His Cys Trp Thr Leu Lys Arg Leu Lys Gly Val Arg His
3265                3270                3275                3280
Gln Gln Tyr Gln Arg Ala Gly Ala Leu Asp Pro Ala Ser Gly Gly Cys
                3285                3290                3295
Leu Ser Val Gly Glu Asn Pro Tyr Pro Pro Lys Ile Thr Gly Ala Ile
            3300                3305                3310
Arg Ala Arg Arg Ser Arg Thr Ala Gln Gly Phe Ser His Val Gly Ser
        3315                3320                3325
Ser His Cys Trp Arg Arg Ser Thr Cys Gln Ala Val Trp Arg Arg Ser
    3330                3335                3340
Arg Leu Ser Asp Arg Gly Cys Arg Leu Cys Ile Gly Cys Gly Arg His
3345                3350                3355                3360
Arg Gln Ser Gly Arg Asp Pro Arg Arg Ser Arg His Gln Ser Gln Arg
                3365                3370                3375
Cys Leu Gly Gly Asp Gly Tyr Phe Gln Ser Gln Ala Val Gln Arg His
            3380                3385                3390
Cys Gln Arg Arg Thr Arg Ser Thr Asp Ala Asp Arg Ser Pro Gln Arg
        3395                3400                3405
Pro Gly Phe Asn Pro Lys Thr Ala Trp Ser Ile His Arg Val Ala Ala
    3410                3415                3420
Gly Gly Ile Ser Asn Ser Leu Ser Lys Leu Lys Arg Ile Cys Phe Phe
3425                3430                3435                3440
Gly Phe Lys Ser Gln Ser His Thr Ala Arg Leu Cys Arg Arg Glu Ser
                3445                3450                3455
Gly Cys Glu Gly Ala Ile Arg Ser Ile Gln Ser Glu Asn Gln Arg Val
            3460                3465                3470
Cys Thr Ala Ile Gly Gly Gly Cys Ala Phe Lys Gly Asp Glu Gln Lys
        3475                3480                3485
Met
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<212> PRT
<213> Xylella fastidiosa

<400> 5

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Ala Leu Trp Leu Thr Leu Gly Trp Val Thr Ile Thr Gly Ile Ala Thr
35 40 45
Ala Gln Val Val Ala Asp Pro His Ala Pro Gly Gln Gln Arg Pro Thr
50 55 60
Val Leu Ala Ala Pro Asn Gly Thr Pro Leu Ile Asn Ile Gln Thr Pro
65 70 75 80
Ser Pro Ala Gly Val Ser Arg Asn Thr Tyr Gln Gln Phe Asp Ile Thr
85 90 95
Pro Gln Gly Ala Ile Leu Asn Asn Ala Arg Thr Pro Thr Gln Thr His
100 105 110
Leu Ala Gly Thr Val Gln Gly Asn Pro Trp Leu Ala Ala Gly Thr Ala
115 120 125
Lys Ile Ile Leu Asn Glu Val Asn Ser Ser Thr Pro Ser Gln Leu His
130 135 140
Gly Ser Met Glu Val Ala Gly Ala Arg Ala Gln Leu Ile Ile Ala Asn
145 150 155 160
Pro Ser Gly Ile Thr Cys Asn Gly Cys Gly Val Ile Asn Ala His Gln
165 170 175
Leu Thr Leu Thr Thr Gly Thr Pro Ile Phe Asn Ala Arg Gly Ala Leu
180 185 190
Asp His Tyr Arg Val Gln Gly Gly Ala Ile Gln Ile Asp Gly Leu Gly
195 200 205
Leu Asp Ser Arg Ser Ala Asp Tyr Thr Ala Leu Ile Ala Arg Thr Val
210 215 220
Gln Leu Asn Ala Gly Leu Trp Ala His Thr Leu Gln Thr Thr Thr Gly
225 230 235 240
Pro Ala Thr Val Ala Leu Asp Gly His Pro Thr Ala Ser Leu Pro Val
245 250 255
Thr Pro Gly Asp Arg Pro Thr Val Ala Leu Asp Val Ser Ala Leu Gly
260 265 270
Gly Met Tyr Ala Gly Lys Ile Thr Leu Ile Gly Thr Glu His Gly Leu
275 280 285
Gly Val Arg Asn Ala Gly Gln Leu Ser Ala Thr Ser Ala Pro Leu Thr
290 295 300
Val Thr Val Asp Gly Leu Leu Glu Asn Thr Gly Arg Leu Gln Ser Ala
305 310 315 320
Thr Asp Thr Gln Leu Asn Ala Thr Ala Glu Val Asn Asn Ser Gly Leu
325 330 335
Ile Ser Ala Ala Gln Thr Leu Thr Leu His Thr Pro Thr Thr Ile Asp
340 345 350
Asn Arg Ser Gly Thr Leu Asn Ala Ala Arg Leu Asp Ile Thr Gly Ala
355 360 365
Arg Leu Asp Asn Arg Gly Gly His Ile Gln Gln Thr Gly Leu Gln Pro
370 375 380
Leu Thr Leu Gln Thr Gln His Leu Asp Asn Gln Asp Gln Gly Arg Leu
385 390 395 400
Gly Val Leu Asp Thr Pro Ala Pro Ala Ser Pro Ala Thr Pro Thr Val
405 410 415
Thr Ala Pro Ile Ser Asn Ala Pro Pro Thr Val Thr Ala Pro Pro Ala
420 425 430
Thr Asp Pro Thr Thr Ser Pro Val Ala Pro Thr Val Pro His Leu Ala
435 440 445
His Gly Thr Leu Thr Leu Thr Gln Thr Ile Asp Asn Arg Gly Gly His
450 455 460
Ile Thr Ala Gly Gly Ala Ile Asp Ala Ile Leu Thr Asp Leu Asp Asn
465 470 475 480
Arg Asp Gly Thr Ala Ala Leu Asn Arg Leu Thr Leu Gln Gly Gln Arg
485 490 495
Leu Asp Asn Gln His Gly Ile Leu Thr Leu Ala Thr Asp Ala Thr Ile

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            500                 505                 510
His Thr His Thr Leu Asn Asn Ala Ala Gly Gln Leu His Ala Asn Gly
        515                 520                 525
Thr Leu Asp Leu Thr Ala Asp Thr Phe Ser Asn Gln Asn Gly Gln Leu
    530                 535                 540
Leu His Thr Gly Ser Gln Asn Ala Thr Leu Thr Ile Thr Asp Leu Leu
545                 550                 555                 560
Asp Asn Gln His Gly Ile Ile Ala Ser Ala Ala Asn Leu Leu Thr Leu
                565                 570                 575
Lys Thr Asp His Leu Asn Asn Ala Ala Gly Gln Leu His Ala Asn Gly
            580                 585                 590
Ala Leu Asp Leu Thr Ala Gln Arg Phe Ser Asn Gln Asn Gly Gln Leu
        595                 600                 605
Leu His Thr Gly Ser Gln Asn Ala Thr Leu Thr Ile Ala Asn Leu Leu
    610                 615                 620
Asp Asn Gln His Gly Leu Val Ala Ser Ala Ala Asn Ala Leu Thr Leu
625                 630                 635                 640
His Thr Gly His Leu Asn Asn Asp Ala Gly Gln Phe Gln Thr Asn Gly
                645                 650                 655
Ala Leu Asp Leu Thr Ala Gln Arg Phe Ser Asn Gln His Gly Gln Phe
            660                 665                 670
Leu His Asn Ser Pro Gln Ser Ala His Leu Arg Ile Asp Gly Gln Leu
        675                 680                 685
Asp Asn Gln Gln Gly Val Leu Ala Ser Asn Ala Ala Glu Leu Thr Leu
    690                 695                 700
Glu Thr Gly Gln Phe Asn Asn Asp Ser Gly Thr Leu Gln Gln Ser Gly
705                 710                 715                 720
Gln Gly Thr Leu His Ile Asp Ala Ala Thr Leu Thr Gly His Gly Gly
                725                 730                 735
Thr Leu Thr Ser Gln Gly Ala Leu Thr Leu Thr Gly Thr His Thr Asp
            740                 745                 750
Leu Ser His Ala Thr Thr Thr Ala Gln His Ile Thr Ile His Thr Asp
        755                 760                 765
Asp Leu Thr Thr Ala Gly Gly His Leu Thr Ala Tyr Gly Glu His Thr
    770                 775                 780
Leu Gln Leu Asn Ala Arg Thr Arg Ile Asp Asn Thr Ala Gly Thr Ile
785                 790                 795                 800
Ala Thr Asn Gly Ser Leu Asp Leu His Thr Ala Ala Leu Asp Asn Thr
                805                 810                 815
Gly Gly Thr Leu His Ser Thr Ala Thr Gly Pro Asn Arg Leu Asp Ile
            820                 825                 830
Thr His Thr Leu Thr Asn Thr Ala Gly His Leu Leu Leu Asn Gly Pro
        835                 840                 845
Thr Thr Leu Thr Thr Gly Thr Trp Thr Asn Thr Gly Gly Gln Leu Gln
    850                 855                 860
Ile Thr Gly Pro Ala Thr Leu His Ala Thr Thr Leu Asp Asn Arg Gly
865                 870                 875                 880
Gly Ile Leu His Thr Ala Thr Gly Pro Leu Asp Leu Arg Val Thr Gly
                885                 890                 895
Thr Ile Asn Asn Gln Asp Asn Gly Ile Leu Ser Ser Thr Ala Ala Leu
            900                 905                 910
Thr Leu Thr Ala Ala Ser Leu His Asn Gln His Gly Thr Leu Asp Ala
        915                 920                 925
Ala Gly Pro Ala His Leu Thr Leu Thr Gly Leu Leu Asp Asn Thr Ala
    930                 935                 940
Gly Leu Leu Gln Thr Ala His Thr Leu Trp Leu Thr Ser Ala Gly Leu
945                 950                 955                 960
Thr Asn Arg Ser Gly Thr Leu Thr Ala Ala Ala Leu Thr Leu Asp Thr
                965                 970                 975
Gln Ala His Thr Leu Asp Asn Thr Ser Gly Arg Leu Gly Thr Thr Thr
            980                 985                 990
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Gly Asn Leu Thr Leu His Thr Gly Leu Leu Asp Asn Thr Ala Gly Leu
995 1000 1005
Leu Gln Thr Ala Ala Thr Leu Thr Ile Asp Thr Gly Ala Ala Pro Leu
1010 1015 1020
Thr Asn Arg Asp Gly Gly Thr Leu Leu Ala Ala Asp Thr Leu Asp Leu
1025 1030 1035 1040
His Thr Thr Thr Leu Asp Asn Arg Gly Gly Thr Ile Asp Ser Gln Thr
1045 1050 1055
Ala Thr His Leu His Thr Thr Thr Ile Asp Asn Thr Thr Ala Gly His
1060 1065 1070
Ile Ser Ser Asn Gly Thr Leu Gln Ile Asp Gly Thr Thr Leu Thr Asn
1075 1080 1085
Thr Gly Gly Arg Leu His Ser Gly Gly Asp Thr Arg Leu His Leu Gln
1090 1095 1100
Asp Thr Leu Asn Asn His Asp Gly Arg Ile Thr Ala Ala Gly Thr Leu
1105 1110 1115 1120
Asp Ile Thr Thr Thr Thr Leu Asp Asn His Ser Thr Pro Leu Thr Ala
1125 1130 1135
Pro Pro Ala Thr Gln Thr Arg Ala Pro Thr Gly Ala Pro Asp Asn Gly
1140 1145 1150
Leu Tyr Ala Thr His Ile Gln Ile Ala Ser Thr Thr Leu Asp Asn Thr
1155 1160 1165
Ala Gly Thr Leu Ser Ala Ala Gln Asn Leu Thr Leu Thr Leu Ser Asp
1170 1175 1180
Thr Leu Thr Asn Thr Ala Gly His Leu Ser Ala Gly Ala Thr Leu Asp
1185 1190 1195 1200
Leu Thr Ala Asp His Leu Ser Asn His Thr Gly Thr Leu Leu Ser Gly
1205 1210 1215
Ala Ser Gln Thr Leu His Leu His Arg Leu Thr Gly Asp Gly Arg Leu
1220 1225 1230
His Ala Gly Asn Ala Leu Thr Leu Thr Leu Gln Asp Ser Leu Asp Thr
1235 1240 1245
Ala Gly Thr Leu Ser Ala Thr Gly Leu Leu Thr Leu Thr Thr Ala Gly
1250 1255 1260
Asp Leu Thr Asn Arg Gly Leu Ile Gln Ala Ala Asp Leu Thr Ala Gln
1265 1270 1275 1280
Ala Arg Asp Ile Thr Thr Thr Ala Thr Gly Gln Leu Leu Thr Thr Gly
1285 1290 1295
His Thr His Leu Thr Ala Thr Gly Thr Leu Asn Asn Ser Gly His Leu
1300 1305 1310
Gln Ala Ala Asp Leu Thr Ala Gln Ala His Asp Ile Thr Thr Thr Ala
1315 1320 1325
Thr Gly Gln Leu Leu Thr Thr Gly His Thr His Leu Thr Ala Thr Gly
1330 1335 1340
Thr Leu Asn Asn Ser Gly His Leu Gln Ala Ala Asp Leu Thr Ala Gln
1345 1350 1355 1360
Ala Asn Thr Ile Thr Asn Thr Gly Thr Phe Leu Ala Thr Ser His Ala
1365 1370 1375
Thr Leu Thr Ala Thr Asp Thr Leu Thr Asn Ser Gly Leu Leu Gln Ala
1380 1385 1390
Ala Asp Leu Thr Ala Gln Ala Asn Thr Ile Thr Asn Thr Ala Thr Gly
1395 1400 1405
Arg Leu Leu Thr Thr Ala His Thr Gln Leu Thr Ala Thr Asp Thr Leu
1410 1415 1420
Thr Asn Ser Gly Leu Val His Ala Gly Asp Leu Thr Val His Ala Arg
1425 1430 1435 1440
Asp Ile Thr Asn Thr Ala Thr Gly Gln Leu Ile Ala Ser Asn Leu Ala
1445 1450 1455
Gln Leu Thr Ala Thr Ala Thr Leu Thr Asn Arg Gly Leu Ile Asp Ala
1460 1465 1470
Phe Thr Thr His Leu Ser Ala Pro Thr Ile Asp Asn Leu Gly Thr Gly

1475 1480 1485
Arg Leu Tyr Gly Asp His Ile Ala Leu Gln Ala His Thr Leu Thr Asn
1490 1495 1500
Arg Asp Glu Thr Ser Asp Gly His Thr His Thr Ala Thr Ile Ala Ala
1505 1510 1515 1520
Arg Glu Arg Leu Asp Ile Gly Ala Asp Thr Leu Arg Asn Thr Ala Asn
1525 1530 1535
Ala Met Ile Leu Ser Asp Gly Asp Ala Ala Ile Gly Ala Thr Leu Asp
1540 1545 1550
Asn Thr Leu His Ala Thr Gly Ile Ala Thr Leu Ile Asp Asn Arg Ser
1555 1560 1565
Ala Thr Ile Asp Ile Thr Gly Thr Leu Asn Ile Thr Thr Thr Thr Leu
1570 1575 1580
Asn Asn Ile Arg Glu Asn Val His Ile Ala His Ala Pro Asp Val Val
1585 1590 1595 1600
Thr Glu Ala Arg Met Tyr Gln Pro His Trp Arg Lys Asn Lys Pro Asn
1605 1610 1615
Gly Gly Ser Gly Asp Phe Arg Leu Ser Ser Asn Tyr Asp Ala His Asp
1620 1625 1630
Ile Tyr Tyr Leu Asn Pro Ala Asp Ile Leu Glu Asp Thr Pro Tyr Ile
1635 1640 1645
Thr Pro Asp Gly Gln Lys Ile His Arg Ala Ile Val Arg Leu Thr Pro
1650 1655 1660
Gln Thr Ser Ala Tyr Phe Tyr Ala Arg Gly Gly Leu Tyr Ala Ser Gln
1665 1670 1675 1680
Ala Glu Arg Arg Arg Leu Asp Leu Thr Ala Arg Thr Gly Asp Ser Leu
1685 1690 1695
Val Leu Tyr Tyr Thr Asp Arg Gln Asp Lys Gln Pro Asn Pro Asp His
1700 1705 1710
Val Ala Ala Ala Ala Thr Asn Asp Ser Ala Phe Ile Gly Leu Asp Thr
1715 1720 1725
Pro Gln Gln Asn Glu Arg Leu Lys Ile Val Pro Ile Thr Tyr Ala Pro
1730 1735 1740
Gly Asp Asp Arg Leu Thr Tyr Asp Pro Thr Tyr Gly Thr Cys Thr Asp
1745 1750 1755 1760
Asp Cys Val Arg Leu Val Thr Trp His Asp Tyr Thr Asp Pro Asp His
1765 1770 1775
Thr Leu Ile Asp Met Arg Arg Gly Pro Asn Asp Val Asp Asp Asn Glu
1780 1785 1790
Arg Glu Arg His Ala Thr Arg Thr Thr Gln Gln Glu Ile Leu Asn Pro
1795 1800 1805
Asp Ala Gly Ala Pro Ala Leu Ile Gln Ser Gly Gly Thr Met Arg Ile
1810 1815 1820
Asp Val Gly Tyr Leu Tyr Asn His Tyr Ala Asp Leu Leu Ala Gly Gly
1825 1830 1835 1840
Asp Gln Thr Ile Val Gly Leu Pro Pro His Pro Thr Lys Glu Thr Ala
1845 1850 1855
Asp Asp Glu His Lys Tyr Asn Arg Ala Leu Leu Ile Asp Asn Arg Ala
1860 1865 1870
Leu Gln Leu Ser Arg Thr Asp Arg Phe Gln Asn Ile Ser Thr Thr Tyr
1875 1880 1885
Arg Gly Lys Asp Ser Ala Pro Trp Ser Asn Glu Ser Arg Thr Thr Pro
1890 1895 1900
Thr Thr Gln Ile Gly Gly Arg Ile Thr Ser Gly Gly His Gln His Ile
1905 1910 1915 1920
Ala Ala Gln Thr Phe Asn Asn Val Thr Asp Ser Thr His Ala Pro Glu
1925 1930 1935
Pro Ile Gln His Val Thr Tyr Asn Pro Ser Thr Gln Thr Leu Thr Ile
1940 1945 1950
Ala Asp Gly His Ile Thr Val Thr Asp Thr Pro Pro Ser Leu His Thr
1955 1960 1965

Val Ser Leu Ala Asp Asn Gly Phe Ser His Gly Gln Glu Leu Thr Tyr
1970 1975 1980
Ile Pro Glu Lys Ser Ile Thr Thr Pro Asn Ala Pro Ile Arg Asp Pro
1985 1990 1995 2000
Ala Ala Pro Pro Ala Val Thr Val Thr Pro Thr Gly Pro Leu Thr Leu
2005 2010 2015
Pro Asn Asn Ser Leu Phe Thr Ile His Pro Asp Thr Ala Thr Leu Ile
2020 2025 2030
Thr Thr Asp Pro Arg Phe Thr Leu Gly Arg Pro Tyr Thr Ser Ala Asp
2035 2040 2045
Ser Gln Leu His Ala Leu Gly Asp His Asp Thr Leu His Lys Arg Leu
2050 2055 2060
Gly Asp Gly Tyr Tyr Glu Gln Arg Leu Ile Arg Glu Gln Ile Ala Gln
2065 2070 2075 2080
Leu Thr Gly Arg Arg Arg Leu Asp Gly Tyr Thr Asp Asp Asp His Gln
2085 2090 2095
Tyr Arg Ala Leu Leu Asp Ala Gly Leu Thr Val Ala Lys Gln His Gln
2100 2105 2110
Leu Arg Pro Gly Ile Ala Leu Ser Ala Asp Gln Met Ala Gln Leu Thr
2115 2120 2125
Ser Asp Ile Val Trp Leu Val Gln Gln Asp Val His Leu Pro Asp Gly
2130 2135 2140

Thr Thr Thr Val Ala Leu Val Pro Arg Leu Tyr Leu Arg Pro Arg Thr
2145 2150 2155 2160
Gly Asp Leu Thr Pro Asp Gly Ala Leu Leu Ala Ala Ala Ser Thr Thr
2165 2170 2175
Ile Asn Ala His Thr Leu Thr Asn Thr Gly Thr Ile Asp Ala Arg Asp
2180 2185 2190
Leu Ile Asn Ile Asn Thr His Ile Met Asp Gln Gln Gly Gly Arg Leu
2195 2200 2205
Thr Ala Asp Ala Ile Asn Ile His Thr Thr Gly Asp Phe Thr Asn Leu
2210 2215 2220
Gly Gly Gln Phe Thr Ala Gly Asp Phe Leu Lys Val His Ala Gln Gly
2225 2230 2235 2240
Asn Phe Leu Ala Ser Ser Thr Leu Arg Asp Ala Thr Thr Gln Gly Thr
2245 2250 2255
Arg His His Ser Val Thr Glu Leu Asp Gln Gln Ala Gly Phe Thr Val
2260 2265 2270
Thr Gly Pro Gly Ala Tyr Leu Gly Leu Ser Thr Asp Gln Ala Met Thr
2275 2280 2285
Gln Gln Ala Val Ala Ile Ser Asn Thr Gly Leu Asp Gly Tyr Thr Ser
2290 2295 2300
Leu Lys Ala Thr Gly Arg Leu His Leu Gly Thr Leu Asn Thr His Arg
2305 2310 2315 2320
Ser Asp Thr Thr Gln Trp Asp Pro Arg Asn Ser Arg His Thr Arg Ile
2325 2330 2335
Asp Thr Glu His Gly Thr Ser Ile Arg Ser Ala Gly Asp Ile Gln Leu
2340 2345 2350
Asn Ser Gly Gln Asp Ile Asn Leu Arg Ala Val Thr Leu His Ser Thr
2355 2360 2365
Gln Gly Thr Val Ser Ala Leu Ala Thr Gly Asn Val Thr Ile Thr His
2370 2375 2380
Gly Asp Thr Leu Gln Tyr Thr Ser Gln Asp Asn His Ser Lys Arg Ser
2385 2390 2395 2400
Gly Leu Leu Asn Ser Arg Thr Thr Thr Thr His Ala Asp Gln Gln Gln
2405 2410 2415
Thr Gln Ala Met Ser Ser Thr Leu Ser Gly Thr Lys Val Leu Val Lys
2420 2425 2430
Gly Asn Asn Ile Thr Val Thr Gly Ser His Leu Leu Ser Asp Ala Gly
2435 2440 2445

Thr Tyr Met Gln Ala Lys Gly Asp Leu Thr Leu Gln Ala Ala Thr Asn
2450 2455 2460
Thr Thr Gln Ser Thr Tyr Ser Glu His Thr Lys Gln Arg Gly Leu Ile
2465 2470 2475 2480
Arg Asn Gly Gly Ala Ser Leu Thr Leu Gly Asn Gln Ser Gln Arg Thr

2485 2490 2495
Asp Ser Thr Thr Thr Ala Thr Thr Thr Thr Gly Ser Leu Ile Gly Ala
2500 2505 2510
Thr Asn Gly Asn Val Thr Leu Leu Ala Gly Gly His Tyr Gln Gln Ile
2515 2520 2525
Gly Ser Asp Val Leu Ser Pro Asn Gly Asp Ile Asp Ile His Ala Lys
2530 2535 2540
Lys Val Asp Ile Ile Gln Ala His His Thr Ser His Thr Thr Gln His
2545 2550 2555 2560
Thr Ala Thr Arg Gln Ser Gly Leu Thr Val Gly Leu Ser Thr Pro Leu
2565 2570 2575
Ile Ala Gly Ala Gln Thr Ala Gln Gln Met Gln His Ala Ala Ala Arg
2580 2585 2590
Ser Gly Asp Pro Arg Leu His Ala Leu Ala Gly Leu Thr Thr Ala Leu
2595 2600 2605
Gly Ala Lys Asn Thr Ile Asp Ala Val Arg Gln Asp Pro Arg Ala Leu
2610 2615 2620
Gly Gly Leu Asn Ala Ser Leu Thr Leu Gly Arg Ser Thr His Asp Ser
2625 2630 2635 2640
Thr Thr Thr Thr Thr Thr Thr Thr Ala Ala Gly Ser Asn Val Asn Ala
2645 2650 2655
Gly Gly Asn Val Arg Ile Ser Ala Thr Gly Asp Gly Glu Ala Ser Thr
2660 2665 2670
Leu Thr Ile Gln Gly Ser His Val Arg Gly Asp Asn Met Thr Tyr Leu
2675 2680 2685
Lys Ala Asp Gly Asp Ile Ala Leu Leu Ala Ala Ala Asn Thr Thr Thr
2690 2695 2700
Ser Asp Arg Gln Ser Arg Gly Arg Ser Ala Gly Val Gly Val Ala Val
2705 2710 2715 2720
Asn Leu Gly Ser Ser Gly Thr Ser Ala Gly Leu Thr Ala His Ala Ser
2725 2730 2735
Thr Ser Thr Gly Ser Gly Gln Ser Thr Asp Leu Thr Trp Thr Asn Ser
2740 2745 2750
His Val Gly Gly Gly Asn Leu Leu Thr Ile Glu Ala Gly Gly Asp Leu
2755 2760 2765
Leu Met Lys Gly Ala Ile Gly Thr Ala Lys His Val Ile Ala Asp Ile
2770 2775 2780
Ala Gly Asn Leu Thr Ile Gln Ser Leu Gln Asp Thr His His Tyr Arg
2785 2790 2795 2800
Ser Lys Asp Arg Ser Leu Gly Gly Ser Leu Thr Val Gly Ala Gly Val
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Ser Val Thr Glu Gln Ser Gly Leu Phe Thr Gly Asp Gly Gly Tyr Asp
2835 2840 2845
Ile Thr Val Gly Gly Gln Thr His Leu Ile Gly Gly Ala Ile Thr Ser
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Asn Ser Thr Ala Ile His Asn Gly Leu Asn Thr Leu Asp Thr Gly Thr
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Leu Ile Leu Gln Asp Ile Glu Asn Arg Ala Thr Tyr Thr Ala Thr Gln
2885 2890 2895
Val Asn Leu Gly Gly Gly Tyr Ser Arg Asn Gly Gly Thr Val Gly Thr
2900 2905 2910
Asp Gln Gln Gly His Ala Ala Thr Ala Thr Gln Val Pro Gly Thr Thr
2915 2920 2925

Leu Pro Thr His Asn Gly Leu Ser Ala Ala Pro Pro Gly Ala Met Thr
2930 2935 2940
Ala Ser Asp Ser Ser His Ser Thr Thr Tyr Ser Gly Ile Ser Gln Gly
2945 2950 2955 2960
Ala Leu Thr Ile Arg Asp Pro Ala Ala Gln His Ala Leu Thr Gly His
2965 2970 2975
Thr Ala Ala Gln Thr Ile Ala Gly Leu Asn Arg Asp Ile Leu Thr Asp
2980 2985 2990
Thr Ala Thr Ser Asn Ala Leu Thr Pro Ile Phe Asp Glu Gln Arg Ile
2995 3000 3005
Asn Ala Ala Phe Asp Ile Val Thr Ala Leu Gln Arg Glu Thr Gly Thr
3010 3015 3020
Phe Ile Asn Asn Arg Ala Ala Glu Ala Thr Gln Ala Gln Gln Ala Leu
3025 3030 3035 3040
Gln Ala Glu His Ala Lys Pro Ala Asp Gln Arg Asp Pro Ala His Ile
3045 3050 3055
Ala Ala Leu Gln Gln Arg Ile Gln Asn Thr Thr Thr Trp Glu Leu Gly
3060 3065 3070
Gly Thr Gly His Thr Ile Val Thr Ala Leu Thr Leu Ala Ala Gly Gln
3075 3080 3085
Gln Val Thr Gly Pro Ala Thr Gln Met Leu Gln Asn Ala Ala Val Asn
3090 3095 3100
Tyr Ile Gln Ser Leu Gly Ala Arg Glu Ile Lys Asp Leu Ala Asp Thr
3105 3110 3115 3120
Leu Gly Ser Asp Thr Ala Arg Ser Ala Leu Gln Gly Leu Leu Gly Cys
3125 3130 3135
Ala Gly Ala Ala Ala Gln Gly Gln Ala Cys Gly Ala Gly Ala Val Gly
3140 3145 3150
Gly Ala Ala Ala Val Val Ile Asn Ser Leu Leu Asp Arg Ala Asn Gly
3155 3160 3165
Ala Glu Ala Ala Ser Leu Ser Ala Glu Glu Lys Gln His Arg Thr Asp
3170 3175 3180
Leu Val Thr Ser Leu Val Ala Gly Ile Thr Thr Ala Ala Gly Gly Asp
3185 3190 3195 3200
Ala Ala Val Ser Ser Ala Ala Ala Arg Leu Glu Thr Glu Asn Asn Ala
3205 3210 3215
Ala Phe Ile Pro Val Ile Leu Gly Ala Val Trp Leu Ala Asp Lys Gly
3220 3225 3230
Ile Thr Ala Tyr Gln Ala Trp Gln Asp Ile Lys Ala Ile Arg Ser Gly
3235 3240 3245
Glu Lys Thr Leu Glu Gln Val Ala Leu Glu Arg Gly Gln Asp Tyr Val
3250 3255 3260
Thr Ser Ile Val Ile Gly Asn Leu Ala Lys Tyr Gly Leu Lys Ala Ala
3265 3270 3275 3280
Met Ile Gly Gly Arg Trp Ile Ser Gly Thr Ala Lys Glu Ile Ala Asn
3285 3290 3295
Ala Glu Lys Glu Ala Leu Arg Gln Ile Arg Asn Asn Pro Lys Gly Pro
3300 3305 3310
Asp Leu Thr Gln Lys Pro Pro Gly Gln Ile Met Ala Leu Gln Arg Gln
3315 3320 3325
Lys Arg Leu Asp Asp Val Lys Ser Val Ile Gly Arg Arg Ser Gln Lys
3330 3335 3340
Asp Thr Leu Val Val Gly Gly Ile Glu Val Lys Ala Val Pro Tyr Asp
3345 3350 3355 3360
Arg Asn Val Pro Gly Gly Ser Asn Lys Ser Gly Thr Thr Lys Val Phe
3365 3370 3375
Asp Ser His Ala Leu Thr Asp Ala Gln Ile Lys Asp Tyr Ala Gln Gln
3380 3385 3390
Leu Thr Gly Gly Val Pro Leu Lys Gln Thr Ser Arg Pro Gly Val Tyr
3395 3400 3405
Thr Ala Lys Leu Ser Asp Gly Ser Thr Val Thr Leu Arg Ser Val Ser

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    3410                3415                3420
Lys Ser Asn Gln Glu Thr Gln Ala Arg Trp Thr Ile Asp Ile Lys Asp
3425                3430                3435                3440
Asn Pro Ala Leu Ser Glu Ile Thr Asn Lys Thr Val Glu Leu Lys Phe
                3445                3450                3455
Arg
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<211> 3848
<212> PRT
<213> E. chrysanthemi

<400> 6

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Met Leu Ser Arg Tyr Trp Ala Phe His Thr Ala Lys Leu Arg Ser Ser
 1               5                  10                  15
Gly Met Lys Ala Val Lys Thr Ser Gln Arg Val Met Val Trp Ala Leu
            20                  25                  30
Val Trp Leu Thr Gly Leu Gln Pro Val Leu Pro Ala Trp Ala Ala Gly
        35                  40                  45
Val Thr Val Ala Ser Gly Asn Thr Ala Leu Glu Ala Ala Gly Asn Gly
    50                  55                  60
Val Pro Val Val Asn Ile Ala Thr Pro Asp Ala Ser Gly Leu Ser His
65                  70                  75                  80
Asn Arg Tyr His Asp Phe Asn Val Asp Asn Arg Gly Leu Ile Leu Asn
                85                  90                  95
Asn Gly Thr Ala Arg Leu Thr Pro Ser Gln Leu Gly Gly Leu Ile Gln
            100                 105                 110
Asn Asn Pro Asn Leu Asn Gly Arg Ala Ala Ala Ala Ile Leu Asn Glu
        115                 120                 125
Val Val Ser Pro Asn Arg Ser Arg Leu Ala Gly Tyr Leu Glu Val Ala
    130                 135                 140
Gly Gln Ala Ala Asn Val Val Val Ala Asn Pro Tyr Gly Ile Thr Cys
145                 150                 155                 160
Ser Gly Cys Gly Phe Leu Asn Thr Pro Arg Leu Thr Leu Thr Thr Gly
                165                 170                 175
Thr Pro Gln Phe Asp Ala Ala Gly Gly Leu Ser Gly Leu Asp Val Arg
            180                 185                 190
Gly Gly Asp Ile Leu Ile Asp Gly Ala Gly Leu Asp Ala Ser Arg Ser
        195                 200                 205
Asp Tyr Phe Gly Leu Ile Ala Arg Thr Ala Ser Leu Gln Ala Gly Leu
    210                 215                 220
Asn Ala Arg Asp Ala Gln Val Val Leu Gly Ala Asn Arg Val Gly Ala
225                 230                 235                 240
Asp Gly Arg Val Thr Ala Gln Ala Gly Ser Gly Pro Ala Pro Val Leu
                245                 250                 255
Ala Leu Asp Thr Gly Ala Leu Gly Gly Met Tyr Ala Asn Arg Ile Arg
            260                 265                 270
Leu Val Ser Thr Glu Gln Gly Val Gly Val Asn Thr Ala Gly Leu Ser
        275                 280                 285
Ala Arg Glu Gly Asp Ile Arg Leu Ser Ala Asn Gly Arg Leu Gln Val
    290                 295                 300

Arg Gly Ala Val Ala Gln Gly Glu Leu Thr Ala Gln Gly Glu Thr Leu
305                 310                 315                 320
Ala Leu Gln Gly Asn Gln Gln Ala Gln Gly Ser Ile Thr Leu Arg Gly
                325                 330                 335
Ala Gln Gly Val Thr Leu Thr Gly Ser Arg Thr Arg Ala Gly Gln Gly
            340                 345                 350
Leu Thr Leu Ala Ser Asp Gly Arg Ile Thr Ala Ala Asp Ala Gly Leu
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        355                 360                 365
Ser Ala Gly Val Arg Glu Asp Gly Thr Val Gln Pro Gly Asp Gly Leu
    370                 375                 380
Ser Leu Thr Gly Arg Glu Leu Ala Leu Gly Gln Ser Gln Leu Ala Gly
385                 390                 395                 400
Asp Arg Val Ser Leu Asn Ser Thr Gly Ala Val Ser Gln Ser Arg Ala
                405                 410                 415
Gly Val Ala Gly Gly Ser Val Leu Thr Val Asn Gly Gly Ala Leu Ser
            420                 425                 430
Leu Asp Gly Asp Ala Gly Ala Gln Thr Leu Thr Val Ser Gly Ser Gly
        435                 440                 445
Leu Ser Gly Ser Gly Arg Trp Gln Ala Thr Gly Asp Leu Thr Leu Asp
    450                 455                 460
Gly Leu Asp Arg Gly Ala Val Gly Arg Gly Ala Ala Gly Gly Arg Gly
465                 470                 475                 480
Ala Val Gly Ala Gly Gly Glu Pro Gly Gln Pro Gly His Ala Gly Gly
                485                 490                 495
Arg Ala Gly Thr Leu Thr Thr Pro Gly Leu Asp Asn Arg Gly Thr Val
            500                 505                 510
Ser Gly Arg Gln Val Ala Val Arg Thr Ala Gln Leu Gly Asn Ala Gly
        515                 520                 525
Thr Leu Ser Ala Asp Glu Thr Leu Thr Ile Gln Ala Gln Thr Gly Leu
    530                 535                 540
Asp Asn Ser Gly Ser Leu Leu Ser Gly Gly Ala Leu Thr Ile Ala Ala
545                 550                 555                 560
Gly Gln Thr Asp Asn Arg Gly Val Leu Ser Gly Gly Ala Val Thr Leu
                565                 570                 575
Ser Gly Asp Ser Leu Trp Asn Gly Gly Thr Leu Gln Gly Arg Gln Ser
            580                 585                 590
Leu Gly Val Asn Ala Leu Ala Gly Phe Ser Gln Thr Ala Asp Gly Ala
        595                 600                 605
Leu Thr Ser Gly Gly Thr Val Thr Val Ser Ser Gly Thr Leu Glu Thr
    610                 615                 620
Ala Gly Ala Leu Ser Ala Gln Gly Leu Gln Leu Arg Thr Gly Leu Trp
625                 630                 635                 640
Arg Asn Gln Gly Ala Val Ser Leu Thr Gly Asp Gly Gln Leu Thr Val

                645                 650                 655
Asp Glu Leu Asp Asn Ser Gly Thr Leu Leu Ser Ser Gly Ala Trp Asp
            660                 665                 670
Ile Ala Gly Gly Arg Leu Gly Asn Ser Gly Thr Leu Gln Gly Asp Arg
        675                 680                 685
Leu Thr Leu Arg Gly Asp Arg Leu Asp Asn Gln Gly Ala Leu Thr Gly
    690                 695                 700
Thr Thr Gln Thr Ala Leu Arg Leu Gly Gly Ala Leu Ala Asn Arg Gly
705                 710                 715                 720
Thr Val Ser Gly Asn Arg Leu Ala Val Thr Ala Ala Ala Leu Asp Asn
                725                 730                 735
Gly Gly Thr Leu Leu Gly Val Glu Ala Leu Thr Leu Thr Thr Asp Gly
            740                 745                 750
Ala Leu Thr Asn Arg Gly Thr Gly Arg Leu Leu Thr Gln Gly Ala Ala
        755                 760                 765
Val Leu Thr Ala Ala Ser Val Val Asn Ala Gly Glu Gly Gln Ala Gly
    770                 775                 780
Arg Leu Gln Leu Thr Gly Gly Thr Leu Ala Asn Thr Gly Thr Leu Ala
785                 790                 795                 800
Val Asn Gly Gly Ala Ser Leu Thr Leu Asp Gly Leu Asp Asn Arg Gly
                805                 810                 815
Thr Leu Ser Ala Gly Gly Asp Leu Thr Val Thr Gly Ala Asp Leu Arg
            820                 825                 830
Asn Ala Gly Gln Met Ala Ala Gln Gly Ala Leu Thr Leu Thr Gly Asn
```

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        835                 840                 845
Tyr Gly Gly Ala Gly Ser Leu Tyr Ser Glu Gly Ala Leu Ser Leu Ser
    850                 855                 860
Gly Ala Ala Leu Val Asn Gly Gly Gly Arg Trp Gln Gly Ala Thr Val
865                 870                 875                 880
Ala Val Arg Gly Gly Pro Leu Thr Asn Ser Gly Thr Val Thr Gly Leu
                885                 890                 895
Thr Ala Leu Thr Val Thr Thr Asp Gly Thr Leu Ser Asn Thr Gly Arg
            900                 905                 910
Leu Glu Gly Arg Arg Leu Asp Leu Thr Ala Glu Ala Leu Asp Asn Gly
        915                 920                 925
Gly Thr Leu Leu Gly Val Asp Ala Leu Thr Leu Ala Ile Thr Gly Thr
    930                 935                 940
Ala Arg Asn Gln Ala Gly Gly Arg Phe Leu Ser Gln Gly Asp Gly Arg
945                 950                 955                 960
Leu Thr Ala Ala Thr Leu Asp Asn Gln Gly Asp Trp Gln Gly Gly Arg
                965                 970                 975
Ile Asp Val Thr Ala Gly Arg Val Arg Asn Ala Gly Gln Val Leu Gly
            980                 985                 990
Ile Ala Ala Leu Thr Leu Thr Ala Asp Asn Ala Leu Thr Asn Thr Gly
        995                 1000                1005
Thr Gly Arg Leu Leu Thr Pro Gly Ala Ala Val Leu Thr Ala Ala Thr
    1010                1015                1020
Ala Val Asn Asp Gly Glu Trp Gln Ala Gly Ser Leu Arg Leu Thr Ala
1025                1030                1035                1040
Asp Arg Leu Arg Asn Gly Gly Arg Ile His Ser Asp Gly Asp Leu Val
                1045                1050                1055
Val Thr Leu Pro Thr Ala Asp Gly Asp Pro Arg Arg Arg Ala Ala Gln
            1060                1065                1070
Arg Leu Ala Gln Glu Val Gln Thr Leu Gly Ala Gly Glu Leu Ser Asn
        1075                1080                1085
Ser Gly Thr Leu Val Ala Asp Gly Asp Gly Arg Leu Thr Ala Arg Gln
    1090                1095                1100
Val Asp Asn Ala Gly Thr Leu Ser Thr Gly Gly Ala Leu Thr Leu Thr
1105                1110                1115                1120
Ala Gly Ala Ile Thr Asn Ala Gly Arg Leu Glu Ser Arg Thr Leu Ser
                1125                1130                1135
Leu Thr Gly Asp Ser Leu Asp Asn Gly Gly Thr Leu Leu Ala Glu Gln
            1140                1145                1150
Gly Gly Gly Leu Thr Leu Ser Asp Arg Leu Thr Val Gly Ala Asp Gly
        1155                1160                1165
Gln Val Leu Ser Asn Gly Asp Trp Gln Ile Gln Ala Gly Ala Val Thr
    1170                1175                1180
Ser Leu Gly Gln Trp Gln Gly Lys Asn Leu Arg Leu Ser Ala Asp Thr
1185                1190                1195                1200
Leu Thr His Asp Gly Val Leu Gln Ala Glu Arg Asp Ile Thr Leu Ala
                1205                1210                1215
Leu Leu Gln Asp Tyr Thr Gly Gly Ala Gly Ser Gln Val Arg Gly Asn
            1220                1225                1230
Gly Ala Val Thr Leu Thr Ala Asp Arg Val Thr Gln Gln Gly Asp Ile
        1235                1240                1245
Gly Gly Glu Arg Leu Gln Leu Thr Thr Gly Thr Leu Thr Asn Gly Gly
    1250                1255                1260
Arg Leu Val Gly Leu Ser Gln Leu Asp Val Thr Ser Arg Gly Gln Leu
1265                1270                1275                1280
Thr Asn Ser Ala Asp Gly Ala Leu Leu Gly Asn Gly Thr Ala Gly Ile
                1285                1290                1295
Thr Ala Ala Ala Leu Ser Asn Ala Gly Val Leu Gln Gly Asp Ala Leu
            1300                1305                1310
Thr Val Arg Ala Gly Thr Val Asp Asn Ala Gly Ser Met Gln Gly Thr
        1315                1320                1325
```

Ala Ala Leu Thr Leu Asp Gly Val Thr Arg Tyr Asp Gly Gly Ala Asp
1330 1335 1340
Ser Arg Leu Leu Ser Gly Gly Ala Met Thr Leu Ala Leu Asp Thr Ala
1345 1350 1355 1360
Asp Asn Gly Gly Val Trp Gln Ala Gly Glu Leu Arg Val Ser Gly Thr
1365 1370 1375
Ser Leu Thr Asn Arg Gly Gln Ile Thr Gly Leu Ser Gly Leu Thr Ile
1380 1385 1390
Asp Ala Thr Gly Leu Ser Asn Ala Gly Arg Leu Ala Thr Gln Gly Arg
1395 1400 1405
Ala Thr Leu Arg Gly Arg Gln Phe Asp Asn Gly Gly Thr Leu Thr Ala
1410 1415 1420
Leu Gly Asp Leu Thr Ala Asp Phe Arg Asp Gly Ile Val Asn Gln Ala
1425 1430 1435 1440
Gly Gly Gln Leu Leu Ser Gly Gly Ala Gly Gln Leu Thr Thr Gly Thr
1445 1450 1455
Leu Thr Asn Ala Gly Trp Val Gln Gly Gln Asp Leu Thr Leu Thr Ala
1460 1465 1470
Asp Thr Leu Phe Asn Gln Gly Ser Leu Leu Gly Leu Asp Asp Gly Ala
1475 1480 1485
Ile Gln Leu Thr Gly Ala Tyr Val Gly Gly Val Asn Ser Arg Val Gly
1490 1495 1500
Gly Asn Gly Ala Phe Ser Leu Ser Ala Ala Thr Ile Asp Gln Ala Gly
1505 1510 1515 1520
Gln Trp Gln Ala Arg Asp Val Thr Leu Arg Ala Thr Arg Leu Arg Asn
1525 1530 1535
Gln Gly Thr Leu Thr Ala Gly Gly Gln Leu Thr Ala Thr Leu Asp Asp
1540 1545 1550
Ala Leu Glu Asn Thr Ala Gly Ala Val Leu Ser Gly Gly Thr Val Ser
1555 1560 1565
Leu Gly Ala Ala Thr Val Ser Asn Ala Gly Gln Leu Glu Gly Arg His
1570 1575 1580
Gly Leu Thr Val Ala Gly Gly Ser Arg Leu Asp Asn Gln Arg Gly Gly
1585 1590 1595 1600
Gln Leu Leu Ser Gly Gly Gln Leu Ala Leu Ser Ala Pro Gln Leu Thr
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Asn Ala Gly Trp Val Gln Gly Gln Asp Leu Thr Leu Thr Thr Ala Gln
1620 1625 1630
Leu Asp Asn Gly Gly Thr Leu Gln Ala Gln Ser Gly Leu Thr Leu His
1635 1640 1645
Leu Pro Gln Trp Thr Asn Arg Gly Thr Val Gln Ala Gly Gln Leu Asp
1650 1655 1660
Ile Thr Thr Asp Gly Ala Leu Glu Asn Arg Gly Thr Leu Leu Gly Leu
1665 1670 1675 1680
Thr Arg Leu Ala Leu Gln Ala Ala Arg Leu Asp Asn Ala Asp Gly Ala
1685 1690 1695
Arg Leu Tyr Ser Ala Gly Asn Leu Gln Leu Arg Thr Gly Gln Leu Val
1700 1705 1710
Gln Asn Gly Gln Leu Ala Ala Leu Gly Asp Leu Arg Ala Asp Ile Gly
1715 1720 1725
Asn Ala Phe Thr Phe Thr Arg Thr Leu Ala Ala Gly Gly Gln Leu Thr
1730 1735 1740
Leu Asn Val Thr Gly Asp Leu Val Gln Ala Gly Thr Leu Gln Gly Asn
1745 1750 1755 1760
Gly Val Thr Val Thr Ser Thr Gly Thr Leu Thr Gln Gln Gly Arg Ile
1765 1770 1775
Val Ala Gly Thr Gly Asp Ser Thr Leu Ser Ala Ala Ala Ile Asn Gln
1780 1785 1790
Thr Ala Ser Gly Ser Ile Gln Ala Gly Gly Ala Leu Arg Leu Arg Ala
1795 1800 1805
Glu Gly Asn Ile Val Asn Arg Gly Phe Val Gly Thr Ala Ala Asp Leu

1810 1815 1820
Leu Leu Gln Ala Gly Gly Val Ile Asp Asn Gly Gly Leu Leu Tyr Gly
1825 1830 1835 1840
Gly Gly Asn Leu Trp Leu Leu Ser Asp Ala Leu Val Asn Arg Phe Gly
1845 1850 1855
Asn Ile Leu Ala Gly Asn Ser Leu Trp Ile Gln Arg Asp Ala Ala Gly
1860 1865 1870
Asn Ala Ser Gly Ser Val Leu Asn Ser Ser Gly Thr Ile Glu Thr Gln
1875 1880 1885
Arg Gly Asp Ile Thr Val Arg Thr Gly Thr Leu Thr Asn Gln Arg Glu
1890 1895 1900
Gly Leu Val Val Thr Glu Gly Glu Ser Lys Thr Glu Val Val Pro Asp
1905 1910 1915 1920
Trp Val Gly Gly Glu Arg Val Glu Val Pro Leu Thr Trp Phe Lys Glu
1925 1930 1935
Gly Glu Leu Gly Ile Ala Glu Phe Tyr Thr Gly Cys Leu Arg Gly Gly
1940 1945 1950
Lys Ala Ser Gly Ala Asn Cys Glu Tyr Ser Ala Gly Tyr Leu Leu Ala
1955 1960 1965
Pro Phe Ser Ser Ala Ala Ile Gln Lys Val Ala Leu Glu Ser Lys Ser
1970 1975 1980
Val Ser Val Ser Ala Gln Gly Gly Glu Ala Arg Ile Asn Ser Ala His
1985 1990 1995 2000
Asp Thr Leu Ile Thr Ser Ser Ile Leu Thr Asn Glu Ala Ser Ala Ile
2005 2010 2015
Tyr Ala Arg Asn Asn Ile Val Leu Ser Gly Asn Ser Leu Asn Asn Thr
2020 2025 2030
Ser Tyr Gln Ala Gly Asp Leu Lys Arg Tyr Leu Thr Tyr Arg Tyr Asp
2035 2040 2045
Ser Val Glu Phe Val Tyr Gly Thr Trp Ser Trp Ile Asn Asp Phe Ala
2050 2055 2060
Asn Asp Asp Gln Ser Ala Tyr Val Gly Gly Gly Ser Ser Pro Ile Thr
2065 2070 2075 2080
Lys Gln Leu Asp Leu Ala Asp Lys Phe Glu Ile Gln Asn Lys His Tyr
2085 2090 2095
Ser Ile Asn Tyr Lys Pro Val Gly Glu Pro Thr Ser Glu Leu Ile Asn
2100 2105 2110
Gly Gln Thr Tyr Ala Ala Thr Ile Gln Ala Gly Gly Ala Ile Thr Ala
2115 2120 2125
Ser Phe Thr Gln Asn Ile Ser Asn Thr Ser Leu Gln Pro Gly Ser Gly
2130 2135 2140
Gly Val Met Pro Ala Leu Ala Thr Pro Thr Leu Ala Gly Val Ser Ala
2145 2150 2155 2160
Phe Thr Pro Val Gly Ala Gln Ala Gly Arg Glu Leu Ser Gly Gly Thr
2165 2170 2175
Ala Ala Ala Val Ser Gly Ser Pro Leu Ser Gly Thr Gly Asn Gly Val
2180 2185 2190
Ala Leu Ala Gly Gln Ala Glu Arg Pro Gly Thr Ala Ala Gly Ala Val
2195 2200 2205
Thr Arg Ala Gly Thr Asp Ala Gly Gly Gly Thr Leu Thr Pro Ala Gly
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Ile Asp Ser Gly Leu Gly Thr Ala Ala Pro Val Ala Pro Gly Ala Leu
2225 2230 2235 2240
Ser Pro Gly Asp Leu Gln Ala Ala Leu Arg Gln Gly Leu Ala Gln Val
2245 2250 2255
Ala Gly Pro Ser Leu Thr Asp Tyr Pro Leu Pro Thr Ser Gln Asn Gly
2260 2265 2270
Leu Phe Val Ala Asp Thr Ala Gly Asp Ser Arg Tyr Leu Ile Arg Ser
2275 2280 2285
Asn Pro Thr Leu Ser Gln Leu Gly Gln Val Asp Asn Ser Leu Phe Gly
2290 2295 2300

Asp Leu Arg Gly Leu Leu Gly Gln Thr Pro Gly Thr Ser Val Pro Val
2305 2310 2315 2320
Glu Thr Thr Pro Thr Leu Thr Asp Pro Thr Gln Phe Leu Gly Ser Ser
2325 2330 2335
Tyr Leu Leu Gly Lys Leu Asn Leu Asp Ala Glu His Asp Tyr Arg Phe
2340 2345 2350
Leu Gly Asp Ala Ala Phe Asp Thr Arg Tyr Ile Ser Asn Ala Val Leu
2355 2360 2365
Ser Gln Thr Gly Gln Arg Tyr Leu Asn Gly Val Gly Ser Glu Leu Ala
2370 2375 2380
Gln Met Gln Gln Leu Met Asp Asn Ala Ala Ala Glu Lys Ser Arg Leu
2385 2390 2395 2400
Asn Leu Gln Leu Gly Val Ser Leu Ser Pro Ala Gln Val Ala Gly Leu
2405 2410 2415
Ser His Ser Ile Val Trp Trp Glu Asn Ile Thr Val Gly Gly Gln Thr
2420 2425 2430
Val Leu Ala Pro Lys Leu Tyr Leu Ala Gln Ala Asp Asn Thr His Leu
2435 2440 2445
Gln Gly Ser Arg Leu Val Ala Asp Arg Val Ser Leu Ser Ala Gly Gly
2450 2455 2460
Asp Ile Asp Asn Arg Gly Ser Thr Val Thr Ala Gln Glu Val Leu Asn
2465 2470 2475 2480
Ile Ala Ser Gly Gly Asn Leu Ser Asn Ser Glu Gly Gly Leu Leu Ser
2485 2490 2495
Ala Gly Gly Ala Leu Asn Leu Val Ala Leu Gly Asn Leu Thr Asn Arg
2500 2505 2510
Ser Ala Thr Leu Gln Gly Asn Thr Val Thr Leu Ala Ser Val Asn Gly
2515 2520 2525
Asp Ile Val Asn Ser Thr Thr Thr Asp Gln Trp Gln Phe Glu Ser Ile
2530 2535 2540
Asn Gly Arg Glu Arg Leu Thr His Thr Asp Ile Gly Gln Thr Gly Leu
2545 2550 2555 2560
Ile Thr Ala Gln Asn Gly Leu Thr Leu Gln Ala Gly His Asp Ile Val
2565 2570 2575
Leu Asn Gly Ala Gln Leu Ser Ala Gly Gly Pro Leu Ala Leu Ala Ala
2580 2585 2590
Gly Asn Asp Ile Gln Leu Asn Ala Leu Thr Thr Leu Thr Asp Thr Val
2595 2600 2605
Arg Glu Gly Gly Gly Ala Thr Thr Glu Arg Arg Ser Gln Gly Leu Val
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Arg Ser Thr Val Ala Gly Gly Gly Asp Leu Ser Leu Ser Ala Gly Arg
2625 2630 2635 2640
Asp Leu Ser Gly Thr Ala Ala Gln Leu Ser Ala Ala Gly Thr Leu Ala
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Leu Ser Ala Gly Arg Asp Leu Ser Leu Leu Ser Ala Arg Glu Glu Gln
2660 2665 2670
Phe Gly Ser Asn Ala Trp Ser Arg His Leu Asp Trp Gln Gln Thr Val
2675 2680 2685
Thr Gln Gln Gly Thr Gly Leu Asn Ala Gly Glu Gly Leu Ser Leu Arg
2690 2695 2700
Ala Gly Gln Asp Leu Thr Leu Gln Gly Ala Gln Ala Glu Thr Arg Gly
2705 2710 2715 2720
Ala Leu Thr Ala Gln Ala Gly Arg Asp Leu Ser Leu Leu Ser Ala Thr
2725 2730 2735
Glu Ser Arg His Asp Phe Phe Glu Glu Thr Thr Val Lys Lys Lys Thr
2740 2745 2750
Phe Ser Thr Thr Val Thr His Thr Val Arg Glu Thr Ala Gln Thr Thr
2755 2760 2765
Glu Lys Gly Thr Leu Leu Ser Ala Gly Ser Val Ala Leu Thr Ala Gly
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Gln Asp Ile Gly Val Gln Gly Ser Ser Val Ala Ala Asp Gly Gly Val

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2835 2840 2845
Leu Glu Ser Ala Gly Thr Thr Gln Ser Gln Ser Val Ser Thr Leu Gly
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Ser Thr Gly Gly Ser Val Ser Leu Arg Ala Gly Gln Asp Val Ser Leu
2865 2870 2875 2880
Thr Gly Thr Asp Val Ile Ala Ala Arg Asp Ile Asp Leu Ser Gly Arg
2885 2890 2895
Asn Val Thr Val Thr Pro Gly His Asp Val Arg Arg Thr Thr Gln Thr
2900 2905 2910
Leu Glu Gln Lys Gln Ser Gly Leu Thr Ile Ala Leu Ser Gly Ser Val
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Gly Gly Ala Leu Asn Ser Met Val Glu Thr Val Gln Ala Val Ser Arg
2930 2935 2940
Glu Ser Asp Ser Arg Leu Lys Ser Leu Ala Gly Val Lys Ala Ala Leu
2945 2950 2955 2960
Ser Ala Gly Gln Gly Ala Gln Ala Thr Arg Leu Ala Met Ala Gln Arg
2965 2970 2975
Glu Ala Ala Gly Ala Lys Thr Ala Ala Gly Ser Gly Glu Glu Gly Glu
2980 2985 2990
Gln Pro Gln Ala Val Gly Val Ser Ile Ser Tyr Gly Ser Gln Ser Ser
2995 3000 3005
Arg Ser Glu Gln Arg Gln Thr Gln Glu Thr Val Ser Gly Ser Ser Val
3010 3015 3020
Thr Ala Gly Asp Asn Leu Arg Ile Arg Ala Thr Asp Gly Asp Ile Thr
3025 3030 3035 3040
Val Val Gly Ser Gln Leu Lys Ala Gly Gln Asp Leu Thr Leu Ala Ala
3045 3050 3055
Thr Gln Asp Ile Arg Leu Leu Ser Gly Ala Asn Thr Gln His Thr Glu
3060 3065 3070
Gly Ser Asn Gln Ser Arg Gly Gly Ser Ile Gly Val Ser Ile Gly Val
3075 3080 3085
Ser Ala Ser Gly Ser Phe Gly Leu Ser Val Ser Ala Ser Val Asn Ala
3090 3095 3100
Ala Lys Gly Asn Leu Arg Gly Asp Gly Leu Thr His Thr Glu Ser Leu
3105 3110 3115 3120
Leu Glu Ala Gly Arg Thr Ala Val Leu Gly Ser Gly Arg Asp Thr Thr
3125 3130 3135
Leu Gln Gly Ala Gln Val Ser Ala Glu Thr Ile Thr Ala Arg Val Gly
3140 3145 3150
Arg Asp Leu Leu Val Arg Ser Glu Gln Asp Ser Asp Arg Tyr Asp Ser
3155 3160 3165
Lys Gln Gln Ser Val Ser Ala Gly Val Thr Ile Pro Ile Tyr Gly Gly
3170 3175 3180
Gly Gly Gly Ala Ser Phe Ser Phe Ser Arg Asp Lys Val His Ser Asn
3185 3190 3195 3200
Phe Asp Ser Val Gln Glu Gln Ser Gly Leu Phe Ala Gly Thr Gly Gly
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Tyr Asp Ile His Val Gly Ser His Thr Gln Leu Asp Gly Gly Ala Ile
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Ala Ser Thr Ala Gly Ala Asp Arg Ser Arg Leu Glu Thr Gly Thr Leu
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Gly Phe Ser Asn Ile Asp Asn Arg Ala Glu Tyr Ser Ala Ser His Thr
3250 3255 3260
Gly Gly Gly Phe Ser Thr Ser Ala Pro Val Gly Leu Gln Val Leu Ser
3265 3270 3275 3280

Asn Val Gly Gly Leu Met Leu Ala Gly Ala Asn Gln Ser Gly Ala Ser
3285 3290 3295
Ser Gly Thr Thr Tyr Ala Ala Val Ser Asp Gly Thr Leu Ile Ile Arg
3300 3305 3310
Asp Arg Ala Gly Gln Gln Gln Val Arg Gly Gly Ala Glu Pro Gly Tyr
3315 3320 3325
Gly Gly Gly Gln Gln Arg Gly Ala Glu Pro Asp Ile Arg Gln Gly Glu
3330 3335 3340
Gly Gly Glu Pro Ala Ala Ala Gly Thr Thr Ala Val Gly His Arg Asp
3345 3350 3355 3360
Ala Gly Ala Gly Tyr Arg Leu Tyr Gly Arg Gly Asp Ser Gly Asp Glu
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Gly Gly Glu Cys Ala Ala Gly Gly Asp Ala Gly Gly Ser Ala Ala Gly
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Glu Gly Gly Arg Ala Gly Glu Gly Leu Ala Gly Gln Gly Gly Asn Ala
3395 3400 3405
Gly Gly Gly Asp Ala Gly Ala Val Pro Gly Val Leu Gln Cys Val Ala
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Glu Arg Leu Gly Val Ser Asp Gly Gly Thr Gly Thr Ser Gly Tyr Pro
3425 3430 3435 3440
Gly Gly Gly Gly Gly Ala Ala Gly Cys Ala Gly Gly Glu Cys Gly Ala
3445 3450 3455
Gly Gly Asp Gly Gly Gly Gly Ala Val Cys Gly Gly Gly Asn Pro Pro
3460 3465 3470
Ser Asp Asp Gly Cys Gly Gly Gln His Glu Arg Asp Gly Glu His Ala
3475 3480 3485
Gly Ala Arg Val Ala Gly Cys Gly Gly Gly Ala Gly Gly Arg Glu Thr
3490 3495 3500
Met Arg Trp Arg Cys Gly Gly Glu Ala Gly Gly Glu Leu Ala Ala Arg
3505 3510 3515 3520
Ala Leu Met Glu Gly Leu Tyr Pro Gly Lys Lys Ala Asp Glu Leu Asn
3525 3530 3535
Glu Asp Gln Arg Gln Leu Leu Ser Thr Leu Ser Thr Ile Ala Gly Gly
3540 3545 3550
Leu Ala Ala Gly Val Val Gly Asn Ser Ser Thr Asp Ala Val Gln Gly
3555 3560 3565
Ala Gln Ser Ala Gln Val Ala Val Glu Asn Asn Leu Leu Ser Ala Lys
3570 3575 3580
Arg Ser Gln Asp Arg Tyr Glu Lys Leu Ala Ala Cys Asn Gly Asp Lys
3585 3590 3595 3600
Ala Cys Val Ala Glu Val Arg Arg Glu Phe Gly Pro Glu Ser Asp Glu
3605 3610 3615
Gln Arg Gln Arg Val Glu Asn Cys Ser Ser Ala Ala Asp Cys Tyr Val
3620 3625 3630
Val Glu Gln Gly Leu Lys Ser Met Arg Ala Glu Tyr Ser Gln Gln Glu
3635 3640 3645
Ala Ala Leu Ala Glu Lys Ala Arg Thr Gln Gly Val Ser Ser Leu Ser
3650 3655 3660
Glu Ala Glu Gln Lys Glu Trp Ile Ala Ala Arg Ser Ala Leu Thr Glu
3665 3670 3675 3680
Leu Asp Ser Gln Ile Asn Leu Ser Leu His Arg Ala Gln Thr Met Gly
3685 3690 3695
Gly Ser Thr Glu Val Ser Ala Glu Val Thr Asn Val Met Gly His Ala
3700 3705 3710
Ala Ile Ala Ser Ala Ala Gly Val Ala Gly Gly Ile Ser Lys Ala Gly
3715 3720 3725
Ala Asn Gly Ser Lys Asn Gln Gly Gly Asn Thr Asp Lys Leu Pro Asn
3730 3735 3740
Gly Gln Gln Val Asn His Phe Glu Glu Ser Leu Tyr Asn Leu Pro Pro
3745 3750 3755 3760
Gly Glu Arg Val Ala Leu Val Lys Gln Met Val Asp Gln Val Ala Pro

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                3765                3770                3775
Ser Asn Gly Met Val Lys Asp Asn Lys Leu Thr Arg Ile Asn Asn Arg
            3780                3785                3790
Asp Val Tyr Arg Gly Asn Asp Gly Tyr Leu Tyr Ala Val Asp Thr Gln
        3795                3800                3805
His Gly Arg Phe Glu Gln Val Asn Ala Lys Thr Gly Lys His Gln Gly
    3810                3815                3820
Glu Val Asp Met Gly Met Met Pro Ile Ser Asn Ser Met Asp Lys Ser
3825                3830                3835                3840
Gly Gly His Asp Leu Lys Val Lys
                3845
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<212> PRT
<213> Xylella fastidiosa

<400> 7

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Met Glu Val Ala Gly Ala Arg Ala Gln Leu Ile Ile Ala Asn Pro Ser
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Gly Ile Thr Cys Asn Gly Cys Gly Val Ile Asn Ala His Gln Leu Thr
            20                  25                  30
Leu Thr Thr Gly Thr Pro Ile Phe Asn Ala Arg Gly Ala Leu Asp His
        35                  40                  45
Tyr Arg Val Gln Gly Gly Ala Ile Gln Ile Asp Gly Leu Gly Leu Asp
    50                  55                  60
Ser His Ser Thr Asp Tyr Thr Ala Leu Ile Ala Arg Thr Val Gln Leu
65                  70                  75                  80
Asn Ala Gly Leu Trp Ala His Thr Leu Gln Thr Thr Thr Gly Pro Ala
                85                  90                  95
Thr Val Ala Leu Asp Gly His Pro Thr Ala Ser Leu Pro Ala Pro Pro
            100                 105                 110
Gly Asp Arg Pro Thr Val Ala Leu Asp Val Ser Ala Leu Gly Gly Met
        115                 120                 125
Tyr Ala Gly Lys Ile Thr Leu Ile Gly Thr Glu His Gly Leu Gly Val
    130                 135                 140
Arg Asn Ala Gly Gln Leu Ser Ala Thr Ser Ala Pro Leu Thr Val Thr
145                 150                 155                 160
Val Asp Gly Leu Leu Glu Asn Thr Gly Arg Leu Gln Ser Ala Thr Asp
                165                 170                 175
Thr Gln Leu Asn Ala Thr Ala Glu Val Asn Asn Ser Gly Leu Ile Ser
            180                 185                 190
Ala Ala Gln Thr Leu Thr Leu His Thr Pro Thr Thr Ile Asp Asn Arg
        195                 200                 205
Ser Gly Thr Leu Asn Ala Ala Arg Leu Asp Ile Thr Gly Ala Arg Leu
    210                 215                 220
Asp Asn Arg Gly Gly His Ile Gln Gln Thr Gly Leu Gln Pro Leu Thr
225                 230                 235                 240
Leu Gln Thr Gln His Leu Asp Asn Gln Asp Gln Gly Arg Leu Gly Val
                245                 250                 255
Leu Asp Thr Pro Ala Pro Ala Ser Pro Ala Thr Pro Thr Val Thr Ala
            260                 265                 270
Pro Ile Ser Asn Ala Pro Pro Thr Val Thr Ala Pro Pro Ala Thr Asp
        275                 280                 285
Pro Thr Thr Ser Pro Val Ala Pro Thr Val Pro His Leu Ala His Gly
    290                 295                 300
Thr Leu Thr Leu Thr Gln Thr Ile Asp Asn Arg Gly Gly His Ile Thr
305                 310                 315                 320
Ala Gly Gly Ala Ile Asp Ala Ile Leu Thr Asp Leu Asp Asn Arg Asp
                325                 330                 335
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Gly Thr Ala Ala Leu Asn Arg Leu Thr Leu Gln Gly Gln Arg Leu Asp
            340                 345                 350
Asn Gln His Gly Ile Leu Thr Leu Ala Thr Asp Ala Thr Ile His Thr
        355                 360                 365
His Thr Leu Asn Asn Ala Ala Gly Gln Leu His Ala Asn Gly Thr Leu
    370                 375                 380
Asp Leu Thr Ala Asp Thr Phe Ser Asn Gln Asn Gly Gln Leu Leu His
385                 390                 395                 400
Thr Gly Ser Gln Asn Ala Thr Leu Thr Ile Thr Asp Leu Leu Asp Asn
                405                 410                 415
Gln His Gly Ile Ile Ala Ser Ala Ala Asn Leu Leu Thr Leu Lys Thr
            420                 425                 430
Asp His Leu Asn Asn Ala Ala Gly Gln Leu His Ala Asn Gly Ala Leu
        435                 440                 445
Asp Leu Thr Ala Gln Arg Phe Ser Asn Gln Asn Gly Gln Leu Leu His
    450                 455                 460
Thr Gly Ser Gln Asn Ala Thr Leu Thr Ile Ala Asn Leu Leu Asp Asn
465                 470                 475                 480
Gln His Gly Leu Val Ala Ser Ala Ala Asn Ala Leu Thr Leu His Thr
                485                 490                 495
Gly His Leu Asn Asn Asp Ala Gly Gln Phe Gln Thr Asn Gly Ala Leu
            500                 505                 510
Asp Leu Thr Ala Gln Arg Phe Ser Asn Gln His Gly Gln Phe Leu His
        515                 520                 525
Asn Ser Pro Gln Ser Ala His Leu Arg Ile Asp Gly Gln Leu Asp Asn
    530                 535                 540
Gln Gln Gly Val Leu Ala Ser Asn Ala Ala Glu Leu Thr Leu Glu Thr
545                 550                 555                 560
Gly Gln Phe Asn Asn Asp Ser Gly Thr Leu Gln Gln Ser Gly Gln Gly
                565                 570                 575
Thr Leu His Ile Asp Ala Ala Thr Leu Thr Gly His Gly Gly Thr Leu
            580                 585                 590
Thr Ser Gln Gly Ala Leu Thr Leu Thr Gly Thr His Thr Asp Leu Ser
        595                 600                 605
His Ala Thr Thr Thr Ala Gln His Ile Thr Ile His Thr Asp Asp Leu
    610                 615                 620
Thr Thr Ala Gly Gly His Leu Thr Ala Tyr Gly Glu His Thr Leu Gln
625                 630                 635                 640
Leu Asn Ala Arg Thr Arg Ile Asp Asn Thr Ala Gly Thr Ile Ala Thr
                645                 650                 655
Asn Gly Ser Leu Asp Leu His Thr Ala Ala Leu Asp Asn Thr Gly Gly
            660                 665                 670
Thr Leu His Ser Thr Ala Thr Gly Pro Asn Arg Leu Asp Ile Thr His
        675                 680                 685
Thr Leu Thr Asn Thr Ala Gly His Leu Leu Leu Asn Gly Pro Thr Thr
    690                 695                 700
Leu Thr Thr Gly Thr Trp Thr Asn Thr Gly Gly Gln Leu Gln Ile Thr
705                 710                 715                 720
Gly Pro Ala Thr Leu His Ala Thr Thr Leu Asp Asn Arg Gly Gly Ile
                725                 730                 735
Leu His Thr Ala Thr Gly Pro Leu Asp Leu Arg Val Thr Gly Thr Ile
            740                 745                 750
Asn Asn Gln Asp Asn Gly Ile Leu Ser Ser Thr Ala Ala Leu Thr Leu
        755                 760                 765
Thr Ala Ala Ser Leu His Asn Gln His Gly Thr Leu Asp Ala Ala Gly
    770                 775                 780
Pro Ala His Leu Thr Leu Thr Gly Leu Leu Asp Asn Thr Ala Gly Leu
785                 790                 795                 800
Leu Gln Thr Ala His Thr Leu Trp Leu Thr Ser Ala Gly Leu Thr Asn
                805                 810                 815
Arg Ser Gly Thr Leu Thr Ala Ala Ala Leu Thr Leu Asp Thr Gln Ala
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            820                 825                 830
His Thr Leu Asp Asn Thr Ser Gly Arg Leu Gly Thr Thr Thr Gly Asn
        835                 840                 845
Leu Thr Leu His Thr Gly Leu Leu Asp Asn Thr Ala Gly Leu Leu Gln
    850                 855                 860
Thr Ala Ala Thr Leu Thr Ile Asp Thr Gly Ala Ala Pro Leu Thr Asn
865                 870                 875                 880
Arg Asp Gly Gly Thr Leu Leu Ala Ala Asp Thr Leu Asp Leu His Thr
                885                 890                 895
Thr Thr Leu Asp Asn Arg Gly Gly Thr Ile Asp Ser Gln Thr Ala Thr
            900                 905                 910
His Leu His Thr Thr Thr Ile Asp Asn Thr Thr Ala Gly His Ile Ser
        915                 920                 925
Ser Asn Gly Thr Leu Gln Ile Asp Gly Thr Thr Leu Thr Asn Thr Gly
    930                 935                 940
Gly Arg Leu His Ser Gly Gly Asp Thr Arg Leu His Leu Gln Asp Thr
945                 950                 955                 960
Leu Asn Asn His Asp Gly Arg Ile Thr Ala Ala Gly Thr Leu Asp Ile
                965                 970                 975
Thr Thr Thr Thr Leu Asp Asn His Ser Thr Pro Leu Thr Ala Pro Pro
            980                 985                 990
Ala Thr Gln Thr Arg Ala Pro Thr Gly Ala Pro Asp Asn Gly Leu Tyr
        995                 1000                1005
Ala Thr His Ile Gln Ile Ala Ser Thr Thr Leu Asp Asn Thr Ala Gly
    1010                1015                1020
Thr Leu Ser Ala Ala Gln Asn Leu Thr Leu Thr Leu Ser Asp Thr Leu
1025                1030                1035                1040
Thr Asn Thr Ala Gly His Leu Ser Ala Gly Ala Thr Leu Asp Leu Thr
                1045                1050                1055
Ala Asp His Leu Ser Asn His Thr Gly Thr Leu Leu Ser Gly Ala Ser
            1060                1065                1070
Gln Thr Leu His Leu His Arg Leu Thr Gly Asp Gly Arg Leu His Ala
        1075                1080                1085
Gly Asn Ala Leu Thr Leu Thr Leu Gln Asp Ser Leu Asp Thr Ala Gly
    1090                1095                1100
Thr Leu Ser Ala Thr Gly Leu Leu Thr Leu Thr Thr Ala Gly Asp Leu
1105                1110                1115                1120
Thr Asn Arg Gly Leu Ile Gln Ala Ala Asp Leu Thr Ala Gln Ala Arg
                1125                1130                1135
Asp Ile Thr Thr Thr Ala Thr Gly Gln Leu Leu Thr Thr Gly His Thr
            1140                1145                1150
His Leu Thr Ala Thr Gly Thr Leu Asn Asn Ser Gly His Leu Gln Ala
        1155                1160                1165
Ala Asp Leu Thr Ala Gln Ala His Asp Ile Thr Thr Thr Ala Thr Gly
    1170                1175                1180
Gln Leu Leu Thr Thr Gly His Thr His Leu Thr Ala Thr Gly Thr Leu
1185                1190                1195                1200
Asn Asn Ser Gly His Leu Gln Ala Ala Asp Leu Thr Ala Gln Ala Asn
                1205                1210                1215
Thr Ile Thr Asn Thr Gly Thr Phe Leu Ala Thr Ser His Ala Thr Leu
            1220                1225                1230
Thr Ala Thr Asp Thr Leu Thr Asn Ser Gly Leu Leu Gln Ala Ala Asp
        1235                1240                1245
Leu Thr Ala Gln Ala Asn Thr Ile Thr Asn Thr Ala Thr Gly Arg Leu
    1250                1255                1260
Leu Thr Thr Ala His Thr Gln Leu Thr Ala Thr Asp Thr Leu Thr Asn
1265                1270                1275                1280
Ser Gly Leu Val His Ala Gly Asp Leu Thr Val His Ala Arg Asp Ile
                1285                1290                1295
Thr Asn Thr Ala Thr Gly Gln Leu Ile Ala Ser Asn Leu Ala Gln Leu
            1300                1305                1310
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Thr Ala Thr Ala Thr Leu Thr Asn Arg Gly Leu Ile Asp Ala Phe Thr
1315 1320 1325
Thr His Leu Ser Ala Pro Thr Ile Asp Asn Leu Gly Thr Gly Arg Leu
1330 1335 1340
Tyr Gly Asp His Ile Ala Leu Gln Ala His Thr Leu Thr Asn Arg Asp
1345 1350 1355 1360
Glu Thr Ser Asp Gly His Thr His Thr Ala Thr Ile Ala Ala Arg Glu
1365 1370 1375
Arg Leu Asp Ile Gly Ala Asp Thr Leu Arg Asn Thr Ala Asn Ala Met
1380 1385 1390
Ile Leu Ser Asp Gly Asp Ala Ala Ile Gly Ala Thr Leu Asp Asn Thr
1395 1400 1405
Leu His Ala Thr Gly Ile Ala Thr Leu Ile Asp Asn Arg Ser Ala Thr
1410 1415 1420
Ile Asp Ile Thr Gly Thr Leu Asn Ile Thr Thr Thr Thr Leu Asn Asn
1425 1430 1435 1440
Ile Arg Glu Asn Val His Ile Ala His Ala Pro Asp Val Val Thr Glu
1445 1450 1455
Thr Pro Met Tyr Gln Pro His Trp Arg Lys Asn Lys Pro Asn Gly Gly
1460 1465 1470
Ser Gly Asp Phe Arg Leu Ser Ser Asn Tyr Asp Ala His Asp Ile Tyr
1475 1480 1485
Tyr Leu Asn Pro Ala Asp Ile Leu Glu Asp Thr Pro Tyr Ile Thr Pro
1490 1495 1500
Asp Gly Gln Lys Ile His Arg Ala Ile Val Arg Leu Thr Pro Gln Thr
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Ser Ala Tyr Phe Tyr Ala Arg Gly Gly Leu His Ala Ser Gln Ala Glu
1525 1530 1535
Arg Arg Arg Leu Asp Leu Thr Ala Arg Thr Gly Asp Ser Val Val Leu
1540 1545 1550
Tyr Tyr Thr Asp Arg Gln Asp Lys Gln Pro Asn Pro Asp His Val Ala
1555 1560 1565
Ala Ala Ala Thr Asn Asp Ser Ala Phe Ile Gly Leu Asp Ala Pro Gln
1570 1575 1580
Gln Asn Glu Arg Leu Lys Ile Val Pro Ile Thr Tyr Ala Pro Gly Asp
1585 1590 1595 1600
Asp Arg Leu Thr Tyr Asp Pro Thr Tyr Gly Thr Cys Thr Asp Asp Cys
1605 1610 1615
Val Arg Leu Val Thr Trp His Asp Tyr Thr Asp Pro Asp His Thr Leu
1620 1625 1630
Ile Asp Met Arg Arg Gly Pro Asn Asp Val Asp Asp Asn Glu Arg Glu
1635 1640 1645
Arg His Ala Thr Arg Thr Thr Gln Gln Glu Ile Leu Asn Pro Asp Ala
1650 1655 1660
Gly Ala Pro Ala Leu Ile Gln Ser Gly Gly Thr Met Arg Ile Asp Val
1665 1670 1675 1680
Gly Tyr Leu Tyr Asn His Tyr Ala Asp Leu Leu Ala Gly Gly Asp Gln
1685 1690 1695
Thr Ile Val Gly Leu Pro Pro His Pro Thr Lys Glu Thr Ala Asp Asp
1700 1705 1710
Glu His Lys Tyr Asn Arg Ala Leu Leu Ile Asp Asn Arg Ala Leu Gln
1715 1720 1725
Leu Ser Arg Thr Asp Arg Phe Gln Asn Ile Ser Thr Thr Tyr Arg Gly
1730 1735 1740
Lys Asp Ser Ala Pro Trp Ser Asn Glu Ser Arg Thr Thr Pro Thr Thr
1745 1750 1755 1760
Gln Ile Gly Gly Arg Ile Thr Ser Gly Gly His Gln His Ile Ala Ala
1765 1770 1775
Gln Thr Phe Asn Asn Val Thr Asp Ser Thr His Ala Pro Glu Pro Ile
1780 1785 1790
Gln His Val Thr Tyr Asn Pro Ser Thr Gln Thr Leu Thr Ile Ala Asp

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        1795                1800                1805
Gly His Ile Thr Val Thr Asp Thr Pro Pro Ser Leu His Thr Val Ser
    1810                1815                1820
Leu Ala Asp Asn Gly Phe Ser His Gly Gln Glu Leu Thr Tyr Ile Pro
1825                1830                1835                1840
Glu Lys Ser Ile Thr Thr Pro Asn Ala Pro Ile Arg Asp Pro Ala Ala
                1845                1850                1855
Pro Pro Arg Arg His Arg His Pro His Arg Pro Pro His Pro Ala Gln
            1860                1865                1870
Gln Gln Pro Leu His His Ser Pro Arg His Arg His Pro His His His
        1875                1880                1885
Arg Pro Pro Leu Tyr Pro Arg Pro Pro Leu His Gln Arg Arg Gln Pro
    1890                1895                1900
Thr Pro Arg Pro Gly Arg Pro Arg His Pro Pro Gln Thr Pro Arg Arg
1905                1910                1915                1920
Arg Leu Leu Arg Thr Thr Pro His Pro Arg Thr Asn His Pro Thr His
                1925                1930                1935
Arg Pro Pro Pro Pro Gly Arg Leu His Arg Arg Arg Pro Pro Ile Pro
            1940                1945                1950
Arg Pro Pro Gly Arg Arg Pro His Arg Arg Gln Thr Ala Pro Thr Ala
        1955                1960                1965
Pro Arg His Cys Pro Gln Cys Arg Pro Asn Gly Pro Thr His Gln Arg
    1970                1975                1980
His Arg Leu Ala Arg Pro Thr Arg Arg Pro Pro Ala Arg Arg His His
1985                1990                1995                2000
His Arg Arg Pro Arg Pro Pro Pro Leu Pro Ala Pro Pro His Arg Arg
                2005                2010                2015
Pro His Pro Arg Arg Arg Pro Pro Gly Gly Arg Gln His His His Gln
            2020                2025                2030
Arg Pro His Pro His Gln His Arg His His Arg Pro Arg Pro His Gln
        2035                2040                2045
His Gln His Pro His His Gly Pro Thr Arg Arg Pro Pro Tyr Arg Arg
    2050                2055                2060
Arg His Gln His Pro His His Arg Arg Leu His Gln Pro Gly Arg Thr
2065                2070                2075                2080
Ile His Arg Arg Arg Leu Pro Gln Ser Pro Cys Pro Arg Gln Leu Pro
                2085                2090                2095
Cys Gln His Pro Thr Arg Arg His His Pro Arg His Pro Pro Pro Gln
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Arg Asp Gly Thr Gly Pro Thr Gly Arg Leu His Arg His Arg Pro Arg
        2115                2120                2125
Arg Leu Pro Arg Leu Glu His Arg Pro Ser His Asp Pro Thr Ser Arg
    2130                2135                2140
Cys His Gln Gln His Arg Pro Arg Leu His Leu Pro Gln Ser His Arg
2145                2150                2155                2160
Pro Pro Thr Pro Gly His Pro Gln His Pro Pro Gln Arg His His Pro
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Val Gly Pro Pro Gln Gln Pro Pro His Pro His Arg Tyr Arg Thr Arg
            2180                2185                2190
His Gln His His Arg Gln Arg Arg Tyr Gln His Gln Arg Arg Cys Arg
        2195                2200                2205
His Gln Arg Pro Cys Arg His Pro Gly Gln Gln Arg Arg Pro Asp Pro
    2210                2215                2220
Asp Leu Gln Thr Arg Gln Arg Asp Pro Ala Gly Arg Arg Ser Thr Pro
2225                2230                2235                2240
Gln Pro Thr Arg Ala His Gln Pro Pro Gln Arg Pro Ala Pro Phe Gln
                2245                2250                2255
Gln Gln Pro Gln His Leu Gln Gln His Arg Tyr Arg Arg Pro Leu Gln
            2260                2265                2270
Arg Pro Gly Arg Gln Glu His His His His Arg Arg Arg His Cys Pro
        2275                2280                2285
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Gln Arg Arg His Pro Val His Cys Ser Arg His Arg His Leu Arg His
2290 2295 2300
Gln Gly Arg Ala Pro Gly Glu Arg Thr Lys His Pro Gln Leu Gln Leu
2305 2310 2315 2320
His Gln Pro Thr Ala Gln Gln Arg Pro Leu Pro Arg Arg Pro Gly Cys
2325 2330 2335
Glu His Arg Leu Gln Pro Ile Gln Thr Arg Arg His Pro Gly His Leu
2340 2345 2350
Gln Arg Cys Gln Tyr Gly Gly Cys Thr Gln Trp Gln His His Tyr Pro
2355 2360 2365
Leu Gln Pro Arg Gln Arg Arg Cys Cys Arg Arg Thr Ala Cys Arg Arg
2370 2375 2380
Gln Pro Gln Arg Gln Arg Arg Gln Arg Pro Gly Arg Gly Leu Arg His
2385 2390 2395 2400
Pro Gln His Pro Arg Thr Ala Ile Gln Gln Thr Lys Arg Pro Asp His
2405 2410 2415
Arg Leu Gln Gln Cys Ser Asn Gln His Arg Ser Gly Arg Leu Gly Pro
2420 2425 2430
Glu Lys Pro Pro Gln Arg Pro His Arg Thr Ala Glu Gln Pro Leu Arg
2435 2440 2445
Leu Ala Cys Pro Glu His Arg Arg Gln Arg Arg Leu Ser Gly Leu Trp
2450 2455 2460
Arg Asn Arg His Pro Ala Gln Asp Gln Gln Pro Ala Glu His Leu Ser
2465 2470 2475 2480
Asn Arg Arg Leu Cys Arg His Gln Gln Gln Pro Lys Pro Lys Gln His
2485 2490 2495
Glu Arg Pro His Arg Pro Arg His Pro Ile Thr Arg Arg Trp His Leu
2500 2505 2510
His His Arg Leu Trp Cys Leu Arg Thr Gly Lys Arg Gln Ser His Thr
2515 2520 2525
Gln Ser Arg His Arg Gln His Gln Arg His Arg Arg Pro Val Gln Gln
2530 2535 2540

Pro Ser Glu Pro His Arg Arg Trp Gln Pro Gly Arg Pro Gln Arg Pro
2545 2550 2555 2560
Glu His Pro Arg Thr Asn Leu Gln Pro Ala Pro Pro Gln Arg Gln Pro
2565 2570 2575
Gly Cys Gln Asp Arg Gly Asp Arg Arg Arg His Gln Arg Gln Arg Arg
2580 2585 2590
Cys Gly Pro Arg Pro Arg Leu Leu Pro Pro Ala Val Arg His Pro Gly
2595 2600 2605
His Arg Leu His Arg Gly Gln Ser Arg His His Gln Arg Trp Arg Arg
2610 2615 2620
Cys His His Glu Gly Gly Pro Pro Gln Arg Pro Leu His Ser His His
2625 2630 2635 2640
Cys Arg Gln Pro Gly His His Gln Pro Ala Arg His Pro Ala Gly Gln
2645 2650 2655
Arg Pro Ala Thr Pro Glu Gln His Arg Arg His Leu Gly His Gln Arg
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Arg Arg Gln His Arg His Leu Gln Pro Gln Pro Pro Arg Arg His Pro
2675 2680 2685
Arg Leu Arg Gln Arg Pro Gln Pro Lys Arg Pro Ile Cys Arg Gly Arg
2690 2695 2700
Trp Leu His His Arg Arg Arg Pro Pro Ile Arg Arg Arg Pro His Gln
2705 2710 2715 2720
His Arg Pro Thr Gly Thr Pro Ser Leu Leu His Gln His His Trp Leu
2725 2730 2735
Tyr Arg His Pro Gln Pro Gln Gln Arg Gln Arg Gln Arg Leu Trp His
2740 2745 2750
His His Arg Gln Pro Gly Gln Arg Pro Glu Gln Lys Gln Pro Gln Arg
2755 2760 2765

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His Arg Gln Pro Trp Phe Val Asp Leu Gln Arg Pro Glu Lys Arg Arg
    2770                2775                2780
Arg Pro Met Asp Gly Gln Cys Arg Pro Gln Arg Pro Thr Gln His His
2785                2790                2795                2800
Arg Cys Arg Gly Gln Arg His Lys His Pro Gly Gln Pro Trp Gln Gln
                2805                2810                2815
Arg Arg Pro Gly His Pro Ala Pro Pro His Arg Arg Pro Pro Gly Leu
            2820                2825                2830
Lys Pro His Arg Pro Gly Arg Pro Ala Asn Arg Cys Pro Ala Ala Gln
        2835                2840                2845
Pro Gly Arg Arg Pro Ala Gly His Arg Pro Tyr His Gly Gly Pro Glu
    2850                2855                2860
His Gln Gln His Ala His Pro His Thr Gln Gln Ser Val Leu His Pro
2865                2870                2875                2880
Thr Thr Leu His Gln Arg Pro Cys Cys Gln Arg Cys Pro Gly Glu Arg

                2885                2890                2895
Thr His Arg Ser Thr Ala Pro Gly Pro Ser Gly Leu Val Gly Pro Lys
            2900                2905                2910
Thr Pro Pro Thr Arg Arg Cys Arg Thr Arg Ala His Arg Pro Gln Arg
        2915                2920                2925
Gln Pro Arg Ala Gly Ser Arg Gln Ser Gln Gly Asp Asp Cys Gln Arg
    2930                2935                2940
Arg Gly Pro Leu Gln Pro Ala Thr Pro Ala Gly Leu Arg Ala Leu Gly
2945                2950                2955                2960
His Gln Pro Arg His Arg Gln Cys Pro Ser Ala Ala Gly Glu Pro Gly
                2965                2970                2975
Arg Pro Gln Pro Leu Ile Gly Arg Arg Lys Glu Thr Arg His Pro Leu
            2980                2985                2990
Arg Gln Arg His Gln Gln Arg His Pro Pro Arg Arg Gly Thr Gly Leu
        2995                3000                3005
Ala Asp Asp Ala Glu Glu Gln Gln Arg Arg His Cys Lys Arg Arg Asn
    3010                3015                3020
Leu Pro Lys His His Leu Pro Gly Val Tyr Gln Thr His Pro Pro Ala
3025                3030                3035                3040
Gly Gly Thr Gly Asp Arg Arg His Glu Thr Ala Gly Asp His Gln Asn
                3045                3050                3055
Arg Gln Pro Arg Leu Ala Ala Gln Gly Arg Gly Gly Gln Arg Ala Asp
            3060                3065                3070
Val Arg Arg Gly Gln Lys Ile Tyr Lys Ser Asp Leu Phe Arg Gly Pro
        3075                3080                3085
Gln Pro Arg His Asp Glu Ala Gln Gln Cys Thr Ala Gly Ala Arg Arg
    3090                3095                3100
Gly Ser Cys Val His Ser Asp Pro Arg Leu Gln Pro Cys Gly Arg Arg
3105                3110                3115                3120
Gln Pro Pro Cys Gly Arg Cys Pro Gly Asp Glu Lys Thr Ser Gln Asp
                3125                3130                3135
Leu Gly Pro Ala Gln Gly Leu Cys Gly Gln Asp Trp Arg Leu Cys Arg
            3140                3145                3150
Gln Cys His Leu Pro Ser Val Gly Asp Leu Pro Asn Gln Leu Leu Arg
        3155                3160                3165
Ala Gln Gln Arg Arg His Arg Arg Pro Gly Gln Arg Leu Lys Pro Cys
    3170                3175                3180
Gln Cys Pro Arg Val Val Gln Leu Arg Arg Pro Gly Tyr Gln Gly His
3185                3190                3195                3200
Glu Arg Gln Ala Ser Gly Ala Asp His Arg Ala Ala Ala Ala Met Ala
                3205                3210                3215
Glu Asp Thr Gln Pro Arg Glu Pro Gly Gly Asp Pro Thr His Pro Val
            3220                3225                3230
Ala Thr Pro Ala Val Ala Ile Gly Pro Val Ala Thr Ala Val Arg Gln
        3235                3240                3245
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Gln Arg Pro Ala Thr Ala Thr Pro Thr Val Ala Pro Val Pro His Pro
3265 3270 3275 3280
Leu Leu

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Tyr Gln Ala Tyr Thr Lys Pro Thr His Gln Leu Gly Glu Leu Val Thr
35 40 45
Ala Gly Ile Glu Lys Leu Leu Glu Ile Thr Lys Ile Ala Ser Pro Ala
50 55 60
Ser Arg Leu Lys Ala Ala Ala Ala Lys Glu Leu Met Tyr Asn Thr Glu
65 70 75 80
Gln Gly Asn Tyr Ser Asn Leu Val Tyr Leu Glu Gly His Ser Arg Gly
85 90 95
Thr Met Thr Leu Ser Asn Ala Leu Arg Val Leu Ala Gly Phe Asn Val
100 105 110
Gly Asp Thr Lys Leu Glu Val Leu Ala Tyr Asn Pro Ala Ala Glu Gly
115 120 125
Asn Arg Leu Asn Thr Thr Tyr Gln Ala Tyr Thr Lys Pro Thr His Gln
130 135 140
Leu Gly Glu Leu Val Thr Ala Gly Ile Glu Lys Leu Leu Glu Ile Thr
145 150 155 160
Lys Ile Ala Ser Pro Ala Ser Arg Leu Lys Ala Ala Ala Ala Lys Glu
165 170 175
Leu Met Tyr Asn Thr Glu Gln Gly Asn Tyr Ser Asn Leu Val Tyr Leu
180 185 190
Glu Gly His Ser Arg Gly Thr Met Thr Leu Ser Asn Ala Leu Arg Val
195 200 205
Leu Ala Ala Asp His Val Leu Ser Asp Thr Leu Glu Ile Arg Ala Tyr
210 215 220
Asn Pro Ala Ala Glu Gly Asn Arg Leu Ala Glu Ala Ala Ala Leu Val
225 230 235 240
Thr Lys Lys Pro Val Lys Thr Trp Ala Pro Pro Lys Asp Phe Val Ala
245 250 255
Asn Lys Ile Gly Gly Tyr Ala Gly Asn Ala Thr Phe His Asp Leu Arg
260 265 270
Glu Ile Phe Gln Thr Asn Tyr Ser Val His Ser Ser Gly Gly Thr Ala
275 280 285
Ala Leu Gly Ser Asp Ser Asn His Val Asp Lys Glu Lys Leu Phe Ser
290 295 300
Tyr Glu Gly Leu Asp Ile Lys Asp Met Asn Ala Lys Arg Gln Gly Arg
305 310 315 320
Thr Ile Gly Leu Leu Gln Gln Trp Gln Lys Thr Arg Arg Pro Glu Asp
325 330 335
Pro Val Ala Thr Gln Leu Thr Gln Leu Gln Arg Leu Leu Trp Gln Ser
340 345 350
Gly Gln Trp Gln Gln Gln Leu Asp Asn Thr Pro Gly Leu Leu Thr Arg
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Pro Thr Pro Thr Thr Pro Asp Ala Pro Ser Ala Arg Gln Gln Gln Leu

370 375 380
Gln Gln Leu Arg Gln Ser Leu Thr Pro Tyr
385 390

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caattgacgt 10

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<400> 30
acgacttgca tagcagtagc 20

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<400> 31
ttgtcctgac ggtcg 15

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<400> 32
ccaccattga caacc 15

<210> 33
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Cys Xaa Xaa Cys
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