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(54) Title: SCHIZOCHYTRIUM PKS GENES

(57) Abrégé/Abstract:
The present invention relates to compositions and methods for preparing poly-unsaturated long chain fatty acids in plants, plant parts and plant cells, such as leaves, roots, fruits and seeds. Nucleic acid sequences and constructs encoding PKS-like genes required for the poly-unsaturated long chain fatty acid production, including the genes responsible for eicosapentenoic acid production of Shewanella putrefaciens and novel genes associated with the production of docosahexenoic acid in Vibrio marinus are used to generate transgenic plants, plant parts and cells which contain and express one or more transgenes encoding one or more of the PKS-like genes associated with such long chain poly-unsaturated fatty acid production. Expression of the PKS-like genes in the plant system permits the large scale production of poly-unsaturated long chain fatty acids such as eicosapentenoic acid and docosahexonoic acid for modification of the fatty acid profile of plants, plant parts and tissues. Manipulation of the fatty acid profiles allows for the production of commercial quantities of novel plant oils and products.

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(57) Abstract

The present invention relates to compositions and methods for preparing poly–unsaturated long chain fatty acids in plants, plant parts and plant cells, such as leaves, roots, fruits and seeds. Nucleic acid sequences and constructs encoding PKS–like genes required for the poly–unsaturated long chain fatty acid production, including the genes responsible for eicosapentenoic acid production of *Shewanella putrefaciens* and novel genes associated with the production of docosahexenoic acid in *Vibrio marinus* are used to generate transgenic plants, plant parts and cells which contain and express one or more transgenes encoding one or more of the PKS–like genes associated with such long chain poly–unsaturated fatty acid production. Expression of the PKS–like genes in the plant system permits the large scale production of poly–unsaturated long chain fatty acids such as eicosapentenoic acid and docosahexonoic acid for modification of the fatty acid profile of plants, plant parts and tissues. Manipulation of the fatty acid profiles allows for the production of commercial quantities of novel plant oils and products.

SCHIZOCHYTRIUM PKS GENES

INTRODUCTION

Field of the Invention

This invention relates to modulating levels of enzymes and/or enzyme components capable of modifying long chain poly-unsaturated fatty acids (PUFAs) in a host cell, and constructs and methods for producing PUFAs in a host cell. The invention is exemplified by production of eicosapentenoic acid (EPA) using genes derived from *Shewanella putrefaciens* and *Vibrio marinus*.

Background

Two main families of poly-unsaturated fatty acids (PUFAs) are the ω3 fatty acids, exemplified by eicosapentenoic acid, and the ω6 fatty acids, exemplified by arachidonic acid. PUFAs are important components of the plasma membrane of the cell, where they can be found in such forms as phospholipids, and also can be found in triglycerides. PUFAs also serve as precursors to other molecules of importance in human beings and animals, including the prostacyclins, leukotrienes and prostaglandins. Long chain PUFAs of importance include docosahexenoic acid (DHA) and eicosapentenoic acid (EPA), which are found primarily in different types of fish oil, gamma-linolenic acid (GLA), which is found in the seeds of a number of plants, including evening primrose (*Oenothera biennis*), borage (*Borago officinalis*) and black currants (*Ribes nigrum*), stearidonic acid (SDA), which is found in marine oils and plant seeds, and arachidonic acid (ARA), which along with GLA is found in filamentous fungi. ARA can be purified from animal tissues including liver and adrenal gland. Several genera of marine bacteria are known which synthesize either EPA or DHA. DHA is present in human milk along with ARA.

PUFAs are necessary for proper development, particularly in the developing infant brain, and for tissue formation and repair. As an example, DHA, is an important constituent of many human cell membranes, in particular nervous cells (gray matter), muscle cells, and spermatozoa and believed to affect the development of brain functions in general and to be essential for the development of eyesight. EPA and DHA have a number of nutritional and pharmacological uses. As an example adults affected by diabetes (especially non insulin-dependent) show

deficiencies and imbalances in their levels of DHA which are believed to contribute to later coronary conditions. Therefore a diet balanced in DHA may be beneficial to diabetics.

For DHA, a number of sources exist for commercial production including a variety of marine organisms, oils obtained from cold water marine fish, and egg yolk fractions. The purification of DHA from fish sources is relatively expensive due to technical difficulties, making DHA expensive and in short supply. In algae such as *Amphidinium* and *Schizochytrium* and marine fungi such as *Thraustochytrium* DHA may represent up to 48% of the fatty acid content of the cell. A few bacteria also are reported to produce DHA. These are generally deep sea bacteria such as *Vibrio marinus*. For ARA, microorganisms including the genera *Mortierella, Entomophthora, Phytium* and *Porphyridium* can be used for commercial production. Commercial sources of SDA include the genera *Trichodesma* and *Echium*. Commercial sources of GLA include evening primrose, black currants and borage. However, there are several disadvantages associated with commercial production of PUFAs from natural sources. Natural sources of PUFA, such as animals and plants, tend to have highly heterogeneous oil compositions. The oils obtained from these sources can require extensive purification to separate out one or more desired PUFA or to produce an oil which is enriched in one or more desired PUFA.

Natural sources also are subject to uncontrollable fluctuations in availability. Fish stocks may undergo natural variation or may be depleted by overfishing. Animal oils, and particularly fish oils, can accumulate environmental pollutants. Weather and disease can cause fluctuation in yields from both fish and plant sources. Cropland available for production of alternate oil-producing crops is subject to competition from the steady expansion of human populations and the associated increased need for food production on the remaining arable land. Crops which do produce PUFAs, such as borage, have not been adapted to commercial growth and may not perform well in monoculture. Growth of such crops is thus not economically competitive where more profitable and better established crops can be grown. Large -scale fermentation of organisms such as *Shewanella* also is expensive. Natural animal tissues contain low amounts of ARA and are difficult to process. Microorganisms such as *Porphyridium* and *Shewanella* are difficult to cultivate on a commercial scale.

Dietary supplements and pharmaceutical formulations containing PUFAs can retain the disadvantages of the PUFA source. Supplements such as fish oil capsules can contain low levels of the particular desired component and thus require large dosages. High dosages result in ingestion of high levels of undesired components, including contaminants. Care must be taken in providing fatty acid supplements, as overaddition may result in suppression of endogenous biosynthetic pathways and lead to competition with other necessary fatty acids in various lipid fractions *in vivo*, leading to undesirable results. For example, Eskimos having a diet high in ω3 fatty acids have an increased tendency to bleed (U.S. Pat. No. 4,874,603). Fish oils have

unpleasant tastes and odors, which may be impossible to economically separate from the desired product, such as a food supplements. Unpleasant tastes and odors of the supplements can make such regimens involving the supplement undesirable and may inhibit compliance by the patient.

A number of enzymes have been identified as being involved in PUFA biosynthesis. Linoleic acid (LA, 18:2 Δ 9, 12) is produced from oleic acid (18:1 Δ9) by a Δ12-desaturase. GLA (18:3 Δ 6, 9, 12) is produced from linoleic acid (LA, 18:2 Δ9, 12) by a Δ6-desaturase. ARA (20:4 Δ 5, 8, 11, 14) is produced from DGLA (20:3 Δ 8, 11, 14), catalyzed by a Δ5-desaturase. Eicosapentenoic acid (EPA) is a 20 carbon, omega 3 fatty acid containing 5 double bonds (Δ 5, 8, 11, 14, 17), all in the *cis* configuration. EPA, and the related DHA (Δ 4, 7, 10, 13, 16, 19, C22:6) are produced from oleic acid by a series of elongation and desaturation reactions. Additionally, an elongase (or elongases) is required to extend the 18 carbon PUFAs out to 20 and 22 carbon chain lengths. However, animals cannot convert oleic acid (18:1 Δ 9) into linoleic acid (18:2 Δ 9, 12). Likewise, μ-linolenic acid (ALA, 18:3 Δ 9, 12, 15) cannot be synthesized by mammals. Other eukaryotes, including fungi and plants, have enzymes which desaturate at positions Δ12 and Δ15. The major poly-unsaturated fatty acids of animals therefore are either derived from diet and/or from desaturation and elongation of linoleic acid (18:2 Δ 9, 12) or μ-linolenic acid (18:3 Δ 9, 12, 15).

Poly-unsaturated fatty acids are considered to be useful for nutritional, pharmaceutical, industrial, and other purposes. An expansive supply of poly-unsaturated fatty acids from natural sources and from chemical synthesis are not sufficient for commercial needs. Because a number of separate desaturase and elongase enzymes are required for fatty acid synthesis from linoleic acid (LA, 18:2 Δ 9, 12), common in most plant species, to the more saturated and longer chain PUFAs, engineering plant host cells for the expression of EPA and DHA may require expression of five or six separate enzyme activities to achieve expression, at least for EPA and DHA, and for production of quantities of such PUFAs additional engineering efforts may be required, for instance the down regulation of enzymes competing for substrate, engineering of higher enzyme activities such as by mutagenesis or targeting of enzymes to plastid organelles. Therefore it is of interest to obtain genetic material involved in PUFA biosynthesis from species that naturally produce these fatty acids and to express the isolated material alone or in combination in a heterologous system which can be manipulated to allow production of commercial quantities of PUFAs.

Relevant Literature

Several genera of marine bacteria have been identified which synthesize either EPA or DHA (DeLong and Yayanos, *Applied and Environmental Microbiology* (1986) 51: 730-737). Researchers of the Sagami Chemical Research Institute have reported EPA production in *E. coli* which have been transformed with a gene cluster from the marine bacterium, *Shewanella*

putrefaciens. A minimum of 5 open reading frames (ORFs) are required for fatty acid synthesis of EPA in *E. coli*. To date, extensive characterization of the functions of the proteins encoded by these genes has not been reported (Yazawa (1996) *Lipids* 31, S-297; WO 93/23545; WO 96/21735).

The protein sequence of open reading frame (ORF) 3 as published by Yazawa, USPN 5,683,898 is not a functional protein. Yazawa defines the protein as initiating at the methionine codon at nucleotides 9016-9014 of the *Shewanella* PKS-like cluster (Genbank accession U73935) and ending at the stop codon at nucleotides 8185-8183 of the *Shewanella* PKS-like cluster. However, when this ORF is expressed under control of a heterologous promoter in an *E. coli* strain containing the entire PKS-like cluster except ORF 3, the recombinant cells do not produce EPA.

Polyketides are secondary metabolites the synthesis of which involves a set of enzymatic reactions analogous to those of fatty acid synthesis (see reviews: Hopwood and Sherman, *Annu. Rev. Genet.* (1990) 24: 37-66, and Katz and Donadio, *in Annual Review of Microbiology* (1993) 47: 875-912). It has been proposed to use polyketide synthases to produce novel antibiotics (Hutchinson and Fujii, *Annual Review of Microbiology* (1995) 49:201-238).

SUMMARY OF THE INVENTION

Novel compositions and methods are provided for preparation of long chain poly-unsaturated fatty acids (PUFAs) using polyketide-like synthesis (PKS-like) genes in plants and plant cells. In contrast to the known and proposed methods for production of PUFAs by means of fatty acid synthesis genes, by the invention constructs and methods are provided for producing PUFAs by utilizing genes of a PKS-like system. The methods involve growing a host cell of interest transformed with an expression cassette functional in the host cell, the expression cassette comprising a transcriptional and translational initiation regulatory region, joined in reading frame 5' to a DNA sequence to a gene or component of a PKS-like system capable of modulating the production of PUFAs (PKS-like gene). An alteration in the PUFA profile of host cells is achieved by expression following introduction of a complete PKS-like system responsible for a PUFA biosynthesis into host cells. The invention finds use for example in the large scale production of DHA and EPA and for modification of the fatty acid profile of host cells and edible plant tissues and/or plant parts.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides designations for the ORFs of the EPA gene cluster of *Shewanella*. Figure 1A shows the organization of the genes; those ORFs essential for EPA production in *E. coli* are numbered. Figure 1B shows the designations given to subclones.

Figure 2 provides the *Shewanella* PKS-like domain structure, motifs and 'Blast' matches of ORF 6 (Figure 2A), ORF 7 (Figure 2B), ORF 8 (Figure 2C), ORF 9 (Figure 2D) and ORF 3 (Figure 2E). Figure 2F shows the structure of the region of the Anabeana chromosome that is related to domains present in *Shewanella* EPA ORFs.

Figure 3 shows results for pantethenylation - ORF 3 in *E. coli* strain SJ16. The image shows [C^{14}] β-Alanine labelled proteins from *E. coli* (strain SJ16) cells transformed with the listed plasmids. Lane 1 represents pUC19, lane 2 represents pPA-NEB (Δ ORF 3), lane 3 represents pAA-Neb (EPA+), lane 4 represents ORF 6 subclone, lane 5 represents ORF 6 + ORF 3 subclones, and lane 6 represents ORF 3 subclone. ACP and an unknown (but previously observed) 35 kD protein were labelled in all of the samples. The high molecular mass proteins detected in lanes 2 and 5 are full-length (largest band) and truncated products of the *Shewanella* ORF-6 gene (confirmed by Western analysis). *E. Coli* strain SJ16 is conditionally blocked in β-alanine synthesis.

Figure 4A shows the DNA sequence (SEQ ID NO:1) for the PKS-like cluster found in *Shewanella*, containing ORF's 3-9. Figure 4B shows the amino acid sequence (SEQ ID NO:2) of ORF 2, which is coded by nucleotides 6121-8103 of the sequence shown in Fig 4A. Figure 4C shows the amino acid sequence (SEQ ID NO:3) of the published, inactive ORF3, translated from the strand complementary to that shown in Figure 4A, nucleotides 9016-8186. Figure 4D shows the nucleotide sequence 8186-9157 (SEQ ID NO:4); its complementary strand codes for ORF 3 active in EPA synthesis. Figures 4E-J show the amino acid sequences (SEQ ID NOS:5-10) corresponding to ORF's 4-9, which are encoded by nucleotides 9681-12590 (SEQ ID NO:81), 13040-13903 (SEQ ID NO:82), 13906-22173 (SEQ ID NO:83), 22203-24515 (SEQ ID NO:84), 24518-30529 (SEQ ID NO:85) and 30730-32358 (SEQ ID NO:86), respectively, of Figure 4A. Figure 4K shows the amino acid sequence (SEQ ID NO:11) corresponding to nucleotides 32834-34327.

Figure 5 shows the sequence (SEQ ID NO:12) for the PKS-like cluster in an approximately 40 kb DNA fragment of *Vibrio marinus*, containing ORFs 6, 7, 8 and 9. The start and last codons for each ORF are as follows: ORF 6: 17394, 25352; ORF 7: 25509, 28160; ORF 8: 28209, 34265; ORF 9: 34454, 36118.

Figure 6 shows the sequence (SEQ ID NO:13) for an approximately 19 kb portion of the PKS-like cluster of Figure 5 which contains the ORFs 6, 7, 8 and 9. The start and last codons for each ORF are as follows: ORF 6: 411, 8369 (SEQ ID NO:77); ORF 7: 8526, 11177 (SEQ ID NO:78); ORF 8: 11226, 17282 (SEQ ID NO:79); ORF 9: 17471, 19135 (SEQ ID NO:80).

Figure 7 shows a comparison of the PKS-like gene clusters of *Shewanella putrefaciens* and *Vibrio marinus*; Figure 7B is the *Vibrio marinus* operon sequence.

Figure 8 is an expanded view of the PKS-like gene cluster portion of *Vibrio marinus* shown in Figure 7B showing that ORFs 6, 7 and 8 are in reading frame 2, while ORF 9 is in reading frame 3.

Figure 9 demonstrates sequence homology of ORF 6 of *Shewanella putrefaciens* and *Vibrio marinus*. The *Shewanella* ORF 6 is depicted on the vertical axis, and the *Vibrio* ORF 6 is depicted on the horizontal axis. Lines indicate regions of the proteins that have a 60% identity. The repeated lines in the middle correspond to the multiple ACP domains found in ORF 6.

Figure 10 demonstrates sequence homology of ORF 7 of *Shewanella putrefaciens* and *Vibrio marinus*. The *Shewanella* ORF 7 is depicted on the vertical axis, and the *Vibrio* ORF 7 is depicted on the horizontal axis. Lines indicate regions of the proteins that have a 60% identity.

Figure 11 demonstrates sequence homology of ORF 8 of *Shewanella putrefaciens* and *Vibrio marinus*. The *Shewanella* ORF 8 is depicted on the vertical axis, and the *Vibro*. ORF 8 is depicted on the horizontal axis. Lines indicate regions of the proteins that have a 60% identity.

Figure 12 demonstrates sequence homology of ORF 9 of *Shewanella putrefaciens* and *Vibrio marinus*. The *Shewanella* ORF 9 is depicted on the vertical axis, and the *Vibrio* ORF 9 is depicted on the horizontal axis. Lines indicate regions of the proteins that have a 60% identity.

Figure 13 is a depiction of various complementation experiments, and resulting PUFA production. On the right, is shown the longest PUFA made in the *E. coli* strain containing the *Vibrio* and *Shewanella* genes depicted on the left. The hollow boxes indicate ORFs from *Shewanella*. The solid boxes indicate ORFs from *Vibrio*.

Figure 14 is a chromatogram showing fatty acid production from complementation of pEPAD8 from *Shewanella* (deletion ORF 8) with ORF 8 from *Shewanella*, in *E. coli* Fad E-. The chromatogram presents an EPA (20:5) peak.

Figure 15 is a chromatogram showing fatty acid production from complementation of pEPAD8 from *Shewanella* (deletion ORF 8) with ORF 8 from *Vibrio marinus*, in *E. coli* Fad E-. The chromatograph presents EPA (20:5) and DHA (22:6) peaks.

Figure 16 is a table of PUFA values from the ORF 8 complementation experiment, the chromatogram of which is shown in Figure 15.

Figure 17 is a plasmid map showing the elements of pCGN7770.

Figure 18 is a plasmid map showing the elements of pCGN8535.

Figure 19 is a plasmid map showing the elements of pCGN8537.

Figure 20 is a plasmid map showing the elements of pCGN8525.

Figure 21 is a comparison of the *Shewanella* ORFs as defined by Yazawa (1996) supra, and those disclosed in Figure 4. When a protein starting at the leucine (TTG) codon at nucleotides 9157-9155 and ending at the stop codon at nucleotides 8185-8183 is expressed under control of a heterologous promoter in an *E. coli* strain containing the entire PKS-like

cluster except ORF 3, the recombinant cells do produce EPA. Thus, the published protein sequence is likely to be wrong, and the coding sequence for the protein may start at the TTG codon at nucleotides 9157-9155 or the TTG codon at nucleotides 9172-9170. This information is critical to the expression of a functional PKS-like cluster heterologous system.

Figure 22 is a plasmid map showing the elements of pCGN8560.

Figure 23 is plasmid map showing the elements of pCGN8556.

Figure 24 shows the translated DNA sequence (SEQ ID NO:14) upstream of the published ORF 3 and the corresponding amino acids for which they code (SEQ ID NO:15). The ATG start codon at position 9016 is the start codon for the protein described by Yazawa *et al* (1996) *supra*. The other arrows depict TTG or ATT codons that can also serve as start codons in bacteria. When ORF 3 is started from the published ATG codon at 9016, the protein is not functional in making EPA. When ORF 3 is initiated at the TTG codon at position 9157, the protein is capable of facilitating EPA synthesis.

Figure 25 shows the PCR product (SEQ ID NO:16) for SS9 Photobacter using primers in Example 1.

Figure 26 shows probe sequences (SEQ ID NOS:17-31) resulting from PCR with primers presented in Example 1.

Figure 27 shows the nucleotide sequence of *Schizochytrium* EST clones A. LIB 3033-047-B5, LIB3033-046-E6 and a bridging PCR product have now been assembled into a partial cDNA sequence (ORF6 homolog), B. LIB3033-046-D2 (hglc/ORF7/ORF8/ORF9 homolog), C. LIB81-015-D5, LIB81-042-B9 and a bridging PCR product have now been assembled into a partial cDNA sequence (ORF8/ORF9 homolog).

Figure 28 shows a schematic of the similarities between *Shewanella* PKS sequences and *Schizochytrium* sequences.

Figure 29 shows the amino acid sequences inferred from *Schizochytrium* EST clones A. ORF6 homolog, B. hglc/ORF7/ORF8/ORF9 homolog, C. ORF8/ORF9 homolog.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the subject invention, novel DNA sequences, DNA constructs and methods are provided, which include some or all of the polyketide-like synthesis (PKS-like) pathway genes from *Shewanella, Vibrio, Schizochytrium* or other microorganisms, for modifying the poly-unsaturated long chain fatty acid content of host cells, particularly host plant cells. The present invention demonstrates that EPA synthesis genes in *Shewanella putrefaciens* constitute a polyketide-like synthesis pathway. Functions are ascribed to the *Shewanella, Schizochytrium* and *Vibrio* genes and methods are provided for the production of EPA and DHA in host cells. The method includes the step of transforming cells with an expression cassette comprising a DNA encoding a polypeptide capable of increasing the amount of one or more

PUFA in the host cell. Desirably, integration constructs are prepared which provide for integration of the expression cassette into the genome of a host cell. Host cells are manipulated to express a sense or antisense DNA encoding a polypeptide(s) that has PKS-like gene activity. By "PKS-like gene" is intended a polypeptide which is responsible for any one or more of the functions of a PKS-like activity of interest. By "polypeptide" is meant any chain of amino acids, regardless of length or post-translational modification, for example, glycosylation or phosphorylation. Depending upon the nature of the host cell, the substrate(s) for the expressed enzyme may be produced by the host cell or may be exogenously supplied. Of particular interest is the selective control of PUFA production in plant tissues and/or plant parts such as leaves, roots, fruits and seeds. The invention can be used to synthesize EPA, DHA, and other related PUFAs in host cells.

There are many advantages to transgenic production of PUFAs. As an example, in transgenic *E. coli* as in *Shewanella*, EPA accumulates in the phospholipid fraction, specifically in the *sn*-2 position. It may be possible to produce a structured lipid in a desired host cell which differs substantially from that produced in either *Shewanella* or *E. coli*. Additionally transgenic production of PUFAs in particular host cells offers several advantages over purification from natural sources such as fish or plants. In transgenic plants, by utilizing a PKS-like system, fatty acid synthesis of PUFAs is achieved in the cytoplasm by a system which produces the PUFAs through *de novo* production of the fatty acids utilizing malonyl Co-A and acetyl Co-A as substrates. In this fashion, potential problems, such as those associated with substrate competition and diversion of normal products of fatty acid synthesis in a host to PUFA production, are avoided.

Production of fatty acids from recombinant plants provides the ability to alter the naturally occurring plant fatty acid profile by providing new synthetic pathways in the host or by suppressing undesired pathways, thereby increasing levels of desired PUFAs, or conjugated forms thereof, and decreasing levels of undesired PUFAs. Production of fatty acids in transgenic plants also offers the advantage that expression of PKS-like genes in particular tissues and/or plant parts means that greatly increased levels of desired PUFAs in those tissues and/or parts can be achieved, making recovery from those tissues more economical. Expression in a plant tissue and/or plant part presents certain efficiencies, particularly where the tissue or part is one which is easily harvested, such as seed, leaves, fruits, flowers, roots, etc. For example, the desired PUFAs can be expressed in seed; methods of isolating seed oils are well established. In addition to providing a source for purification of desired PUFAs, seed oil components can be manipulated through expression of PKS-like genes, either alone or in combination with other genes such as elongases, to provide seed oils having a particular PUFA profile in concentrated form. The concentrated seed oils then can be added to animal milks and/or synthetic or

semisynthetic milks to serve as infant formulas where human nursing is impossible or undesired, or in cases of malnourishment or disease in both adults and infants.

Transgenic microbial production of fatty acids offers the advantages that many microbes are known with greatly simplified oil compositions as compared with those of higher organisms, making purification of desired components easier. Microbial production is not subject to fluctuations caused by external variables such as weather and food supply. Microbially produced oil is substantially free of contamination by environmental pollutants. Additionally, microbes can provide PUFAs in particular forms which may have specific uses. For example, *Spirulina* can provide PUFAs predominantly at the first and third positions of triglycerides; digestion by pancreatic lipases preferentially releases fatty acids from these positions. Following human or animal ingestion of triglycerides derived from *Spirulina*, these PUFAs are released by pancreatic lipases as free fatty acids and thus are directly available, for example, for infant brain development. Additionally, microbial oil production can be manipulated by controlling culture conditions, notably by providing particular substrates for microbially expressed enzymes, or by addition of compounds which suppress undesired biochemical pathways. In addition to these advantages, production of fatty acids from recombinant microbes provides the ability to alter the naturally occurring microbial fatty acid profile by providing new synthetic pathways in the host or by suppressing undesired pathways, thereby increasing levels of desired PUFAs, or conjugated forms thereof, and decreasing levels of undesired PUFAs.

Production of fatty acids in animals also presents several advantages. Expression of desaturase genes in animals can produce greatly increased levels of desired PUFAs in animal tissues, making recovery from those tissues more economical. For example, where the desired PUFAs are expressed in the breast milk of animals, methods of isolating PUFAs from animal milk are well established. In addition to providing a source for purification of desired PUFAs, animal breast milk can be manipulated through expression of desaturase genes, either alone or in combination with other human genes, to provide animal milks with a PUFA composition substantially similar to human breast milk during the different stages of infant development. Humanized animal milks could serve as infant formulas where human nursing is impossible or undesired, or in the cases of malnourishment or disease.

DNAs encoding desired PKS-like genes can be identified in a variety of ways. In one method, a source of a desired PKS-like gene, for example genomic libraries from a *Shewanella, Schizochytrium* or *Vibrio* spp., is screened with detectable enzymatically- or chemically-synthesized probes. Sources of ORFs having PKS-like genes are those organisms which produce a desired PUFA, including DHA-producing or EPA-producing deep sea bacteria growing preferentially under high pressure or at relatively low temperature. Microorgansims such as *Shewanella* which produce EPA or DHA also can be used as a source of PKS-like genes. The probes can be made from DNA, RNA, or non-naturally occurring nucleotides, or mixtures

thereof. Probes can be enzymatically synthesized from DNAs of known PKS-like genes for normal or reduced-stringency hybridization methods. For discussions of nucleic acid probe design and annealing conditions, see, for example, Sambrook *et al*, *Molecular Cloning: A Laboratory Manual* (2nd ed.), Vols. 1-3, *Cold Spring Harbor Laboratory*, (1989) or *Current Protocols in Molecular Biology*, F. Ausubel *et al*, ed., Greene Publishing and Wiley-Interscience, New York (1987). Techniques for manipulation of nucleic acids encoding PUFA enzymes such as subcloning nucleic acid sequences encoding polypeptides into expression vectors, labelling probes, DNA hybridization, and the like are described generally in Sambrook, *supra*.

Oligonucleotide probes also can be used to screen sources and can be based on sequences of known PKS-like genes, including sequences conserved among known PKS-like genes, or on peptide sequences obtained from a desired purified protein. Oligonucleotide probes based on amino acid sequences can be degenerate to encompass the degeneracy of the genetic code, or can be biased in favor of the preferred codons of the source organism. Alternatively, a desired protein can be entirely sequenced and total synthesis of a DNA encoding that polypeptide performed.

Once the desired DNA has been isolated, it can be sequenced by known methods. It is recognized in the art that such methods are subject to errors, such that multiple sequencing of the same region is routine and is still expected to lead to measurable rates of mistakes in the resulting deduced sequence, particularly in regions having repeated domains, extensive secondary structure, or unusual base compositions, such as regions with high GC base content. When discrepancies arise, resequencing can be done and can employ special methods. Special methods can include altering sequencing conditions by using: different temperatures; different enzymes; proteins which alter the ability of oligonucleotides to form higher order structures; altered nucleotides such as ITP or methylated dGTP; different gel compositions, for example adding formamide; different primers or primers located at different distances from the problem region; or different templates such as single stranded DNAs. Sequencing of mRNA can also be employed.

For the most part, some or all of the coding sequences for the polypeptides having PKS-like gene activity are from a natural source. In some situations, however, it is desirable to modify all or a portion of the codons, for example, to enhance expression, by employing host preferred codons. Host preferred codons can be determined from the codons of highest frequency in the proteins expressed in the largest amount in a particular host species of interest. Thus, the coding sequence for a polypeptide having PKS-like gene activity can be synthesized in whole or in part. All or portions of the DNA also can be synthesized to remove any destabilizing sequences or regions of secondary structure which would be present in the transcribed mRNA. All or portions of the DNA also can be synthesized to alter the base

composition to one more preferable to the desired host cell. Methods for synthesizing sequences and bringing sequences together are well established in the literature. *In vitro* mutagenesis and selection, site-directed mutagenesis, or other means can be employed to obtain mutations of naturally occurring PKS-like genes to produce a polypeptide having PKS-like gene activity *in vivo* with more desirable physical and kinetic parameters for function in the host cell, such as a longer half-life or a higher rate of production of a desired polyunsaturated fatty acid.

Of particular interest are the *Shewanella putrefaciens* ORFs and the corresponding ORFs of *Vibrio marinus* and *Schizochytrium*. The *Shewanella putrefaciens* PKS-like genes can be expressed in transgenic plants to effect biosynthesis of EPA. Other DNAs which are substantially identical in sequence to the *Shewanella putrefaciens* PKS-like genes, or which encode polypeptides which are substantially similar to PKS-like genes of *Shewanella putrefaciens* can be used, such as those identified from *Vibrio marinus* or *Schizochytrium*. By substantially identical in sequence is intended an amino acid sequence or nucleic acid sequence exhibiting in order of increasing preference at least 60%, 80%, 90% or 95% homology to the DNA sequence of the *Shewanella putrefaciens* PKS-like genes or nucleic acid sequences encoding the amino acid sequences for such genes. For polypeptides, the length of comparison sequences generally is at least 16 amino acids, preferably at least 20 amino acids, and most preferably 35 amino acids. For nucleic acids, the length of comparison sequences generally is at least 50 nucleotides, preferably at least 60 nucleotides, and more preferably at least 75 nucleotides, and most preferably, 110 nucleotides.

Homology typically is measured using sequence analysis software, for example, the Sequence Analysis software package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, Wisconsin 53705, MEGAlign (DNAStar, Inc., 1228 S. Park St., Madison, Wisconsin 53715), and MacVector (Oxford Molecular Group, 2105 S. Bascom Avenue, Suite 200, Campbell, California 95008). BLAST (National Center for Biotechnology Information (WCBI); FASTA (Pearson and Lipman, *Science* (1985) 227:1435-1446). Such software matches similar sequences by assigning degrees of homology to various substitutions, deletions, and other modifications. Conservative substitutions typically include substitutions within the following groups: glycine and alanine; valine, isoleucine and leucine; aspartic acid, glutamic acid, asparagine, and glutamine; serine and threonine; lysine and arginine; and phenylalanine and tyrosine. Substitutions may also be made on the basis of conserved hydrophobicity or hydrophilicity (Kyte and Doolittle, *J. Mol. Biol.* (1982) 157: 105-132), or on the basis of the ability to assume similar polypeptide secondary structure (Chou and Fasman, *Adv. Enzymol.* (1978) 47: 45-148, 1978). A related protein to the probing sequence is identified when $p \geq 0.01$, preferably $p \geq 10^{-7}$ or 10^{-8}.

Encompassed by the present invention are related PKS-like genes from the same or other organisms. Such related PKS-like genes include variants of the disclosed PKS-like ORFs that occur naturally within the same or different species of *Shewanella*, as well as homologues of the disclosed PKS-like genes from other species and evolutionarily related proteins having analogous function and activity. Also included are PKS-like genes which, although not substantially identical to the *Shewanella putrefaciens* PKS-like genes, operate in a similar fashion to produce PUFAs as part of a PKS-like system. Related PKS-like genes can be identified by their ability to function substantially the same as the disclosed PKS-like genes; that is, they can be substituted for corresponding ORFs of *Shewanella*, *Schizochytrium* or *Vibrio* and still effectively produce EPA or DHA. Related PKS-like genes also can be identified by screening sequence databases for sequences homologous to the disclosed PKS-like genes, by hybridization of a probe based on the disclosed PKS-like genes to a library constructed from the source organism, or by RT-PCR using mRNA from the source organism and primers based on the disclosed PKS-like gene. Thus, the phrase "PKS-like genes" refers not only to the nucleotide sequences disclosed herein, but also to other nucleic acids that are allelic or species variants of these nucleotide sequences. It is also understood that these terms include nonnatural mutations introduced by deliberate mutation using recombinant technology such as single site mutation or by excising short sections of DNA open reading frames coding for PUFA enzymes or by substituting new codons or adding new codons. Such minor alterations substantially maintain the immunoidentity of the original expression product and/or its biological activity. The biological properties of the altered PUFA enzymes can be determined by expressing the enzymes in an appropriate cell line and by determining the ability of the enzymes to synthesize PUFAs. Particular enzyme modifications considered minor would include substitution of amino acids of similar chemical properties, e.g., glutamic acid for aspartic acid or glutamine for asparagine.

When utilizing a PUFA PKS-like system from another organism, the regions of a PKS-like gene polypeptide important for PKS-like gene activity can be determined through routine mutagenesis, expression of the resulting mutant polypeptides and determination of their activities. The coding region for the mutants can include deletions, insertions and point mutations, or combinations thereof. A typical functional analysis begins with deletion mutagenesis to determine the N- and C-terminal limits of the protein necessary for function, and then internal deletions, insertions or point mutants are made in the open ready frame to further determine regions necessary for function. Other techniques such as cassette mutagenesis or total synthesis also can be used. Deletion mutagenesis is accomplished, for example, by using exonucleases to sequentially remove the 5' or 3' coding regions. Kits are available for such techniques. After deletion, the coding region is completed by ligating oligonucleotides containing start or stop codons to the deleted coding region after 5' or 3' deletion, respectively.

Alternatively, oligonucleotides encoding start or stop codons are inserted into the coding region by a variety of methods including site-directed mutagenesis, mutagenic PCR or by ligation onto DNA digested at existing restriction sites. Internal deletions can similarly be made through a variety of methods including the use of existing restriction sites in the DNA, by use of mutagenic primers via site directed mutagenesis or mutagenic PCR. Insertions are made through methods such as linker-scanning mutagenesis, site-directed mutagenesis or mutagenic PCR. Point mutations are made through techniques such as site-directed mutagenesis or mutagenic PCR.

Chemical mutagenesis also can be used for identifying regions of a PKS-like gene polypeptide important for activity. A mutated construct is expressed, and the ability of the resulting altered protein to function as a PKS-like gene is assayed. Such structure-function analysis can determine which regions may be deleted, which regions tolerate insertions, and which point mutations allow the mutant protein to function in substantially the same way as the native PKS-like gene. All such mutant proteins and nucleotide sequences encoding them are within the scope of the present invention. EPA is produced in *Shewanella* as the product of a PKS-like system, such that the EPA genes encode components of this system. In *Vibrio*, DHA is produced by a similar system. The enzymes which synthesize these fatty acids are encoded by a cluster of genes which are distinct from the fatty acid synthesis genes encoding the enzymes involved in synthesis of the C16 and C18 fatty acids typically found in bacteria and in plants. As the *Shewanella* EPA genes represent a PKS-like gene cluster, EPA production is, at least to some extent, independent of the typical bacterial type II FAS system. Thus, production of EPA in the cytoplasm of plant cells can be achieved by expression of the PKS-like pathway genes in plant cells under the control of appropriate plant regulatory signals.

EPA production in *E. coli* transformed with the *Shewanella* EPA genes proceeds during anaerobic growth, indicating that O_2-dependent desaturase reactions are not involved. Analyses of the proteins encoded by the ORFs essential for EPA production reveals the presence of domain structures characteristic of PKS-like systems. Fig. 2A shows a summary of the domains, motifs, and also key homologies detected by "BLAST" data bank searches. Because EPA is different from many of the other substances produced by PKS-like pathways, i.e., it contains 5, *cis* double bonds, spaced at 3 carbon intervals along the molecule, a PKS-like system for synthesis of EPA is not expected.

Further, BLAST searches using the domains present in the *Shewanella* EPA ORFs reveal that several are related to proteins encoded by a PKS-like gene cluster found in Anabeana. The structure of that region of the Anabeana chromosome is shown in Fig. 2F. The Anabeana PKS-like genes have been linked to the synthesis of a long-chain (C26), hydroxy-fatty acid found in a glycolipid layer of heterocysts. The EPA protein domains with homology to the Anabeana proteins are indicated in Fig. 2F.

ORF 6 of *Shewanella* contains a KAS domain which includes an active site motif (DXAC*), SEQ ID NO:32, as well as a "GFGG", SEQ ID NO:33, motif which is present at the end of many Type II KAS proteins (see Fig. 2A). Extended motifs are present but not shown here. Next is a malonyl-CoA:ACP acyl transferase (AT) domain. Sequences near the active site motif (GHS*XG), SEQ ID NO:34, suggest it transfers malonate rather than methylmalonate, i.e., it resembles the acetate-like ATs. Following a linker region, there is a cluster of 6 repeating domains, each ~100 amino acids in length, which are homologous to PKS-like ACP sequences. Each contains a pantetheine binding site motif (LGXDS*(L/I)), SEQ ID NOS:35 and 36. The presence of 6 such ACP domains has not been observed previously in fatty acid synthases (FAS) or PKS-like systems. Near the end of the protein is a region which shows homology to ß-keto-ACP reductases (KR). It contains a pyridine nucleotide binding site motif "GXGXX(G/A/P)", SEQ ID NOS:37, 38 and 39.

The *Shewanella* ORF 8 begins with a KAS domain, including active site and ending motifs (Fig. 2C). The best match in the data banks is with the Anabeana HglD. There is also a domain which has sequence homology to the N- terminal one half of the Anabeana HglC. This region also shows weak homology to KAS proteins although it lacks the active site and ending motifs. It has the characteristics of the so-called chain length factors (CLF) of Type II PKS-like systems. ORF 8 appears to direct the production of EPA versus DHA by the PKS-like system. ORF 8 also has two domains with homology to ß-hydroxyacyl-ACP dehydrases (DH). The best match for both domains is with *E. coli* FabA, a bi-functional enzyme which carries out both the dehydrase reaction and an isomerization (*trans* to *cis*) of the resulting double bond. The first DH domain contains both the active site histidine (H) and an adjacent cysteine (C) implicated in FabA catalysis. The second DH domain has the active site H but lacks the adjacent C (Fig. 2C). Blast searches with the second DH domain also show matches to FabZ, a second *E. coli* DH, which does not possess isomerase activity.

The N-terminal half of ORF 7 (Fig. 2B) has no significant matches in the data banks. The best match of the C-terminal half is with a C-terminal portion of the Anabeana HglC. This domain contains an acyl-transferase (AT) motif (GXSXG), SEQ ID NO:40. Comparison of the extended active site sequences, based on the crystal structure of the *E. coli* malonyl-CoA:ACP AT, reveals that ORF 7 lacks two residues essential for exclusion of water from the active site (*E. coli* nomenclature; Q11 and R117). These data suggest that ORF 7 may function as a thioesterase.

ORF 9 (Fig. 2D) is homologous to an ORF of unknown function in the Anabeana Hgl cluster. It also exhibits a very weak homology to NIFA, a regulatory protein in nitrogen fixing bacteria. A regulatory role for the ORF 9 protein has not been excluded. ORF 3 (Fig. 2E) is homologous to the Anabeana HetI as well as EntD from *E. coli* and Sfp of *Bacillus*. Recently, a new enzyme family of phosphopantetheinyl transferases has been identified that includes HetI,

EntD and Sfp (Lamblot RH, *et al.* (1996) A new enzyme superfamily - the phophopantetheinyl transferases. *Chemistry & Biology*, Vol 3, #11, 923-936). The data of Fig. 3 demonstrates that the presence of ORF 3 is required for addition of ß-alanine (i.e. pantetheine) to the ORF 6 protein. Thus, ORF 3 encodes the phosphopantetheinyl transferase specific for the ORF 6 ACP domains. (*See*, Haydock SF *et al.* (1995) Divergent sequence motifs correlated with the substrate specificity of (methyl)malonyl-CoA:acyl carrier protein transacylase domains in modular polyketide synthases, *FEBS Lett.*, 374, 246-248). Malonate is the source of the carbons utilized in the extension reactions of EPA synthesis. Additionally, malonyl-CoA rather than malonyl-ACP is the AT substrate, i.e., the AT region of ORF 6 uses malonyl Co-A.

Once the DNA sequences encoding the PKS-like genes of an organism responsible for PUFA production have been obtained, they are placed in a vector capable of replication in a host cell, or propagated *in vitro* by means of techniques such as PCR or long PCR. Replicating vectors can include plasmids, phage, viruses, cosmids and the like. Desirable vectors include those useful for mutagenesis of the gene of interest or for expression of the gene of interest in host cells. A PUFA synthesis enzyme or a homologous protein can be expressed in a variety of recombinantly engineered cells. Numerous expression systems are available for expression of DNA encoding a PUFA enzyme. The expression of natural or synthetic nucleic acids encoding PUFA enzyme is typically achieved by operably linking the DNA to a promoter (which is either constitutive or inducible) within an expression vector. By expression vector is meant a DNA molecule, linear or circular, that comprises a segment encoding a PUFA enzyme, operably linked to additional segments that provide for its transcription. Such additional segments include promoter and terminator sequences. An expression vector also may include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc. Expression vectors generally are derived from plasmid or viral DNA, and can contain elements of both. The term "operably linked" indicates that the segments are arranged so that they function in concert for their intended purposes, for example, transcription initiates in the promoter and proceeds through the coding segment to the terminator. *See* Sambrook *et al*, *supra*.

The technique of long PCR has made *in vitro* propagation of large constructs possible, so that modifications to the gene of interest, such as mutagenesis or addition of expression signals, and propagation of the resulting constructs can occur entirely *in vitro* without the use of a replicating vector or a host cell. *In vitro* expression can be accomplished, for example, by placing the coding region for the desaturase polypeptide in an expression vector designed for *in vitro* use and adding rabbit reticulocyte lysate and cofactors; labeled amino acids can be incorporated if desired. Such *in vitro* expression vectors may provide some or all of the expression signals necessary in the system used. These methods are well known in the art and the components of the system are commercially available. The reaction mixture can then be

assayed directly for PKS-like enzymes for example by determining their activity, or the synthesized enzyme can be purified and then assayed.

Expression in a host cell can be accomplished in a transient or stable fashion. Transient expression can occur from introduced constructs which contain expression signals functional in the host cell, but which constructs do not replicate and rarely integrate in the host cell, or where the host cell is not proliferating. Transient expression also can be accomplished by inducing the activity of a regulatable promoter operably linked to the gene of interest, although such inducible systems frequently exhibit a low basal level of expression. Stable expression can be achieved by introduction of a nucleic acid construct that can integrate into the host genome or that autonomously replicates in the host cell. Stable expression of the gene of interest can be selected for through the use of a selectable marker located on or transfected with the expression construct, followed by selection for cells expressing the marker. When stable expression results from integration, integration of constructs can occur randomly within the host genome or can be targeted through the use of constructs containing regions of homology with the host genome sufficient to target recombination with the host locus. Where constructs are targeted to an endogenous locus, all or some of the transcriptional and translational regulatory regions can be provided by the endogenous locus. To achieve expression in a host cell, the transformed DNA is operably associated with transcriptional and translational initiation and termination regulatory regions that are functional in the host cell.

Transcriptional and translational initiation and termination regions are derived from a variety of nonexclusive sources, including the DNA to be expressed, genes known or suspected to be capable of expression in the desired system, expression vectors, chemical synthesis The termination region can be derived from the 3' region of the gene from which the initiation region was obtained or from a different gene. A large number of termination regions are known to and have been found to be satisfactory in a variety of hosts from the same and different genera and species. The termination region usually is selected more as a matter of convenience rather than because of any particular property. When expressing more than one PKS-like ORF in the same cell, appropriate regulatory regions and expression methods should be used. Introduced genes can be propagated in the host cell through use of replicating vectors or by integration into the host genome. Where two or more genes are expressed from separate replicating vectors, it is desirable that each vector has a different means of replication. Each introduced construct, whether integrated or not, should have a different means of selection and should lack homology to the other constructs to maintain stable expression and prevent reassortment of elements among constructs. Judicious choices of regulatory regions, selection means and method of propagation of the introduced construct can be experimentally determined so that all introduced genes are expressed at the necessary levels to provide for synthesis of the desired products.

A variety of procaryotic expression systems can be used to express PUFA enzyme. Expression vectors can be constructed which contain a promoter to direct transcription, a ribosome binding site, and a transcriptional terminator. Examples of regulatory regions suitable for this purpose in *E. coli* are the promoter and operator region of the *E. coli* tryptophan biosynthetic pathway as described by Yanofsky (1984) *J. Bacteriol.*, 158:1018-1024 and the leftward promoter of phage lambda (Pλ) as described by Herskowitz and Hagen, (1980) *Ann. Rev. Genet.*, 14:399-445. The inclusion of selection markers in DNA vectors transformed in *E.coli* is also useful. Examples of such markers include genes specifying resistance to ampicillin, tetracycline, or chloramphenicol. Vectors used for expressing foreign genes in bacterial hosts generally will contain a selectable marker, such as a gene for antibiotic resistance, and a promoter which functions in the host cell. Plasmids useful for transforming bacteria include pBR322 (Bolivar, *et al*, (1977) *Gene* 2:95-113), the pUC plasmids (Messing,(1983) *Meth. Enzymol.* 101:20-77, Vieira and Messing, (1982) *Gene* 19:259-268), pCQV2 (Queen, *ibid.*), and derivatives thereof. Plasmids may contain both viral and bacterial elements. Methods for the recovery of the proteins in biologically active form are discussed in U.S. Patent Nos. 4,966,963 and 4,999,422. See Sambrook, *et al* for a description of other prokaryotic expression systems.

For expression in eukaryotes, host cells for use in practicing the present invention include mammalian, avian, plant, insect, and fungal cells. As an example, for plants, the choice of a promoter will depend in part upon whether constitutive or inducible expression is desired and whether it is desirable to produce the PUFAs at a particular stage of plant development and/or in a particular tissue. Considerations for choosing a specific tissue and/or developmental stage for expression of the ORFs may depend on competing substrates or the ability of the host cell to tolerate expression of a particular PUFA. Expression can be targeted to a particular location within a host plant such as seed, leaves, fruits, flowers, and roots, by using specific regulatory sequences, such as those described in USPN 5,463,174, USPN 4,943,674, USPN 5,106,739, USPN 5,175,095, USPN 5,420,034, USPN 5,188,958, and USPN 5,589,379. Where the host cell is a yeast, transcription and translational regions functional in yeast cells are provided, particularly from the host species. The transcriptional initiation regulatory regions can be obtained, for example from genes in the glycolytic pathway, such as alcohol dehydrogenase, glyceraldehyde-3-phosphate dehydrogenase (GPD), phosphoglucoisomerase, phosphoglycerate kinase, etc. or regulatable genes such as acid phosphatase, lactase, metallothionein, glucoamylase, etc. Any one of a number of regulatory sequences can be used in a particular situation, depending upon whether constitutive or induced transcription is desired, the particular efficiency of the promoter in conjunction with the open-reading frame of interest, the ability to join a strong promoter with a control region from a different promoter which allows for inducible transcription, ease of construction, and the like. Of particular interest are promoters

which are activated in the presence of galactose. Galactose-inducible promoters (GAL1, GAL7, and GAL10) have been extensively utilized for high level and regulated expression of protein in yeast (Lue *et al,* (1987) *Mol. Cell. Biol.* 7:3446; Johnston, (1987) *Microbiol. Rev.* 51:458). Transcription from the GAL promoters is activated by the GAL4 protein, which binds to the promoter region and activates transcription when galactose is present. In the absence of galactose, the antagonist GAL80 binds to GAL4 and prevents GAL4 from activating transcription. Addition of galactose prevents GAL80 from inhibiting activation by GAL4. Preferably, the termination region is derived from a yeast gene, particularly *Saccharomyces, Schizosaccharomyces, Candida* or *Kluyveromyces*. The 3' regions of two mammalian genes, γ interferon and α2 interferon, are also known to function in yeast.

Nucleotide sequences surrounding the translational initiation codon ATG have been found to affect expression in yeast cells. If the desired polypeptide is poorly expressed in yeast, the nucleotide sequences of exogenous genes can be modified to include an efficient yeast translation initiation sequence to obtain optimal gene expression. For expression in *Saccharomyces*, this can be done by site-directed mutagenesis of an inefficiently expressed gene by fusing it in-frame to an endogenous *Saccharomyces* gene, preferably a highly expressed gene, such as the lactase gene.

As an alternative to expressing the PKS-like genes in the plant cell cytoplasm, is to target the enzymes to the chloroplast. One method to target proteins to the chloroplast entails use of leader peptides attached to the N-termini of the proteins. Commonly used leader peptides are derived from the small subunit of plant ribulose bis phosphate carboxylase. Leader sequences from other chloroplast proteins may also be used. Another method for targeting proteins to the chloroplast is to transform the chloroplast genome (Stable transformation of chloroplasts of *Chlamydomonas reinhardtii* (1 green alga) using bombardment of recipient cells with high-velocity tungsten microprojectiles coated with foreign DNA has been described. *See*, for example, Blowers *et al Plant Cell* (1989) *1*:123-132 and Debuchy *et al EMBO J* (1989) *8*:2803-2809. The transformation technique, using tungsten microprojectiles, is described by Kline *et al*, *Nature* (London) (1987) *327*:70-73). The most common method of transforming chloroplasts involves using biolistic techniques, but other techniques developed for the purpose may also be used. (Methods for targeting foreign gene products into chloroplasts (Shrier *et al EMBO J.* (1985) *4*:25-32) or mitochnodria (Boutry *et al*, *supra*) have been described. *See* also Tomai *et al Gen. Biol. Chem.* (1988) *263*:15104-15109 and US Patent No. 4,940,835 for the use of transit peptides for translocating nuclear gene products into the chloroplast. Methods for directing the transport of proteins to the chloroplast are reviewed in Kenauf *TIBTECH* (1987) *5*:40-47.

For producing PUFAs in avian species and cells, gene transfer can be performed by introducing a nucleic acid sequence encoding a PUFA enzyme into the cells following procedures known in the art. If a transgenic animal is desired, pluripotent stem cells of embryos

can be provided with a vector carrying a PUFA enzyme encoding transgene and developed into adult animal (USPN 5,162,215; Ono *et al.* (1996) *Comparative Biochemistry and Physiology A 113*(3):287-292; WO 9612793; WO 9606160). In most cases, the transgene is modified to express high levels of the PKS-like enzymes in order to increase production of PUFAs. The transgenes can be modified, for example, by providing transcriptional and/or translational regulatory regions that function in avian cells, such as promoters which direct expression in particular tissues and egg parts such as yolk. The gene regulatory regions can be obtained from a variety of sources, including chicken anemia or avian leukosis viruses or avian genes such as a chicken ovalbumin gene.

Production of PUFAs in insect cells can be conducted using baculovirus expression vectors harboring PKS-like transgenes. Baculovirus expression vectors are available from several commercial sources such as Clonetech. Methods for producing hybrid and transgenic strains of algae, such as marine algae, which contain and express a desaturase transgene also are provided. For example, transgenic marine algae can be prepared as described in USPN 5,426,040. As with the other expression systems described above, the timing, extent of expression and activity of the desaturase transgene can be regulated by fitting the polypeptide coding sequence with the appropriate transcriptional and translational regulatory regions selected for a particular use. Of particular interest are promoter regions which can be induced under preselected growth conditions. For example, introduction of temperature sensitive and/or metabolite responsive mutations into the desaturase transgene coding sequences, its regulatory regions, and/or the genome of cells into which the transgene is introduced can be used for this purpose.

The transformed host cell is grown under appropriate conditions adapted for a desired end result. For host cells grown in culture, the conditions are typically optimized to produce the greatest or most economical yield of PUFAs, which relates to the selected desaturase activity. Media conditions which may be optimized include: carbon source, nitrogen source, addition of substrate, final concentration of added substrate, form of substrate added, aerobic or anaerobic growth, growth temperature, inducing agent, induction temperature, growth phase at induction, growth phase at harvest, pH, density, and maintenance of selection. Microorganisms such as yeast, for example, are preferably grown using selected media of interest, which include yeast peptone broth (YPD) and minimal media (contains amino acids, yeast nitrogen base, and ammonium sulfate, and lacks a component for selection, for example uracil). Desirably, substrates to be added are first dissolved in ethanol. Where necessary, expression of the polypeptide of interest may be induced, for example by including or adding galactose to induce expression from a GAL promoter.

When increased expression of the PKS-like gene polypeptide in a host cell which expresses PUFA from a PKS-like system is desired, several methods can be employed.

Additional genes encoding the PKS-like gene polypeptide can be introduced into the host organism. Expression from the native PKS-like gene locus also can be increased through homologous recombination, for example by inserting a stronger promoter into the host genome to cause increased expression, by removing destabilizing sequences from either the mRNA or the encoded protein by deleting that information from the host genome, or by adding stabilizing sequences to the mRNA (*see* USPN 4,910,141 and USPN 5,500,365). Thus, the subject host will have at least have one copy of the expression construct and may have two or more, depending upon whether the gene is integrated into the genome, amplified, or is present on an extrachromosomal element having multiple copy numbers. Where the subject host is a yeast, four principal types of yeast plasmid vectors can be used: Yeast Integrating plasmids (YIps), Yeast Replicating plasmids (YRps), Yeast Centromere plasmids (YCps), and Yeast Episomal plasmids (YEps). YIps lack a yeast replication origin and must be propagated as integrated elements in the yeast genome. YRps have a chromosomally derived autonomously replicating sequence and are propagated as medium copy number (20 to 40), autonomously replicating, unstably segregating plasmids. YCps have both a replication origin and a centromere sequence and propagate as low copy number (10-20), autonomously replicating, stably segregating plasmids. YEps have an origin of replication from the yeast 2μm plasmid and are propagated as high copy number, autonomously replicating, irregularly segregating plasmids. The presence of the plasmids in yeast can be ensured by maintaining selection for a marker on the plasmid. Of particular interest are the yeast vectors pYES2 (a YEp plasmid available from Invitrogen, confers uracil prototrophy and a GAL1 galactose-inducible promoter for expression), and pYX424 (a YEp plasmid having a constitutive TP1 promoter and conferring leucine prototrophy; (Alber and Kawasaki (1982). *J. Mol. & Appl. Genetics* 1: 419).

The choice of a host cell is influenced in part by the desired PUFA profile of the transgenic cell, and the native profile of the host cell. Even where the host cell expresses PKS-like gene activity for one PUFA, expression of PKS-like genes of another PKS-like system can provide for production of a novel PUFA not produced by the host cell. In particular instances where expression of PKS-like gene activity is coupled with expression of an ORF 8 PKS-like gene of an organism which produces a different PUFA, it can be desirable that the host cell naturally have, or be mutated to have, low PKS-like gene activity for ORF 8. As an example, for production of EPA, the DNA sequence used encodes the polypeptide having PKS-like gene activity of an organism which produces EPA, while for production of DHA, the DNA sequences used are those from an organism which produces DHA. For use in a host cell which already expresses PKS-like gene activity it can be necessary to utilize an expression cassette which provides for overexpression of the desired PKS-like genes alone or with a construct to downregulate the activity of an existing ORF of the existing PKS-like system, such as by antisense or co-suppression. Similarly, a combination of ORFs derived from separate organisms

which produce the same or different PUFAs using PKS-like systems may be used. For instance, the ORF 8 of *Vibrio* directs the expression of DHA in a host cell, even when ORFs 3, 6, 7 and 9 are from *Shewanella*, which produce EPA when coupled to ORF 8 of *Shewanella*. Therefore, for production of eicosapentanoic acid (EPA), the expression cassettes used generally include one or more cassettes which include ORFs 3, 6, 7, 8 and 9 from a PUFA-producing organism such as the marine bacterium *Shewanella putrefaciens* (for EPA production) or *Vibrio marinus* (for DHA production). ORF 8 can be used for induction of DHA production, and ORF 8 of *Vibrio* can be used in conjunction with ORFs 3, 6, 7 and 9 of *Shewanella* to produce DHA. The organization and numbering scheme of the ORFs identified in the *Shewanella* gene cluster are shown in Fig 1A. Maps of several subclones referred to in this study are shown in Fig 1B. For expression of a PKS-like gene polypeptide, transcriptional and translational initiation and termination regions functional in the host cell are operably linked to the DNA encoding the PKS-like gene polypeptide.

Constructs comprising the PKS-like ORFs of interest can be introduced into a host cell by any of a variety of standard techniques, depending in part upon the type of host cell. These techniques include transfection, infection, bolistic impact, electroporation, microinjection, scraping, or any other method which introduces the gene of interest into the host cell (*see* USPN 4,743,548, USPN 4,795,855, USPN 5,068,193, USPN 5,188,958, USPN 5,463,174, USPN 5,565,346 and USPN 5,565,347). Methods of transformation which are used include lithium acetate transformation (*Methods in Enzymology*, (1991) 194:186-187). For convenience, a host cell which has been manipulated by any method to take up a DNA sequence or construct will be referred to as "transformed" or "recombinant" herein. The subject host will have at least have one copy of the expression construct and may have two or more, depending upon whether the gene is integrated into the genome, amplified, or is present on an extrachromosomal element having multiple copy numbers.

For production of PUFAs, depending upon the host cell, the several polypeptides produced by pEPA, ORFs 3, 6, 7, 8 and 9, are introduced as individual expression constructs or can be combined into two or more cassettes which are introduced individually or co-transformed into a host cell. A standard transformation protocol is used. For plants, where less than all PKS-like genes required for PUFA synthesis have been inserted into a single plant, plants containing a complementing gene or genes can be crossed to obtain plants containing a full complement of PKS-like genes to synthesize a desired PUFA.

The PKS-like-mediated production of PUFAs can be performed in either prokaryotic or eukaryotic host cells. The cells can be cultured or formed as part or all of a host organism including an animal. Viruses and bacteriophage also can be used with appropriate cells in the production of PUFAs, particularly for gene transfer, cellular targeting and selection. Any type of plant cell can be used for host cells, including dicotyledonous plants, monocotyledonous plants,

and cereals. Of particular interest are crop plants such as *Brassica*, *Arabidopsis*, soybean, corn, and the like. Prokaryotic cells of interest include *Eschericia, Baccillus, Lactobaccillus, cyanobacteria* and the like. Eukaryotic cells include plant cells, mammalian cells such as those of lactating animals, avian cells such as of chickens, and other cells amenable to genetic manipulation including insect, fungal, and algae cells. Examples of host animals include mice, rats, rabbits, chickens, quail, turkeys, cattle, sheep, pigs, goats, yaks, etc., which are amenable to genetic manipulation and cloning for rapid expansion of a transgene expressing population. For animals, PKS-like transgenes can be adapted for expression in target organelles, tissues and body fluids through modification of the gene regulatory regions. Of particular interest is the production of PUFAs in the breast milk of the host animal.

Examples of host microorganisms include *Saccharomyces cerevisiae*, *Saccharomyces carlsbergensis*, or other yeast such as *Candida, Kluyveromyces* or other fungi, for example, filamentous fungi such as *Aspergillus, Neurospora, Penicillium*, etc. Desirable characteristics of a host microorganism are, for example, that it is genetically well characterized, can be used for high level expression of the product using ultra-high density fermentation, and is on the GRAS (generally recognized as safe) list since the proposed end product is intended for ingestion by humans. Of particular interest is use of a yeast, more particularly baker's yeast (*S. cerevisiae*), as a cell host in the subject invention. Strains of particular interest are SC334 (Mat α pep4-3 prbl-1122 ura3-52 leu2-3, 112 regl-501 gal1; (Hovland *et al* (1989) Gene 83:57-64); BJ1995 (Yeast Genetic Stock Centre, 1021 Donner Laboratory, Berkeley, CA 94720), INVSC1 (Mat α hiw3Δ1 leu2 trp1-289 ura3-52 (Invitrogen, 1600 Faraday Ave., Carlsbad, CA 92008) and INVSC2 (Mat α his3Δ200 ura3-167; (Invitrogen). Bacterial cells also may be used as hosts. This includes *E. coli*, which can be useful in fermentation processes. Alternatively, a host such as a *Lactobacillus* species can be used as a host for introducing the products of the PKS-like pathway into a product such as yogurt.

The transformed host cell can be identified by selection for a marker contained on the introduced construct. Alternatively, a separate marker construct can be introduced with the desired construct, as many transformation techniques introduce multiple DNA molecules into host cells. Typically, transformed hosts are selected for their ability to grow on selective media. Selective media can incorporate an antibiotic or lack a factor necessary for growth of the untransformed host, such as a nutrient or growth factor. An introduced marker gene therefor may confer antibiotic resistance, or encode an essential growth factor or enzyme, and permit growth on selective media when expressed in the transformed host cell. Desirably, resistance to kanamycin and the amino glycoside G418 are of particular interest (*see* USPN 5,034,322). For yeast transformants, any marker that functions in yeast can be used, such as the ability to grow on media lacking uracil, lencine, lysine or tryptophan.

Selection of a transformed host also can occur when the expressed marker protein can be detected, either directly or indirectly. The marker protein can be expressed alone or as a fusion to another protein. The marker protein can be one which is detected by its enzymatic activity; for example ß-galactosidase can convert the substrate X-gal to a colored product, and luciferase can convert luciferin to a light-emitting product. The marker protein can be one which is detected by its light-producing or modifying characteristics; for example, the green fluorescent protein of *Aequorea victoria* fluoresces when illuminated with blue light. Antibodies can be used to detect the marker protein or a molecular tag on, for example, a protein of interest. Cells expressing the marker protein or tag can be selected, for example, visually, or by techniques such as FACS or panning using antibodies.

The PUFAs produced using the subject methods and compositions are found in the host plant tissue and/or plant part as free fatty acids and/or in conjugated forms such as acylglycerols, phospholipids, sulfolipids or glycolipids, and can be extracted from the host cell through a variety of means well-known in the art. Such means include extraction with organic solvents, sonication, supercritical fluid extraction using for example carbon dioxide, and physical means such as presses, or combinations thereof. Of particular interest is extraction with methanol and chloroform. Where appropriate, the aqueous layer can be acidified to protonate negatively charged moieties and thereby increase partitioning of desired products into the organic layer. After extraction, the organic solvents can be removed by evaporation under a stream of nitrogen. When isolated in conjugated forms, the products are enzymatically or chemically cleaved to release the free fatty acid or a less complex conjugate of interest, and are then subjected to further manipulations to produce a desired end product. Desirably, conjugated forms of fatty acids are cleaved with potassium hydroxide.

If further purification is necessary, standard methods can be employed. Such methods include extraction, treatment with urea, fractional crystallization, HPLC, fractional distillation, silica gel chromatography, high speed centrifugation or distillation, or combinations of these techniques. Protection of reactive groups, such as the acid or alkenyl groups, can be done at any step through known techniques, for example alkylation or iodination. Methods used include methylation of the fatty acids to produce methyl esters. Similarly, protecting groups can be removed at any step. Desirably, purification of fractions containing DHA and EPA is accomplished by treatment with urea and/or fractional distillation.

The uses of the subject invention are several. Probes based on the DNAs of the present invention find use in methods for isolating related molecules or in methods to detect organisms expressing PKS-like genes. When used as probes, the DNAs or oligonucleotides need to be detectable. This is usually accomplished by attaching a label either at an internal site, for example via incorporation of a modified residue, or at the 5' or 3' terminus. Such labels can be directly detectable, can bind to a secondary molecule that is detectably labeled, or can bind to an

unlabelled secondary molecule and a detectably labeled tertiary molecule; this process can be extended as long as is practicable to achieve a satisfactorily detectable signal without unacceptable levels of background signal. Secondary, tertiary, or bridging systems can include use of antibodies directed against any other molecule, including labels or other antibodies, or can involve any molecules which bind to each other, for example a biotin-streptavidin/avidin system. Detectable labels typically include radioactive isotopes, molecules which chemically or enzymatically produce or alter light, enzymes which produce detectable reaction products, magnetic molecules, fluorescent molecules or molecules whose fluorescence or light-emitting characteristics change upon binding. Examples of labelling methods can be found in USPN 5,011,770. Alternatively, the binding of target molecules can be directly detected by measuring the change in heat of solution on binding of a probe to a target via isothermal titration calorimetry, or by coating the probe or target on a surface and detecting the change in scattering of light from the surface produced by binding of a target or a probe, respectively, is done with the BIAcore system.

PUFAs produced by recombinant means find applications in a wide variety of areas. Supplementation of humans or animals with PUFAs in various forms can result in increased levels not only of the added PUFAs, but of their metabolic progeny as well. Complex regulatory mechanisms can make it desirable to combine various PUFAs, or to add different conjugates of PUFAs, in order to prevent, control or overcome such mechanisms to achieve the desired levels of specific PUFAs in an individual. In the present case, expression of PKS-like gene genes, or antisense PKS-like gene transcripts, can alter the levels of specific PUFAs, or derivatives thereof, found in plant parts and/or plant tissues. The PKS-like gene polypeptide coding region is expressed either by itself or with other genes, in order to produce tissues and/or plant parts containing higher proportions of desired PUFAs or containing a PUFA composition which more closely resembles that of human breast milk (Prieto *et al.*, PCT publication WO 95/24494) than does the unmodified tissues and/or plant parts.

PUFAs, or derivatives thereof, made by the disclosed method can be used as dietary supplements for patients undergoing intravenous feeding or for preventing or treating malnutrition. For dietary supplementation, the purified PUFAs, or derivatives thereof, can be incorporated into cooking oils, fats or margarines formulated so that in normal use the recipient receives a desired amount of PUFA. The PUFAs also can be incorporated into infant formulas, nutritional supplements or other food products, and find use as anti-inflammatory or cholesterol lowering agents.

Particular fatty acids such as EPA can be used to alter the composition of infant formulas to better replicate the PUFA composition of human breast milk. The predominant triglyceride in human milk is reported to be 1,3-di-oleoyl-2-palmitoyl, with 2-palmitoyl glycerides reported as better absorbed than 2-oleoyl or 2-lineoyl glycerides (*see* USPN 4,876,107). Typically, human

breast milk has a fatty acid profile comprising from about 0.15 % to about 0.36 % as DHA, from about 0.03 % to about 0.13 % as EPA, from about 0.30 % to about 0.88 % as ARA, from about 0.22 % to about 0.67 % as DGLA, and from about 0.27 % to about 1.04 % as GLA. A preferred ratio of GLA:DGLA:ARA in infant formulas is from about 1:1:4 to about 1:1:1, respectively. Amounts of oils providing these ratios of PUFA can be determined without undue experimentation by one of skill in the art. PUFAs, or host cells containing them, also can be used as animal food supplements to alter an animal's tissue or milk fatty acid composition to one more desirable for human or animal consumption.

For pharmaceutical use (human or veterinary), the compositions generally are administered orally but can be administered by any route by which they may be successfully absorbed, e.g., parenterally (i.e. subcutaneously, intramuscularly or intravenously), rectally or vaginally or topically, for example, as a skin ointment or lotion. Where available, gelatin capsules are the preferred form of oral administration. Dietary supplementation as set forth above also can provide an oral route of administration. The unsaturated acids of the present invention can be administered in conjugated forms, or as salts, esters, amides or prodrugs of the fatty acids. Any pharmaceutically acceptable salt is encompassed by the present invention; especially preferred are the sodium, potassium or lithium salts. Also encompassed are the N-alkylpolyhydroxamine salts, such as N-methyl glucamine, described in PCT publication WO 96/33155. Preferred esters are the ethyl esters.

The PUFAs of the present invention can be administered alone or in combination with a pharmaceutically acceptable carrier or excipient. As solid salts, the PUFAs can also be administered in tablet form. For intravenous administration, the PUFAs or derivatives thereof can be incorporated into commercial formulations such as Intralipids. Where desired, the individual components of formulations can be individually provided in kit form, for single or multiple use. A typical dosage of a particular fatty acid is from 0.1 mg to 20 g, or even 100 g daily, and is preferably from 10 mg to 1, 2, 5 or 10 g daily as required, or molar equivalent amounts of derivative forms thereof. Parenteral nutrition compositions comprising from about 2 to about 30 weight percent fatty acids calculated as triglycerides are encompassed by the present invention. Other vitamins, and particularly fat-soluble vitamins such as vitamin A, D, E and L-carnitine optionally can be included. Where desired, a preservative such as a tocopherol can be added, typically at about 0.1% by weight.

The following examples are presented by way of illustration, not of limitation.

EXAMPLES

Example 1

The Identity of ORFs Derived from *Vibrio marinus*

Using polymerase chain reaction (PCR) with primers based on ORF 6 of *Shewanella* (Sp ORF 6) sequences (FW 5' primers CUACUACUACUACCAAGCT AAAGCACTTAACCGTG, SEQ ID NO:41, and CUACUACUACUAACAGCGAAATG CTTATCAAG, SEQ ID NO:42, for *Vibrio* and SS9 respectively and 3' BW primers: CAUCAUCAUCAUGCGACCAAAACCAAATGAGCTAATAC, SEQ ID NO:43, for both *Vibrio* and SS9) and genomic DNAs templates from *Vibrio* and a borophyllic *photobacter* producing EPA (provided by Dr. Bartlett, UC San Diego), resulted in PCR products of *ca.*400 bases for *Vibrio marinus* (*Vibrio*) and *ca.*900 bases for SS9 presenting more than 75% homology with corresponding fragments of Sp ORF 6 (*see* Figure 25) as determined by direct counting of homologous amino acids.

A *Vibrio* cosmid library was then prepared and using the *Vibrio* ORF 6 PCR product as a probe (*see* Figure 26); clones containing at least ORF 6 were selected by colony hybridization.

Through additional sequences of the selected cosmids such as cosmid #9 and cosmid #21, a *Vibrio* cluster (Figure 5) with ORFs homologous to, and organized in the same sequential order (ORFs 6-9) as ORFs 6-9 of *Shewanella*, was obtained (Figure 7). The *Vibrio* ORFs from this sequence are found at 17394 to 36115 and comprehend ORFs 6-9.

Table

Vibrio operon figures

17394	to 25349	length = 7956 nt
25509	to 28157	length = 2649 nt
28209	to 34262	length = 6054 nt
34454	to 36115	length = 1662 nt

The ORF designations for the *Shewanella* genes are based on those disclosed in Figure 4, and differ from those published for the *Shewanella* cluster (Yazawa *et al*, USPN 5,683,898). For instance, ORF 3 of Figure 4 is read in the opposite direction from the other ORFs and is not disclosed in Yazawa *et al* USPN 5,683,898 (See Fig. 24) for comparison with Yazawa *et al* USPN 5,683,898.

Sequences homologous to ORF 3, were not found in the proximity of ORF 6 (17000 bases upstream of ORF 6) or of ORF 9 (*ca.*4000 bases downstream of ORF 9). Motifs characteristic of phosphopantethenyl transferases (Lambalot *et al* (1996) *Current Biology* 3:923-

936) were absent from the *Vibrio* sequences screened for these motifs. In addition, there was no match to Sp ORF 3 derived probes in genomic digests of *Vibrio* and of SC2A *Shewanella* (another bacterium provided by the University of San Diego and also capable of producing EPA). Although ORF 3 may exist in *Vibrio*, its DNA may not be homologous to that of Sp ORF 3 and/or could be located in portions of the genome that were not sequenced.

Figure 6 provides the sequence of an approximately 19 kb *Vibrio* clone comprising ORFs 6-9. Figures 7 and 8 compare the gene cluster organizations of the PKS-like systems of *Vibrio marinus* and *Shewanella putrefacians*. Figures 9 through 12 show the levels of sequence homology between the corresponding ORFs 6, 7, 8 and 9, respectively.

Example 2

ORF 8 Directs DHA Production

As described in example 1, DNA homologous to *Sp* ORF 6 was found in an unrelated species, SS9 *Photobacter*, which also is capable of producing EPA. Additionally, ORFs homologous to *Sp* ORF 6-9 were found in the DHA producing V*brio marinus* (*Vibrio*). From these ORFs a series of experiments was designed in which deletions in each of *Sp* ORFs 6-9 that suppressed EPA synthesis in *E. coli* (Yazawa (1996) *supra*) were complemented by the corresponding homologous genes from *Vibrio*.

The *Sp* EPA cluster was used to determine if any of the *Vibrio* ORFs 6-9 was responsible for the production of DHA. Deletion mutants provided for each of the *Sp* ORFs are EPA and DHA null. Each deletion was then complemented by the corresponding *Vibrio* ORF expressed behind a *lac* promoter (Figure 13).

The complementation of a *Sp* ORF 6 deletion by a *Vibrio* ORF 6 reestablished the production of EPA. Similar results were obtained by complementing the *Sp* ORF 7 and ORF 9 deletions. By contrast, the complementation of a *Sp* ORF 8 deletion resulted in the production of C22:6. *Vibrio* ORF 8 therefore appears to be a key element in the synthesis of DHA. Figures 14 and 15 show chromatograms of fatty acid profiles from the respective complementations of Sp del ORF 6 with *Vibrio* ORF 6 (EPA and no DHA) and *Sp* del ORF 8 with *Vibrio* ORF 8 (DHA). Figure 16 shows the fatty acid percentages for the ORF 8 complementation, again demonstrating that ORF 8 is responsible for DHA production.

These data show that polyketide-like synthesis genes with related or similar ORFs can be combined and expressed in a heterologous system and used to produce a distinct PUFA species in the host system, and that ORF 8 has a role in determining the ultimate chain length. The *Vibrio* ORFs 6, 7, 8, and 9 reestablish EPA synthesis. In the case of *Vibrio* ORF 8, DHA is also present (*ca.* 0.7%) along with EPA (*ca.* 0.6%) indicating that this gene plays a significant role in directing synthesis of DHA *vs* EPA for these systems.

Example 3

Requirements for Production of DHA

To determine how *Vibrio* ORFs of the cluster ORF 6-9 are used in combination with *Vibrio* ORF 8, some combinations of *Vibrio* ORF 8 with some or all of the other *Vibrio* ORFS 6-9 cluster were created to explain the synthesis of DHA.

Vibrio ORFs 6-9 were complemented with *Sp* ORF 3. The results of this complementation are presented in Figures 16b and 16c. The significant amounts of DHA measured (greater than about 9%) and the absence of EPA suggest that no ORFs other than those of *Vibrio* ORFs 6-9 are required for DHA synthesis when combined with *Sp* ORF 3. This suggests that *Sp* ORF 3 plays a general function in the synthesis of bacterial PUFAs.

With respect to the DHA vs EPA production, it may be necessary to combine *Vibrio* ORF 8 with other *Vibrio* ORFs of the 6-9 cluster in order to specifically produce DHA. The roles of *Vibrio* ORF 9 and each of the combinations of *Vibrio* ORFs (6,8), (7, 8), (8, 9), etc in the synthesis of DHA are being studied.

Example 4

Plant Expression Constructs

A cloning vector with very few restriction sites was designed to facilitate the cloning of large fragments and their subsequent manipulation. An adapter was assembled by annealing oligonucleotides with the sequences AAGCCCGGGCTT, SEQ ID NO:44, and GTACAAGCCCGGGCTTAGCT, SEQ ID NO:45. This adapter was ligated to the vector pBluescript II SK+ (Stratagene) after digestion of the vector with the restriction endonucleases *Asp*718 and *Sst*I. The resulting vector, pCGN7769 had a single *Srf*I (and embedded *Sma*I) cloning site for the cloning of blunt ended DNA fragments.

A plasmid containing the napin cassette from pCGN3223, (USPN 5,639,790) was modified to make it more useful for cloning large DNA fragments containing multiple restriction sites, and to allow the cloning of multiple napin fusion genes into plant binary transformation vectors. An adapter comprised of the self annealed oligonucleotide of sequence CGCGATTTAAATGGCGCGCCCTGCAGGCGGCCGCCTGCAGGGCGC GCCATTTAAAT, SEQ ID NO:46, was ligated into the vector pBC SK+ (Stratagene) after digestion of the vector with the restriction endonuclease *Bss*HII to construct vector pCGN7765. Plamids pCGN3223 and pCGN7765 were digested with *Not*I and ligated together. The resultant vector, pCGN7770 (Figure 17), contains the pCGN7765 backbone and the napin seed specific expression cassette from pCGN3223.

Shewanella constructs

Genes encoding the *Shewanella* proteins were mutagenized to introduce suitable cloning sites 5' and 3' ORFs using PCR. The template for the PCR reactions was DNA of the cosmid pEPA (Yazawa *et al, supra)*. PCR reactions were performed using Pfu DNA polymerase according to the manufacturers' protocols. The PCR products were cloned into *Srf*I digested pCGN7769. The primers CTGCAGCTCGAGACAATGTTGATT TCCTTATACTTCTGTCC, SEQ ID NO:47, and GGATCCAGATCTCTAGCTAGTC TTAGCTGAAGCTCGA, SEQ ID NO:48, were used to amplify ORF 3, and to generate plasmid pCGN8520. The primers TCTAGACTCGAGACAATGAGCCAGACCTC TAAACCTACA, SEQ ID NO:49, and CCCGGGCTCGAGCTAATTCGCCTCACTGTC GTTTGCT, SEQ ID NO:50, were used to amplify ORF 6, and generate plasmid pCGN7776. The primers GAATTCCTCGAGACAATGCCGCTGCGCATCG CACTTATC, SEQ ID NO: 51, and GGTACCAGATCTTTAGACTTCCCCTTGAAG TAAATGG, SEQ ID NO:52, were used to amplify ORF 7, and generate plasmid pCGN7771. The primers GAATTCGTCGACACAATGTCATTACCAGACAATGC TTCT, SEQ ID NO:53, and TCTAGAGTCGACTTATACAGATTCTTCGATGCT GATAG, SEQ ID NO:54, were used to amplify ORF 8, and generate plasmid pCGN7775. The primers GAATTCGTCGACACAATGAATCCTACAGCAACTAACGAA, SEQ ID NO:55, and TCTAGAGGATCCTTAGGCCATTCTTTGGTTTGGCTTC, SEQ ID NO:56, were used to amplify ORF 9, and generate plasmid pCGN7773.

The integrity of the PCR products was verified by DNA sequencing of the inserts of pCGN7771, PCGN8520, and pCGN7773. ORF 6 and ORF 8 were quite large in size. In order to avoid sequencing the entire clones, the center portions of the ORFs were replaced with restriction fragments of pEPA. The 6.6 kilobase *Pac*I/*Bam*HI fragment of pEPA containing the central portion of ORF 6 was ligated into *Pac*I/*Bam*HI digested pCGN7776 to yield pCGN7776B4. The 4.4 kilobase *Bam*HI/*Bgl*II fragment of pEPA containing the central portion of ORF 8 was ligated into *Bam*HI/*Bgl*II digested pCGN7775 to yield pCGN7775A. The regions flanking the pEPA fragment and the cloning junctions were verified by DNA sequencing.

Plasmid pCGN7771 was cut with *Xho*I and *Bgl*II and ligated to pCGN7770 after digestion with *Sal*I and BglII. The resultant napin/ORF 7 gene fusion plasmid was designated pCGN7783. Plasmid pCGN8520 was cut with *Xho*I and *Bgl*II and ligated to pCGN7770 after digestion with *Sal*I and *Bgl*II. The resultant napin/ORF 3 gene fusion plasmid was designated pCGN8528. Plasmid pCGN7773 was cut with *Sal*I and *Bam*HI and ligated to pCGN7770 after digestion with *Sal*I and *Bgl*II. The resultant napin/ORF 9 gene fusion plasmid was designated pCGN7785. Plasmid pCGN7775A was cut with *Sal*I and ligated to pCGN7770 after digestion with *Sal*I. The resultant napin/ORF 8 gene fusion plasmid was designated pCGN7782. Plasmid pCGN7776B4 was cut with *Xho*I and ligated to pCGN7770 after digestion with *Sal*I. The resultant napin/ORF 6 gene fusion plasmid was designated pCGN7786B4.

A binary vector for plant transformation, pCGN5139, was constructed from pCGN1558 (McBride and Summerfelt (1990) *Plant Molecular Biology*, 14:269-276). The polylinker of pCGN1558 was replaced as a *Hin*dIII/*Asp*718 fragment with a polylinker containing unique restriction endonuclease sites, *Asc*I, *Pac*I, *Xba*I, *Swa*I, *Bam*HI, and *Not*I. The *Asp*718 and *Hin*dIII restriction endonuclease sites are retained in pCGN5139. PCGN5139 was digested with *Not*I and ligated with *Not*I digested pCGN7786B4. The resultant binary vector containing the napin/ORF 6 gene fusion was designated pCGN8533. Plasmid pCGN8533 was digested with *Sse*8387I and ligated with *Sse*8387I digested pCGN7782. The resultant binary vector containing the napin/ORF 6 gene fusion and the napin/ORF 8 gene fusion was designated pCGN8535 (Figure 18).

The plant binary transformation vector, pCGN5139, was digested with *Asp*718 and ligated with *Asp*718 digested pCGN8528. The resultant binary vector containing the napin/ORF 3 gene fusion was designated pCGN8532. Plasmid pCGN8532 was digested with *Not*I and ligated with *Not*I digested pCGN7783. The resultant binary vector containing the napin/ORF 3 gene fusion and the napin/ORF 7 gene fusion was designated pCGN8534. Plasmid pCGN8534 was digested with *Sse*8387I and ligated with *Sse*8387I digested pCGN7785. The resultant binary vector containing the napin/ORF 3 gene fusion, the napin/ORF 7 gene fusion and the napin/ORF 9 gene fusion was designated pCGN8537 (Figure 19).

Vibrio constructs

The *Vibrio* ORFs for plant expression were all obtained using *Vibrio* cosmid #9 as a starting molecule. *Vibrio* cosmid #9 was one of the cosmids isolated from the *Vibrio* cosmid library using the *Vibrio* ORF 6 PCR product described in Example 1.

A gene encoding *Vibrio* ORF 7 (Figure 6) was mutagenized to introduce a *Sal*I site upstream of the open reading frame and *Bam*HI site downstream of the open reading frame using the PCR primers: TCTAGAGTCGACACAATGGCGGAATTAGCTG TTATTGGT, SEQ ID NO:57, and GTCGACGGATCCCTATTTGTTCGTGTTTGCTA TATG, SEQ ID NO:58. A gene encoding *Vibrio* ORF 9 (Figure 6) was mutagenized to introduce a *Bam*HI site upstream of the open reading frame and an *Xho*HI site downstream of the open reading frame using the PCR primers: GTCGACGGATCCA CAATGAATATAGTAAGTAATCATTCGGCA, SEQ ID NO:59, and GTCGACCTC GAGTTAATCACTCGTACGATAACTTGCC, SEQ ID NO:60. The restriction sites were introduced using PCR, and the integrity of the mutagenized plasmids was verified by DNA sequence. The *Vibrio* ORF 7 gene was cloned as a *Sal*I-*Bam*HI fragment into the napin cassette of *Sal-Bgl*I digested pCGN7770 (Figure 17) to yield pCGN8539. The *Vibrio* ORF 9 gene was cloned as a *Sal*I-*Bam*HI fragment into the napin cassette of *Sal-Bal*I digested pCGN7770 (Figure 17) to yield pCGN8543.

Genes encoding the *Vibrio* ORF 6 and ORF 8 were mutagenized to introduce *Sal*I sites flanking the open reading frames. The *Sal*I sites flanking ORF 6 were introduced using PCR. The primers used were: CCCGGGTCGACACAATGGCTAAAAAGAACA CCACATCGA, SEQ ID NO:61, and CCCGGGTCGACTCATGACATATCGTTCAAA ATGTCACTGA, SEQ ID NO:62. The central 7.3 kb *Bam*HI-*Xho*I fragment of the PCR product was replaced with the corresponding fragment from *Vibrio* cosmid #9. The mutagenized ORF 6 were cloned into the *Sal*I site of the napin cassette of pCGN7770 to yield plasmid pCGN8554.

The mutagenesis of ORF 8 used a different strategy. A *Bam*HI fragment containing ORF 8 was subcloned into plasmid pHC79 to yield cosmid #9". A *Sal*I site upstream of the coding region was introduced on and adapter comprised of the oligonucleotides TCGACATGGAAAATATTGCAGTAGTAGGTATTGCTAATTT GTTC, SEQ ID NO:63, and CCGGGAACAAATTAGCAATACCTACTACTGCAAT ATTTTCCATG, SEQ ID NO:64. The adapter was ligated to cosmid #9" after digestion with *Sal*I and *Xma*I. A *Sal*I site was introduced downstream of the stop codon by using PCR for mutagenesis. A DNA fragment containing the stop codon was generated using cosmid #9" as a template with the primers TCAGATGAACTTTATCGATAC, SEQ ID NO:65 and TCATGAGACGTCGTCGACTTACGCTTCAACAATACT, SEQ ID NO:66. The PCR product was digested with the restriction endonucleases *Cla*I and *Aat*II and was cloned into the cosmid 9" derivative digested with the same enzymes to yield plasmid 8P3. The *Sal*I fragment from 8P3 was cloned into *Sal*I digested pCGN7770 to yield pCGN8515.

PCGN8532, a binary plant transformation vector that contains a *Shewannella* ORF 3 under control of the napin promoter was digested with *Not*I, and a *Not*I fragment of pCGN8539 containing a napin *Vibrio* ORF 7 gene fusion was inserted to yield pCGN8552. Plasmid pCGN8556 (Figure 23), which contains *Shewannella* ORF 3, and *Vibrio* ORFs 7 and 9 under control of the napin promoter was constructed by cloning the *Sse*8357 fragment from pCGN8543 into *Sse*8387 digested pCGN8552.

The *Not*I digested napin/ORF 8 gene from plasmid pCGN8515 was cloned into a *Not*I digested plant binary transformation vector pCGN5139 to yield pCGN8548. The *Sse*8387 digested napin/ORF 6 gene from pCGN8554 was subsequently cloned into the *Sse*8387 site of pCGN8566. The resultant binary vector containing the napin/ORF 6 gene fusion and napin/ORF 8 gene fusion was designated pCGN8560 (Figure 22).

Example 5
Plant Transformation and PUFA Production

EPA production

The *Shewanella* constructs pCGN8535 and pCGN8537 can be transformed into the same or separate plants. If separate plants are used, the transgenic plants can be crossed resulting in heterozygous seed which contains both constructs.

pCGN8535 and pCGN8537 are separately transformed into *Brassica napus*. Plants are selected on media containing kanamycin and transformation by full length inserts of the constructs is verified by Southern analysis. Immature seeds also can be tested for protein expression of the enzyme encoded by ORFs 3, 6, 7, 8, or 9 using western analysis, in which case, the best expressing pCGNE8535 and pCGN8537 T_1 transformed plants are chosen and are grown out for further experimentation and crossing. Alternatively, the T_1 transformed plants showing insertion by Southern are crossed to one another producing T_2 seed which has both insertions. In this seed, half seeds may be analyzed directly from expression of EPA in the fatty acid fraction. Remaining half-seed of events with the best EPA production are grown out and developed through conventional breeding techniques to provide *Brassica* lines for production of EPA.

Plasmids pCGN7792 and pCGN7795 also are simultaneously introduced into *Brassica napus* host cells. A standard transformation protocol is used (*see* for example USPN 5,463,174 and USPN 5,750,871, however *Agrobacteria* containing both plasmids are mixed together and incubated with *Brassica* cotyledons during the cocultivation step. Many of the resultant plants are transformed with both plasmids.

DHA production

A plant is transformed for production of DHA by introducing pCGN8556 and pCGN8560, either into separate plants or simultaneously into the same plants as described for EPA production.

Alternatively, the *Shewanella* ORFs can be used in a concerted fashion with ORFs 6 and 8 of *Vibrio*, such as by transforming with a plant the constructs pCGN8560 and pCGN7795, allowing expression of the corresponding ORFs in a plant cell. This combination provides a PKS-like gene arrangement comprising ORFs 3, 7 and 9 of *Shewanella*, with an ORF 6 derived from *Vibrio* and also an OFR 8 derived from *Vibrio*. As described above, ORF 8 is the PKS-like gene which controls the identity of the final PUFA product. Thus, the resulting transformed plants produce DHA in plant oil.

Example 6

Transgenic plants containing the *Shewanella* PUFA genes

Brassica plants

Fifty-two plants cotransformed with plasmids pCGN8535 andpCGN8537 were analyzed using PCR to determine if the *Shewanella* ORFs were present in the transgenic plants. Forty-one plants contained plasmid pCGN8537, and thirty-five plants contained pCGN8535. 11 of the plants contained all five ORFs required for the synthesis of EPA. Several plants contained genes from both of the binary plasmids but appeared to be missing at least one of the ORFs. Analysis is currently being performed on approximately twenty additional plants.

Twenty-three plants transformed with pCGN8535 alone were analyzed using PCR to determine if the *Shewanella* ORFs were present in the transgenic plants. Thirteen of these plants contained both *Shewanella* ORF 6 and *Shewanella* ORF 8. Six of the plants contained only one ORF.

Nineteen plants transformed with pCGN8537 were alone analyzed using PCR to determine if the *Shewanella* ORFs were present in the transgenic plants. Eighteen of the plants contained *Shewanella* ORF 3, *Shewanella* ORF 7, and *Shewanella* ORF 9. One plant contained *Shewanella* ORFs 3 and 7.

Arabidopsis

More than 40 transgenic Arabidopsis plants cotransformed with plasmids pCGN8535 and pCGN8537 are growing in our growth chambers. PCR analysis to determine which of the ORFs are present in the plants is currently underway.

Example 7

Evidence of A PKS System of PUFA Synthesis In *Schizochytrium*

The purpose of this experiment was to identify additional sources of PKS genes. Polyunsaturated long chain fatty acids were identified in *Schizochytrium* oil. Furthermore, production of polyunsaturated fatty acids was detected in a culture of *Schizochytrium*. A freshly diluted culture of *Schizochytrium* was incubated at 24°C in the presence of [^{14}C]-acetate (5uCi/mL) for 30 min with shaking (150 rpm). The cells were then collected by centrifugation, lyophilized and subjected to a transesterification protocol that involved heating to 90°C for 90 minutes in the presence of acidic (9% H_2SO_4) methanol with toluene (1 volume of toluene per two volumes of acidic methanol) as a second solvent. The resulting methylesters were extracted with an organic solvent (hexane) and separated by TLC (silica gel G, developed three times with hexane:diethyl ether (19:1)). Radioactivity on the TLC plate was detected using a scanner (AMBIS). Two prominent bands were detected on the TLC plate. These bands migrated on the TLC plate in positions expected for short chain (14 to 16 carbon), saturated methyl esters (the upper band) and with methylesters of polyunsaturated long chain (20 to 22 carbon) fatty acids (the lower band). These were also the major types of fatty acids detected by GC analysis of FAMEs of *Schizochytrium* oil.

In a parallel experiment thiolactomycin, a well known inhibitor of Type II fatty acid synthesis systems as well as several polyketide synthesis systems including EPA production by *E. coli* transformed with PKS genes derived from *Shewanella,* was added to the test tubes of varying concentrations (0, 1, 10 and 100 μg/ml) prior to addition of the S*chizochytrium* cell cultures and [^{14}C] acetate. Analysis of incorporation of [^{14}C] acetate, as described above, revealed that 100 ug/mL thiolactomycin completely blocked synthesis of polyunsaturated fatty acids, while partial inhibition of synthesis of polyunsaturated fatty acids was observed at 10 ug/mL thiolactomycin. Synthesis of the short chain saturated fatty acids was unaffected at all tested thiolactomycin concentrations. Thiolactomycin does not inhibit Type I fatty acid synthesis systems and is not toxic to mice, suggesting that it does not inhibit the elongation system leading to EPA or DHA formation. Furthermore, thiolactomycin did not inhibit the elongation system leading to PUFA synthesis in *Phaeodactylum tricornutum*. Therefore, although *Schizochytrium* is known to possess a Type I fatty acid synthesis system, the data suggested that the polyunsaturated fatty acids produced in this organism were derived from a system which was distinct from the Type I fatty acid synthesis system which produced short chain fatty acids, and from a system that was similar to the elongation/desaturation pathway found in mice and *Phaeodactylum*. The data are consistent with DHA formation being a result of a PKS pathway as found in *Vibrio marinus* and *Shewanella putrefaciens*.

Example 8

PKS Related Sequences From *Schizochytrium*

The purpose of this experiment was to identify sequences from *Schizochytrium* that encoded PKS genes. A cDNA library from *Schizochytrium* was constructed and approximately 8,000 random clones (ESTs) were sequenced. The protein sequence encoded by *Shewanella* EPA synthesis genes was compared to the predicted amino acid sequences of the *Schizochytrium* ESTs using a Smith/Waterman alignment algorithm. When the protein sequence of ORF6 (*Shewanella*) was compared with the amino acid sequences from *Schizochytrium* ESTs, 38 EST clones showed a significant degree of identity ($P<0.01$). When the protein sequence of ORF7 was compared by *Schizochytrium* ESTs, 4 EST clones showed significant identity ($P<0.01$) suggesting that the molecules were homologous. When the protein sequence of ORF8 and ORF9 were compared with the *Schizochytrium* ESTs, 7 and 14 clones respectively showed significant identity ($P<0.01$).

Example 9

Analysis of *Schizochytrium* cDNA Clones

Restriction enzyme analysis of the *Schizochytrium* EST clones was used to determine the longest clones, which were subsequently sequenced in their entirety. All of the EST sequences described in Example 8 were determined to be part of 5 cDNA clones.

Two of the cDNA clones were homologous to *Shewanella* ORF6. LIB3033-047-B5 was homologous to the C-terminus of ORF6. The sequence of LIB3033-047-B5 could be aligned with *Shewanella* ORF6 from amino acids 2093 onwards. The open reading frame of LIB3033-047-B5 extended all the way to the 5' end of the sequence, thus this clone was not likely to be full length. LIB3033-046-E6 shared homology to the ACP domain of ORF6. It contained 6 ACP repeats. This cDNA clone did not have a poly-A-tail, and therefore, it was likely to be a partial cDNA with additional regions of the cDNA found downstream of the sequence. The PCR primers GTGATGATCTTTCCCTGATGCACGCCAAGG (SEQ ID NO: 67) and AGCTCGAGACCGGCAACCCGCAGCGCCAGA (SEQ ID NO: 68) were used to amplify a fragment of approximately 500 nucleotides from *Schizochytrium* genomic DNA. Primer GTGATGATCTTTCCCTGATGCACGCCAAGG was derived from LIB3033-046-E6, and primer AGCTCGAGACCGGCAACCCGCAGCGCCAGA was derived from LIB3033-047-B5. Thus, LIB3033-046-E6 and LIB3033-047-B5 represented different portions of the same mRNA (see Figure 28) and could be assembled into a single partial cDNA sequence (see Figure 27A), SEQ ID NO: 69, that was predicted to encode a protein with the sequence in Figure 29A (SEQ ID NO: 70). The open reading frame extended all the way to the 5' end of the sequence, thus this partial cDNA was not likely to be full length. Analysis of additional cDNA or genomic clones will allow the determination of the full extent of the mRNA represented by clones LIB3033-046-E6 and LIB3033-047-B5. It may contain condensing enzyme related domains similar to those found near the N-terminus of *Shewanella* ORF6.

One of the cDNA clones, LIB3033-046-D2, was homologous to *Shewanella* ORF9 at its 3' end. This clone was homologous to the chain length factor region of *Shewanella* ORF8 at its 5' end. This clone was also homologous to the entire open reading frame of the *Anabaena* HglC ORF. The *Anabaena* HglC ORF is homologous to the chain length factor region of *Shewanella* ORF8 and *Shewanella* ORF7. Thus this cDNA (Figure 27B), SEQ ID NO: 71, was homologous to part of *Shewanella* ORF8, *Shewanella* ORF7 and *Shewanella* ORF9 (see Figure 28). The amino acid sequence (Figure 29B), SEQ ID NO: 72, encoded by the open reading frame of LIB3033-046-D2 extended all the way to the 5' end of the sequence; thus this clone was not likely to be full length. Analysis of additional cDNA or genomic clones will allow the determination of the full extent of the mRNA represented by LIB3033-046-E6. It may contain condensing enzyme related domains similar to those found near the N-terminus of *Shewanella* ORF8.

Two additional cDNA clones were homologous to *Shewanella* ORF8. LIB81-015-D5 was homologous to the C-terminus of ORF8. The 5' sequence of LIB81-015-D5 could be

aligned with *Shewanella* ORF8 from amino acids 1900 onwards. The 3' end of LIB81-015-D5 could be aligned with *Shewanella* ORF9 (see Figure 28). The amino acid sequence (Figure 29C), SEQ ID NO: 73, encoded by the open reading frame of LIB81-015-D5 extended all the way to the 5' end of the sequence; thus this clone was not likely to be full length. LIB81-042-B9 was homologous to amino acids 1150 to 1850 of *Shewanella* ORF8. LIB81-042-B9 did not have a poly-A-tail, and therefore, it was likely to be a partial cDNA with additional regions of the cDNA found downstream of the sequence. The PCR primers TACCGCGGCAAGACTATCCGCAACGTCACC (SEQ ID NO: 74) and GCCGTCGTGGGCGTCCACGGACACGATGTG (SEQ ID NO: 75) were used to amplify a fragment of approximately 500 nucleotides from *Schizochytrium* genomic DNA. Primer TACCGCGGCAAGACTATCCGCAACGTCACC was derived from LIB81-042-B9, and primer GCCGTCGTGGGCGTCCACGGACACGATGTG was derived from LIB81-015-D5. Thus, LIB81-042-and LIB81-015-D5 represented different portions of the same mRNA and were assembled into a single partial cDNA sequence (see Figure 27C), SEQ ID NO: 76. The open reading frame of LIB81-042-B9 also extended all the way to the 5' end of the sequence, thus this clone was also not likely to be full length. Analysis of additional cDNA or genomic clones will allow the determination of the full extent of the mRNA represented by LIB81-042-B9.

By the present invention PKS-like genes from various organisms can now be used to transform plant cells and modify the fatty acid compositions of plant cell membranes or plant seed oils through the biosynthesis of PUFAs in the transformed plant cells. Due to the nature of the PKS-like systems, fatty acid end-products produced in the plant cells can be selected or designed to contain a number of specific chemical structures. For example, the fatty acids can comprise the following variants: Variations in the numbers of keto or hydroxyl groups at various positions along the carbon chain; variations in the numbers and types (*cis* or *trans*) of double bonds; variations in the numbers and types of branches off of the linear carbon chain (methyl, ethyl, or longer branched moieties); and variations in saturated carbons. In addition, the particular length of the end-product fatty acid can be controlled by the particular PKS-like genes utilized.

All publications and patent applications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

SEQUENCE LISTING

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tcgtttctca gcatatatca aaatacacag caaaaatttg gggttagcta tatagctaac 35400

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Asn Ala Leu Ala Ala Gln His Glu His Asp His Ile Thr Val Asp Tyr
20 25 30

Glu Gly Lys Ala Ala Thr Glu His Thr Ile Ala His Asn Gln Ala Val
35 40 45

Ala Lys Thr Leu Asn Phe Ala Asp Thr Arg Ala Phe Glu Gln Ser Ser
50 55 60

Lys Asn Leu Val Ala Lys Phe Asp Lys Ala Thr Ala Asp Ile Leu Arg
65 70 75 80

Ala Glu Phe Ala Phe Ile Ser Asp Glu Ile Pro Asp Ser Val Asn Pro
85 90 95

Ser Leu Tyr Arg Gln Ala Gln Leu Asn Met Val Pro Asn Gly Tyr Lys
100 105 110

Val Ser Asp Gly Ile Tyr Gln Val Arg Gly Thr Asp Leu Ser Asn Leu
115 120 125

Thr Leu Ile Arg Ser Asp Asn Gly Trp Ile Ala Tyr Asp Val Leu Leu
130 135 140

```
Thr Lys Glu Ala Ala Lys Ala Ser Leu Gln Phe Ala Leu Lys Asn Leu
145                 150                 155                 160

Pro Lys Asp Gly Asp Pro Val Val Ala Met Ile Tyr Ser His Ser His
                165                 170                 175

Ala Asp His Phe Gly Gly Ala Arg Gly Val Gln Glu Met Phe Pro Asp
            180                 185                 190

Val Lys Val Tyr Gly Ser Asp Asn Ile Thr Lys Glu Ile Val Asp Glu
        195                 200                 205

Asn Val Leu Ala Gly Asn Ala Met Ser Arg Arg Ala Ala Tyr Gln Tyr
    210                 215                 220

Gly Ala Thr Leu Gly Lys His Asp His Gly Ile Val Asp Ala Ala Leu
225                 230                 235                 240

Gly Lys Gly Leu Ser Lys Gly Glu Ile Thr Tyr Val Ala Pro Asp Tyr
                245                 250                 255

Thr Leu Asn Ser Glu Gly Lys Trp Glu Thr Leu Thr Ile Asp Gly Leu
            260                 265                 270

Glu Met Val Phe Met Asp Ala Ser Gly Thr Glu Ala Glu Ser Glu Met
        275                 280                 285

Ile Thr Tyr Ile Pro Ser Lys Lys Ala Leu Trp Thr Ala Glu Leu Thr
    290                 295                 300

Tyr Gln Gly Met His Asn Ile Tyr Thr Leu Arg Gly Ala Lys Val Arg
305                 310                 315                 320

Asp Ala Leu Lys Trp Ser Lys Asp Ile Asn Glu Met Ile Asn Ala Phe
                325                 330                 335

Gly Gln Asp Val Glu Val Leu Phe Ala Ser His Ser Ala Pro Val Trp
            340                 345                 350
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Gly Asn Gln Ala Ile Asn Asp Phe Leu Arg Leu Gln Arg Asp Asn Tyr
        355                 360                 365

Gly Leu Val His Asn Gln Thr Leu Arg Leu Ala Asn Asp Gly Val Gly
    370                 375                 380

Ile Gln Asp Ile Gly Asp Ala Ile Gln Asp Thr Ile Pro Glu Ser Ile
385                 390                 395                 400

Tyr Lys Thr Trp His Thr Asn Gly Tyr His Gly Thr Tyr Ser His Asn
                405                 410                 415

Ala Lys Ala Val Tyr Asn Lys Tyr Leu Gly Tyr Phe Asp Met Asn Pro
            420                 425                 430

Ala Asn Leu Asn Pro Leu Pro Thr Lys Gln Glu Ser Ala Lys Phe Val
        435                 440                 445

Glu Tyr Met Gly Gly Ala Asp Ala Ala Ile Lys Arg Ala Lys Asp Asp
    450                 455                 460

Tyr Ala Gln Gly Glu Tyr Arg Phe Val Ala Thr Ala Leu Asn Lys Val
465                 470                 475                 480

Val Met Ala Glu Pro Glu Asn Asp Ser Ala Arg Gln Leu Leu Ala Asp
                485                 490                 495

Thr Tyr Glu Gln Leu Gly Tyr Gln Ala Glu Gly Ala Gly Trp Arg Asn
            500                 505                 510

Ile Tyr Leu Thr Gly Ala Gln Glu Leu Arg Val Gly Ile Gln Ala Gly
        515                 520                 525

Ala Pro Lys Thr Ala Ser Ala Asp Val Ile Ser Glu Met Asp Met Pro
    530                 535                 540

Thr Leu Phe Asp Phe Leu Ala Val Lys Ile Asp Ser Gln Gln Ala Ala
545                 550                 555                 560

Lys His Gly Leu Val Lys Met Asn Val Ile Thr Pro Asp Thr Lys Asp
                565                 570                 575
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Ile Leu Tyr Ile Glu Leu Ser Asn Gly Asn Leu Ser Asn Ala Val Val
            580                 585                 590

Asp Lys Glu Gln Leu Met Val Asn Lys Ala Asp Val Asn Arg Ile Leu
        595                 600                 605

Leu Gly Gln Val Thr Leu Lys Ala Leu Leu Ala Ser Gly Asp Ala Lys
    610                 615                 620

Leu Thr Gly Asp Lys Thr Ala Phe Ser Lys Ile Ala Asp Ser Met Val
625                 630                 635                 640

Glu Phe Thr Pro Asp Phe Glu Ile Val Pro Thr Pro Val Lys
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Ala Ala Ile Ser Ile Gln Gln Cys Gln Gly Ile Ser Leu Ala Phe Arg
            20                  25                  30

Tyr Ser Asp Asp Leu His Gly Leu Leu Cys His Trp Asn Asp Ala Ala
        35                  40                  45

Asn Met Gln Gln Glu Lys Ala Glu Ile Leu Gly Leu Gly Ser Lys Gln
    50                  55                  60

Pro Glu Ala Asn Pro Lys Asn Ser Ser Ser Glu Leu Leu Ala Leu Gly
65                  70                  75                  80

Ile Asp Gln Lys Leu Leu Val Gln Arg Gln Asn Leu Gln His Glu Val
                85                  90                  95

Lys His Asp Ala Ile Ala Asp Ser Ile Asp Val Cys His Ser Leu Ser
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100 105 110

Lys Pro Ala Asn Val Gly Leu Phe Thr Glu Ser Leu Ala Ser Phe Asp
115 120 125

Phe Ala Phe Ser Lys Leu Ser Leu Ala Leu Gly Leu Gly Lys Ala Lys
130 135 140

Ile Tyr Ser Glu Lys Leu Ala Trp Leu Asp Phe Phe Arg Asp Arg Gln
145 150 155 160

Leu Ala Glu Pro Leu Ala Leu Leu Ala Arg Lys Glu Ser Glu Ser Phe
165 170 175

Tyr His Ser Leu Ile Ser His Ile Asn Thr Ser Asn Arg Cys Arg Glu
180 185 190

Ile Asp Val Gly Phe Glu Ile Ser Ala Ser Asp Thr Glu Glu Lys Ser
195 200 205

Ala Gln Ser Ala Gly Lys Asn Asp Ala Thr Cys Ile Gly Val Leu Leu
210 215 220

Trp Asp Gly Ser His Ser Val Asn Phe His Val Gly Thr Gln Ala Phe
225 230 235 240

Gln Ala Asp Ser Leu Arg Pro Lys Gly Lys Asp Gly Tyr Glu Phe Arg
245 250 255

Trp Glu Asn Pro Arg Ile Glu Ser His Gln Ser Leu Leu Ala Arg Leu
260 265 270

Tyr Gly Arg Val Met
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<213> Shewanella putrefaciens

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1 5 10 15

Ile Ser Ala Gly Leu Thr Ala Ser Leu Ala Met Pro Val Phe Ala Glu
20 25 30

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Glu Thr Ala Ala Glu Glu Gln Ile Glu Arg Val Ala Val Thr Gly Ser
        35                  40                  45

Arg Ile Ala Lys Ala Glu Leu Thr Gln Pro Ala Pro Val Val Ser Leu
    50                  55                  60

Ser Ala Glu Glu Leu Thr Lys Phe Gly Asn Gln Asp Leu Gly Ser Val
65                  70                  75                  80

Leu Ala Glu Leu Pro Ala Ile Gly Ala Thr Asn Thr Ile Ile Gly Asn
                85                  90                  95

Asn Asn Ser Asn Ser Ser Ala Gly Val Ser Ser Ala Asp Leu Arg Arg
            100                 105                 110

Leu Gly Ala Asn Arg Thr Leu Val Leu Val Asn Gly Lys Arg Tyr Val
        115                 120                 125

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

Ser Met Ile Ser Arg Val Glu Ile Val Thr Gly Gly Ala Ser Ala Ile
145                 150                 155                 160

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

Asp Phe Glu Gly Phe Glu Phe Asn Ala Arg Thr Ser Gly Ser Thr Glu
            180                 185                 190

Ser Val Gly Thr Gln Glu His Ser Phe Asp Ile Leu Gly Gly Ala Asn
        195                 200                 205

Val Ala Asp Gly Arg Gly Asn Val Thr Phe Tyr Ala Gly Tyr Glu Arg
    210                 215                 220

Thr Lys Glu Val Met Ala Thr Asp Ile Arg Gln Phe Asp Ala Trp Gly
225                 230                 235                 240

Thr Ile Lys Asn Glu Ala Asp Gly Gly Glu Asp Asp Gly Ile Pro Asp
                245                 250                 255
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```
Arg Leu Arg Val Pro Arg Val Tyr Ser Glu Met Ile Asn Ala Thr Gly
            260                 265                 270

Val Ile Asn Ala Phe Gly Gly Gly Ile Gly Arg Ser Thr Phe Asp Ser
        275                 280                 285

Asn Gly Asn Pro Ile Ala Gln Gln Glu Arg Asp Gly Thr Asn Ser Phe
    290                 295                 300

Ala Phe Gly Ser Phe Pro Asn Gly Cys Asp Thr Cys Phe Asn Thr Glu
305                 310                 315                 320

Ala Tyr Glu Asn Tyr Ile Pro Gly Val Glu Arg Ile Asn Val Gly Ser
                325                 330                 335

Ser Phe Asn Phe Asp Phe Thr Asp Asn Ile Gln Phe Tyr Thr Asp Phe
            340                 345                 350

Arg Tyr Val Lys Ser Asp Ile Gln Gln Gln Phe Gln Pro Ser Phe Arg
        355                 360                 365

Phe Gly Asn Ile Asn Ile Asn Val Glu Asp Asn Ala Phe Leu Asn Asp
    370                 375                 380

Asp Leu Arg Gln Gln Met Leu Asp Ala Gly Gln Thr Asn Ala Ser Phe
385                 390                 395                 400

Ala Lys Phe Phe Asp Glu Leu Gly Asn Arg Ser Ala Glu Asn Lys Arg
                405                 410                 415

Glu Leu Phe Arg Tyr Val Gly Gly Phe Lys Gly Gly Phe Asp Ile Ser
            420                 425                 430

Glu Thr Ile Phe Asp Tyr Asp Leu Tyr Tyr Val Tyr Gly Glu Thr Asn
        435                 440                 445

Asn Arg Arg Lys Thr Leu Asn Asp Leu Ile Pro Asp Asn Phe Val Ala
    450                 455                 460
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Ala Val Asp Ser Val Ile Asp Pro Asp Thr Gly Leu Ala Ala Cys Arg
465                 470                 475                 480

Ser Gln Val Ala Ser Ala Gln Gly Asp Asp Tyr Thr Asp Pro Ala Ser
                485                 490                 495

Val Asn Gly Ser Asp Cys Val Ala Tyr Asn Pro Phe Gly Met Gly Gln
            500                 505                 510

Ala Ser Ala Glu Ala Arg Asp Trp Val Ser Ala Asp Val Thr Arg Glu
        515                 520                 525

Asp Lys Ile Thr Gln Gln Val Ile Gly Gly Thr Leu Gly Thr Asp Ser
    530                 535                 540

Glu Glu Leu Phe Glu Leu Gln Gly Gly Ala Ile Ala Met Val Val Gly
545                 550                 555                 560

Phe Glu Tyr Arg Glu Glu Thr Ser Gly Ser Thr Thr Asp Glu Phe Thr
                565                 570                 575

Lys Ala Gly Phe Leu Thr Ser Ala Ala Thr Pro Asp Ser Tyr Gly Glu
            580                 585                 590

Tyr Asp Val Thr Glu Tyr Phe Val Glu Val Asn Ile Pro Val Leu Lys
        595                 600                 605

Glu Leu Pro Phe Ala His Glu Leu Ser Phe Asp Gly Ala Tyr Arg Asn
    610                 615                 620

Ala Asp Tyr Ser His Ala Gly Lys Thr Glu Ala Trp Lys Ala Gly Met
625                 630                 635                 640

Phe Tyr Ser Pro Leu Glu Gln Leu Ala Leu Arg Gly Thr Val Gly Glu
                645                 650                 655

Ala Val Arg Ala Pro Asn Ile Ala Glu Ala Phe Ser Pro Arg Ser Pro
            660                 665                 670

Gly Phe Gly Arg Val Ser Asp Pro Cys Asp Ala Asp Asn Ile Asn Asp
        675                 680                 685
```

```
Asp Pro Asp Arg Val Ser Asn Cys Ala Ala Leu Gly Ile Pro Pro Gly
    690                 695                 700

Phe Gln Ala Asn Asp Asn Val Ser Val Asp Thr Leu Ser Gly Gly Asn
705                 710                 715                 720

Pro Asp Leu Lys Pro Glu Thr Ser Thr Ser Phe Thr Gly Gly Leu Val
                725                 730                 735

Trp Thr Pro Thr Phe Ala Asp Asn Leu Ser Phe Thr Val Asp Tyr Tyr
            740                 745                 750

Asp Ile Gln Ile Glu Asp Ala Ile Leu Ser Val Ala Thr Gln Thr Val
        755                 760                 765

Ala Asp Asn Cys Val Asp Ser Thr Gly Gly Pro Asp Thr Asp Phe Cys
    770                 775                 780

Ser Gln Val Asp Arg Asn Pro Thr Thr Tyr Asp Ile Glu Leu Val Arg
785                 790                 795                 800

Ser Gly Tyr Leu Asn Ala Ala Ala Leu Asn Thr Lys Gly Ile Glu Phe
                805                 810                 815

Gln Ala Ala Tyr Ser Leu Asp Leu Glu Ser Phe Asn Ala Pro Gly Glu
            820                 825                 830

Leu Arg Phe Asn Leu Leu Gly Asn Gln Leu Leu Glu Leu Glu Arg Leu
        835                 840                 845

Glu Phe Gln Asn Arg Pro Asp Glu Ile Asn Asp Glu Lys Gly Glu Val
    850                 855                 860

Gly Asp Pro Glu Leu Gln Phe Arg Leu Gly Ile Asp Tyr Arg Leu Asp
865                 870                 875                 880

Asp Leu Ser Val Ser Trp Asn Thr Arg Tyr Ile Asp Ser Val Val Thr
                885                 890                 895
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```
Tyr Asp Val Ser Glu Asn Gly Gly Ser Pro Glu Asp Leu Tyr Pro Gly
            900                 905                 910

His Ile Gly Ser Met Thr Thr His Asp Leu Ser Ala Thr Tyr Tyr Ile
        915                 920                 925

Asn Glu Asn Phe Met Ile Asn Gly Gly Val Arg Asn Leu Phe Asp Ala
    930                 935                 940

Leu Pro Pro Gly Tyr Thr Asn Asp Ala Leu Tyr Asp Leu Val Gly Arg
945                 950                 955                 960

Arg Ala Phe Leu Gly Ile Lys Val Met Met
                965                 970
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<210> 6
<211> 288
<212> PRT
<213> Shewanella putrefaciens

<400> 6

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Met Ala Lys Ile Asn Ser Glu His Leu Asp Glu Ala Thr Ile Thr Ser
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Asn Lys Cys Thr Gln Thr Glu Thr Glu Ala Arg His Arg Asn Ala Thr
            20                  25                  30

Thr Thr Pro Glu Met Arg Arg Phe Ile Gln Glu Ser Asp Leu Ser Val
        35                  40                  45

Ser Gln Leu Ser Lys Ile Leu Asn Ile Ser Glu Ala Thr Val Arg Lys
    50                  55                  60

Trp Arg Lys Arg Asp Ser Val Glu Asn Cys Pro Asn Thr Pro His His
65                  70                  75                  80

Leu Asn Thr Thr Leu Thr Pro Leu Gln Glu Tyr Val Val Val Gly Leu
                85                  90                  95

Arg Tyr Gln Leu Lys Met Pro Leu Asp Arg Leu Leu Lys Ala Thr Gln
            100                 105                 110
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```
Glu Phe Ile Asn Pro Asn Val Ser Arg Ser Gly Leu Ala Arg Cys Leu
        115                 120                 125

Lys Arg Tyr Gly Val Ser Arg Val Ser Asp Ile Gln Ser Pro His Val
    130                 135                 140

Pro Met Arg Tyr Phe Asn Gln Ile Pro Val Thr Gln Gly Ser Asp Val
145                 150                 155                 160

Gln Thr Tyr Thr Leu His Tyr Glu Thr Leu Ala Lys Thr Leu Ala Leu
                165                 170                 175

Pro Ser Thr Asp Gly Asp Asn Val Val Gln Val Val Ser Leu Thr Ile
            180                 185                 190

Pro Pro Lys Leu Thr Glu Glu Ala Pro Ser Ser Ile Leu Leu Gly Ile
        195                 200                 205

Asp Pro His Ser Asp Trp Ile Tyr Leu Asp Ile Tyr Gln Asp Gly Asn
    210                 215                 220

Thr Gln Ala Thr Asn Arg Tyr Met Ala Tyr Val Leu Lys His Gly Pro
225                 230                 235                 240

Phe His Leu Arg Lys Leu Leu Val Arg Asn Tyr His Thr Phe Leu Gln
                245                 250                 255

Arg Phe Pro Gly Ala Thr Gln Asn Arg Arg Pro Ser Lys Asp Met Pro
            260                 265                 270

Glu Thr Ile Asn Lys Thr Pro Glu Thr Gln Ala Pro Ser Gly Asp Ser
        275                 280                 285


<210>  7
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<213>  Shewanella putrefaciens

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Met Ser Gln Thr Ser Lys Pro Thr Asn Ser Ala Thr Glu Gln Ala Gln
1               5                   10                  15
```

Asp Ser Gln Ala Asp Ser Arg Leu Asn Lys Arg Leu Lys Asp Met Pro
20 25 30

Ile Ala Ile Val Gly Met Ala Ser Ile Phe Ala Asn Ser Arg Tyr Leu
35 40 45

Asn Lys Phe Trp Asp Leu Ile Ser Glu Lys Ile Asp Ala Ile Thr Glu
50 55 60

Leu Pro Ser Thr His Trp Gln Pro Glu Glu Tyr Tyr Asp Ala Asp Lys
65 70 75 80

Thr Ala Ala Asp Lys Ser Tyr Cys Lys Arg Gly Gly Phe Leu Pro Asp
85 90 95

Val Asp Phe Asn Pro Met Glu Phe Gly Leu Pro Pro Asn Ile Leu Glu
100 105 110

Leu Thr Asp Ser Ser Gln Leu Leu Ser Leu Ile Val Ala Lys Glu Val
115 120 125

Leu Ala Asp Ala Asn Leu Pro Glu Asn Tyr Asp Arg Asp Lys Ile Gly
130 135 140

Ile Thr Leu Gly Val Gly Gly Gly Gln Lys Ile Ser His Ser Leu Thr
145 150 155 160

Ala Arg Leu Gln Tyr Pro Val Leu Lys Lys Val Phe Ala Asn Ser Gly
165 170 175

Ile Ser Asp Thr Asp Ser Glu Met Leu Ile Lys Lys Phe Gln Asp Gln
180 185 190

Tyr Val His Trp Glu Glu Asn Ser Phe Pro Gly Ser Leu Gly Asn Val
195 200 205

Ile Ala Gly Arg Ile Ala Asn Arg Phe Asp Phe Gly Gly Met Asn Cys
210 215 220

```
Val Val Asp Ala Ala Cys Ala Gly Ser Leu Ala Ala Met Arg Met Ala
225                 230                 235                 240

Leu Thr Glu Leu Thr Glu Gly Arg Ser Glu Met Met Ile Thr Gly Gly
                245                 250                 255

Val Cys Thr Asp Asn Ser Pro Ser Met Tyr Met Ser Phe Ser Lys Thr
            260                 265                 270

Pro Ala Phe Thr Thr Asn Glu Thr Ile Gln Pro Phe Asp Ile Asp Ser
        275                 280                 285

Lys Gly Met Met Ile Gly Glu Gly Ile Gly Met Val Ala Leu Lys Arg
    290                 295                 300

Leu Glu Asp Ala Glu Arg Asp Gly Asp Arg Ile Tyr Ser Val Ile Lys
305                 310                 315                 320

Gly Val Gly Ala Ser Ser Asp Gly Lys Phe Lys Ser Ile Tyr Ala Pro
                325                 330                 335

Arg Pro Ser Gly Gln Ala Lys Ala Leu Asn Arg Ala Tyr Asp Asp Ala
            340                 345                 350

Gly Phe Ala Pro His Thr Leu Gly Leu Ile Glu Ala His Gly Thr Gly
        355                 360                 365

Thr Ala Ala Gly Asp Ala Ala Glu Phe Ala Gly Leu Cys Ser Val Phe
    370                 375                 380

Ala Glu Gly Asn Asp Thr Lys Gln His Ile Ala Leu Gly Ser Val Lys
385                 390                 395                 400

Ser Gln Ile Gly His Thr Lys Ser Thr Ala Gly Thr Ala Gly Leu Ile
                405                 410                 415

Lys Ala Ala Leu Ala Leu His His Lys Val Leu Pro Pro Thr Ile Asn
            420                 425                 430

Val Ser Gln Pro Ser Pro Lys Leu Asp Ile Glu Asn Ser Pro Phe Tyr
        435                 440                 445
```

```
Leu Asn Thr Glu Thr Arg Pro Trp Leu Pro Arg Val Asp Gly Thr Pro
    450                 455                 460

Arg Arg Ala Gly Ile Ser Ser Phe Gly Phe Gly Gly Thr Asn Phe His
465                 470                 475                 480

Phe Val Leu Glu Glu Tyr Asn Gln Glu His Ser Arg Thr Asp Ser Glu
                485                 490                 495

Lys Ala Lys Tyr Arg Gln Arg Gln Val Ala Gln Ser Phe Leu Val Ser
            500                 505                 510

Ala Ser Asp Lys Ala Ser Leu Ile Asn Glu Leu Asn Val Leu Ala Ala
        515                 520                 525

Ser Ala Ser Gln Ala Glu Phe Ile Leu Lys Asp Ala Ala Ala Asn Tyr
    530                 535                 540

Gly Val Arg Glu Leu Asp Lys Asn Ala Pro Arg Ile Gly Leu Val Ala
545                 550                 555                 560

Asn Thr Ala Glu Glu Leu Ala Gly Leu Ile Lys Gln Ala Leu Ala Lys
                565                 570                 575

Leu Ala Ala Ser Asp Asp Asn Ala Trp Gln Leu Pro Gly Gly Thr Ser
            580                 585                 590

Tyr Arg Ala Ala Ala Val Glu Gly Lys Val Ala Ala Leu Phe Ala Gly
        595                 600                 605

Gln Gly Ser Gln Tyr Leu Asn Met Gly Arg Asp Leu Thr Cys Tyr Tyr
    610                 615                 620

Pro Glu Met Arg Gln Gln Phe Val Thr Ala Asp Lys Val Phe Ala Ala
625                 630                 635                 640

Asn Asp Lys Thr Pro Leu Ser Gln Thr Leu Tyr Pro Lys Pro Val Phe
                645                 650                 655
```

```
Asn Lys Asp Glu Leu Lys Ala Gln Glu Ala Ile Leu Thr Asn Thr Ala
            660                 665                 670

Asn Ala Gln Ser Ala Ile Gly Ala Ile Ser Met Gly Gln Tyr Asp Leu
        675                 680                 685

Phe Thr Ala Ala Gly Phe Asn Ala Asp Met Val Ala Gly His Ser Phe
    690                 695                 700

Gly Glu Leu Ser Ala Leu Cys Ala Ala Gly Val Ile Ser Ala Asp Asp
705                 710                 715                 720

Tyr Tyr Lys Leu Ala Phe Ala Arg Gly Glu Ala Met Ala Thr Lys Ala
                725                 730                 735

Pro Ala Lys Asp Gly Val Glu Ala Asp Ala Gly Ala Met Phe Ala Ile
            740                 745                 750

Ile Thr Lys Ser Ala Ala Asp Leu Glu Thr Val Glu Ala Thr Ile Ala
        755                 760                 765

Lys Phe Asp Gly Val Lys Val Ala Asn Tyr Asn Ala Pro Thr Gln Ser
    770                 775                 780

Val Ile Ala Gly Pro Thr Ala Thr Thr Ala Asp Ala Ala Lys Ala Leu
785                 790                 795                 800

Thr Glu Leu Gly Tyr Lys Ala Ile Asn Leu Pro Val Ser Gly Ala Phe
                805                 810                 815

His Thr Glu Leu Val Gly His Ala Gln Ala Pro Phe Ala Lys Ala Ile
            820                 825                 830

Asp Ala Ala Lys Phe Thr Lys Thr Ser Arg Ala Leu Tyr Ser Asn Ala
        835                 840                 845

Thr Gly Gly Leu Tyr Glu Ser Thr Ala Ala Lys Ile Lys Ala Ser Phe
    850                 855                 860

Lys Lys His Met Leu Gln Ser Val Arg Phe Thr Ser Gln Leu Glu Ala
865                 870                 875                 880
```

Met Tyr Asn Asp Gly Ala Arg Val Phe Val Glu Phe Gly Pro Lys Asn
885 890 895

Ile Leu Gln Lys Leu Val Gln Gly Thr Leu Val Asn Thr Glu Asn Glu
900 905 910

Val Cys Thr Ile Ser Ile Asn Pro Asn Pro Lys Val Asp Ser Asp Leu
915 920 925

Gln Leu Lys Gln Ala Ala Met Gln Leu Ala Val Thr Gly Val Val Leu
930 935 940

Ser Glu Ile Asp Pro Tyr Gln Ala Asp Ile Ala Ala Pro Ala Lys Lys
945 950 955 960

Ser Pro Met Ser Ile Ser Leu Asn Ala Ala Asn His Ile Ser Lys Ala
965 970 975

Thr Arg Ala Lys Met Ala Lys Ser Leu Glu Thr Gly Ile Val Thr Ser
980 985 990

Gln Ile Glu His Val Ile Glu Glu Lys Ile Val Glu Val Glu Lys Leu
995 1000 1005

Val Glu Val Glu Lys Ile Val Glu Lys Val Val Glu Val Glu Lys
1010 1015 1020

Val Val Glu Val Glu Ala Pro Val Asn Ser Val Gln Ala Asn Ala
1025 1030 1035

Ile Gln Thr Arg Ser Val Val Ala Pro Val Ile Glu Asn Gln Val
1040 1045 1050

Val Ser Lys Asn Ser Lys Pro Ala Val Gln Ser Ile Ser Gly Asp
1055 1060 1065

Ala Leu Ser Asn Phe Phe Ala Ala Gln Gln Gln Thr Ala Gln Leu
1070 1075 1080

```
His Gln  Gln Phe Leu Ala Ile  Pro Gln Gln Tyr Gly  Glu Thr Phe
    1085                1090                1095

Thr Thr  Leu Met Thr Glu Gln  Ala Lys Leu Ala Ser  Ser Gly Val
    1100                1105                1110

Ala Ile  Pro Glu Ser Leu Gln  Arg Ser Met Glu Gln  Phe His Gln
    1115                1120                1125

Leu Gln  Ala Gln Thr Leu Gln  Ser His Thr Gln Phe  Leu Glu Met
    1130                1135                1140

Gln Ala  Gly Ser Asn Ile Ala  Ala Leu Asn Leu Leu  Asn Ser Ser
    1145                1150                1155

Gln Ala  Thr Tyr Ala Pro Ala  Ile His Asn Glu Ala  Ile Gln Ser
    1160                1165                1170

Gln Val  Val Gln Ser Gln Thr  Ala Val Gln Pro Val  Ile Ser Thr
    1175                1180                1185

Gln Val  Asn His Val Ser Glu  Gln Pro Thr Gln Ala  Pro Ala Pro
    1190                1195                1200

Lys Ala  Gln Pro Ala Pro Val  Thr Thr Ala Val Gln  Thr Ala Pro
    1205                1210                1215

Ala Gln  Val Val Arg Gln Ala  Ala Pro Val Gln Ala  Ala Ile Glu
    1220                1225                1230

Pro Ile  Asn Thr Ser Val Ala  Thr Thr Thr Pro Ser  Ala Phe Ser
    1235                1240                1245

Ala Glu  Thr Ala Leu Ser Ala  Thr Lys Val Gln Ala  Thr Met Leu
    1250                1255                1260

Glu Val  Val Ala Glu Lys Thr  Gly Tyr Pro Thr Glu  Met Leu Glu
    1265                1270                1275

Leu Glu  Met Asp Met Glu Ala  Asp Leu Gly Ile Asp  Ser Ile Lys
    1280                1285                1290
```

```
Arg Val  Glu Ile Leu Gly Thr  Val Gln Asp Glu Leu  Pro Gly Leu
    1295                 1300                 1305

Pro Glu  Leu Ser Pro Glu Asp  Leu Ala Glu Cys Arg  Thr Leu Gly
    1310                 1315                 1320

Glu Ile  Val Asp Tyr Met Gly  Ser Lys Leu Pro Ala  Glu Gly Ser
    1325                 1330                 1335

Met Asn  Ser Gln Leu Ser Thr  Gly Ser Ala Ala Ala  Thr Pro Ala
    1340                 1345                 1350

Ala Asn  Gly Leu Ser Ala Glu  Lys Val Gln Ala Thr  Met Met Ser
    1355                 1360                 1365

Val Val  Ala Glu Lys Thr Gly  Tyr Pro Thr Glu Met  Leu Glu Leu
    1370                 1375                 1380

Glu Met  Asp Met Glu Ala Asp  Leu Gly Ile Asp Ser  Ile Lys Arg
    1385                 1390                 1395

Val Glu  Ile Leu Gly Thr Val  Gln Asp Glu Leu Pro  Gly Leu Pro
    1400                 1405                 1410

Glu Leu  Ser Pro Glu Asp Leu  Ala Glu Cys Arg Thr  Leu Gly Glu
    1415                 1420                 1425

Ile Val  Asp Tyr Met Asn Ser  Lys Leu Ala Asp Gly  Ser Lys Leu
    1430                 1435                 1440

Pro Ala  Glu Gly Ser Met Asn  Ser Gln Leu Ser Thr  Ser Ala Ala
    1445                 1450                 1455

Ala Ala  Thr Pro Ala Ala Asn  Gly Leu Ser Ala Glu  Lys Val Gln
    1460                 1465                 1470

Ala Thr  Met Met Ser Val Val  Ala Glu Lys Thr Gly  Tyr Pro Thr
    1475                 1480                 1485
```

```
Glu Met  Leu Glu Leu Glu Met  Asp Met Glu Ala Asp  Leu Gly Ile
    1490                 1495                 1500

Asp Ser  Ile Lys Arg Val Glu  Ile Leu Gly Thr Val  Gln Asp Glu
    1505                 1510                 1515

Leu Pro  Gly Leu Pro Glu Leu  Asn Pro Glu Asp Leu  Ala Glu Cys
    1520                 1525                 1530

Arg Thr  Leu Gly Glu Ile Val  Thr Tyr Met Asn Ser  Lys Leu Ala
    1535                 1540                 1545

Asp Gly  Ser Lys Leu Pro Ala  Glu Gly Ser Met His  Tyr Gln Leu
    1550                 1555                 1560

Ser Thr  Ser Thr Ala Ala Ala  Thr Pro Val Ala Asn  Gly Leu Ser
    1565                 1570                 1575

Ala Glu  Lys Val Gln Ala Thr  Met Met Ser Val Val  Ala Asp Lys
    1580                 1585                 1590

Thr Gly  Tyr Pro Thr Glu Met  Leu Glu Leu Glu Met  Asp Met Glu
    1595                 1600                 1605

Ala Asp  Leu Gly Ile Asp Ser  Ile Lys Arg Val Glu  Ile Leu Gly
    1610                 1615                 1620

Thr Val  Gln Asp Glu Leu Pro  Gly Leu Pro Glu Leu  Asn Pro Glu
    1625                 1630                 1635

Asp Leu  Ala Glu Cys Arg Thr  Leu Gly Glu Ile Val  Asp Tyr Met
    1640                 1645                 1650

Gly Ser  Lys Leu Pro Ala Glu  Gly Ser Ala Asn Thr  Ser Ala Ala
    1655                 1660                 1665

Ala Ser  Leu Asn Val Ser Ala  Val Ala Ala Pro Gln  Ala Ala Ala
    1670                 1675                 1680

Thr Pro  Val Ser Asn Gly Leu  Ser Ala Glu Lys Val  Gln Ser Thr
    1685                 1690                 1695
```

```
Met Met  Ser Val Val Ala Glu  Lys Thr Gly Tyr Pro  Thr Glu Met
    1700                1705                1710

Leu Glu  Leu Gly Met Asp Met  Glu Ala Asp Leu Gly  Ile Asp Ser
    1715                1720                1725

Ile Lys  Arg Val Glu Ile Leu  Gly Thr Val Gln Asp  Glu Leu Pro
    1730                1735                1740

Gly Leu  Pro Glu Leu Asn Pro  Glu Asp Leu Ala Glu  Cys Arg Thr
    1745                1750                1755
```

```
Leu Gly  Glu Ile Val Asp Tyr  Met Asn Ser Lys Leu  Ala Asp Gly
    1760                1765                1770

Ser Lys  Leu Pro Ala Glu Gly  Ser Ala Asn Thr Ser  Ala Thr Ala
    1775                1780                1785

Ala Thr  Pro Ala Val Asn Gly  Leu Ser Ala Asp Lys  Val Gln Ala
    1790                1795                1800

Thr Met  Met Ser Val Val Ala  Glu Lys Thr Gly Tyr  Pro Thr Glu
    1805                1810                1815

Met Leu  Glu Leu Gly Met Asp  Met Glu Ala Asp Leu  Gly Ile Asp
    1820                1825                1830
```

```
Ser Ile  Lys Arg Val Glu Ile  Leu Gly Thr Val Gln  Asp Glu Leu
    1835                1840                1845

Pro Gly  Leu Pro Glu Leu Asn  Pro Glu Asp Leu Ala  Glu Cys Arg
    1850                1855                1860

Thr Leu  Gly Glu Ile Val Ser  Tyr Met Asn Ser Gln  Leu Ala Asp
    1865                1870                1875

Gly Ser  Lys Leu Ser Thr Ser  Ala Ala Glu Gly Ser  Ala Asp Thr
    1880                1885                1890
```

```
Ser Ala  Ala Asn Ala Ala Lys  Pro Ala Ala Ile Ser  Ala Glu Pro
    1895                 1900                 1905

Ser Val  Glu Leu Pro Pro His  Ser Glu Val Ala Leu  Lys Lys Leu
    1910                 1915                 1920

Asn Ala  Ala Asn Lys Leu Glu  Asn Cys Phe Ala Ala  Asp Ala Ser
    1925                 1930                 1935

Val Val  Ile Asn Asp Asp Gly  His Asn Ala Gly Val  Leu Ala Glu
    1940                 1945                 1950

Lys Leu  Ile Lys Gln Gly Leu  Lys Val Ala Val Val  Arg Leu Pro
    1955                 1960                 1965

Lys Gly  Gln Pro Gln Ser Pro  Leu Ser Ser Asp Val  Ala Ser Phe
    1970                 1975                 1980

Glu Leu  Ala Ser Ser Gln Glu  Ser Glu Leu Glu Ala  Ser Ile Thr
    1985                 1990                 1995

Ala Val  Ile Ala Gln Ile Glu  Thr Gln Val Gly Ala  Ile Gly Gly
    2000                 2005                 2010

Phe Ile  His Leu Gln Pro Glu  Ala Asn Thr Glu Glu  Gln Thr Ala
    2015                 2020                 2025

Val Asn  Leu Asp Ala Gln Ser  Phe Thr His Val Ser  Asn Ala Phe
    2030                 2035                 2040

Leu Trp  Ala Lys Leu Leu Gln  Pro Lys Leu Val Ala  Gly Ala Asp
    2045                 2050                 2055

Ala Arg  Arg Cys Phe Val Thr  Val Ser Arg Ile Asp  Gly Gly Phe
    2060                 2065                 2070

Gly Tyr  Leu Asn Thr Asp Ala  Leu Lys Asp Ala Glu  Leu Asn Gln
    2075                 2080                 2085

Ala Ala  Leu Ala Gly Leu Thr  Lys Thr Leu Ser His  Glu Trp Pro
    2090                 2095                 2100
```

```
Gln Val  Phe Cys Arg Ala Leu  Asp Ile Ala Thr Asp  Val Asp Ala
    2105                 2110                 2115

Thr His  Leu Ala Asp Ala Ile  Thr Ser Glu Leu Phe  Asp Ser Gln
    2120                 2125                 2130

Ala Gln  Leu Pro Glu Val Gly  Leu Ser Leu Ile Asp  Gly Lys Val
    2135                 2140                 2145

Asn Arg  Val Thr Leu Val Ala  Ala Glu Ala Ala Asp  Lys Thr Ala
    2150                 2155                 2160

Lys Ala  Glu Leu Asn Ser Thr  Asp Lys Ile Leu Val  Thr Gly Gly
    2165                 2170                 2175

Ala Lys  Gly Val Thr Phe Glu  Cys Ala Leu Ala Leu  Ala Ser Arg
    2180                 2185                 2190

Ser Gln  Ser His Phe Ile Leu  Ala Gly Arg Ser Glu  Leu Gln Ala
    2195                 2200                 2205

Leu Pro  Ser Trp Ala Glu Gly  Lys Gln Thr Ser Glu  Leu Lys Ser
    2210                 2215                 2220

Ala Ala  Ile Ala His Ile Ile  Ser Thr Gly Gln Lys  Pro Thr Pro
    2225                 2230                 2235

Lys Gln  Val Glu Ala Ala Val  Trp Pro Val Gln Ser  Ser Ile Glu
    2240                 2245                 2250

Ile Asn  Ala Ala Leu Ala Ala  Phe Asn Lys Val Gly  Ala Ser Ala
    2255                 2260                 2265

Glu Tyr  Val Ser Met Asp Val  Thr Asp Ser Ala Ala  Ile Thr Ala
    2270                 2275                 2280

Ala Leu  Asn Gly Arg Ser Asn  Glu Ile Thr Gly Leu  Ile His Gly
    2285                 2290                 2295
```

```
Ala Gly  Val Leu Ala Asp Lys  His Ile Gln Asp Lys  Thr Leu Ala
    2300                 2305                 2310

Glu Leu  Ala Lys Val Tyr Gly  Thr Lys Val Asn Gly  Leu Lys Ala
    2315                 2320                 2325

Leu Leu  Ala Ala Leu Glu Pro  Ser Lys Ile Lys Leu  Leu Ala Met
    2330                 2335                 2340

Phe Ser  Ser Ala Ala Gly Phe  Tyr Gly Asn Ile Gly  Gln Ser Asp
    2345                 2350                 2355

Tyr Ala  Met Ser Asn Asp Ile  Leu Asn Lys Ala Ala  Leu Gln Phe
    2360                 2365                 2370

Thr Ala  Arg Asn Pro Gln Ala  Lys Val Met Ser Phe  Asn Trp Gly
    2375                 2380                 2385

Pro Trp  Asp Gly Gly Met Val  Asn Pro Ala Leu Lys  Lys Met Phe
    2390                 2395                 2400

Thr Glu  Arg Gly Val Tyr Val  Ile Pro Leu Lys Ala  Gly Ala Glu
    2405                 2410                 2415

Leu Phe  Ala Thr Gln Leu Leu  Ala Glu Thr Gly Val  Gln Leu Leu
    2420                 2425                 2430

Ile Gly  Thr Ser Met Gln Gly  Gly Ser Asp Thr Lys  Ala Thr Glu
    2435                 2440                 2445

Thr Ala  Ser Val Lys Lys Leu  Asn Ala Gly Glu Val  Leu Ser Ala
    2450                 2455                 2460

Ser His  Pro Arg Ala Gly Ala  Gln Lys Thr Pro Leu  Gln Ala Val
    2465                 2470                 2475

Thr Ala  Thr Arg Leu Leu Thr  Pro Ser Ala Met Val  Phe Ile Glu
    2480                 2485                 2490

Asp His  Arg Ile Gly Gly Asn  Ser Val Leu Pro Thr  Val Cys Ala
    2495                 2500                 2505
```

```
Ile Asp  Trp Met Arg Glu Ala  Ala Ser Asp Met Leu  Gly Ala Gln
    2510                 2515                 2520

Val Lys  Val Leu Asp Tyr Lys  Leu Leu Lys Gly Ile  Val Phe Glu
    2525                 2530                 2535

Thr Asp  Glu Pro Gln Glu Leu  Thr Leu Glu Leu Thr  Pro Asp Asp
    2540                 2545                 2550

Ser Asp  Glu Ala Thr Leu Gln  Ala Leu Ile Ser Cys  Asn Gly Arg
    2555                 2560                 2565

Pro Gln  Tyr Lys Ala Thr Leu  Ile Ser Asp Asn Ala  Asp Ile Lys
    2570                 2575                 2580

Gln Leu  Asn Lys Gln Phe Asp  Leu Ser Ala Lys Ala  Ile Thr Thr
    2585                 2590                 2595

Ala Lys  Glu Leu Tyr Ser Asn  Gly Thr Leu Phe His  Gly Pro Arg
    2600                 2605                 2610

Leu Gln  Gly Ile Gln Ser Val  Val Gln Phe Asp Asp  Gln Gly Leu
    2615                 2620                 2625

Ile Ala  Lys Val Ala Leu Pro  Lys Val Glu Leu Ser  Asp Cys Gly
    2630                 2635                 2640

Glu Phe  Leu Pro Gln Thr His  Met Gly Gly Ser Gln  Pro Phe Ala
    2645                 2650                 2655

Glu Asp  Leu Leu Leu Gln Ala  Met Leu Val Trp Ala  Arg Leu Lys
    2660                 2665                 2670

Thr Gly  Ser Ala Ser Leu Pro  Ser Ser Ile Gly Glu  Phe Thr Ser
    2675                 2680                 2685

Tyr Gln  Pro Met Ala Phe Gly  Glu Thr Gly Thr Ile  Glu Leu Glu
    2690                 2695                 2700
```

```
Val Ile  Lys His Asn Lys Arg  Ser Leu Glu Ala Asn  Val Ala Leu
    2705                 2710                 2715

Tyr Arg  Asp Asn Gly Glu Leu  Ser Ala Met Phe Lys  Ser Ala Lys
    2720                 2725                 2730

Ile Thr  Ile Ser Lys Ser Leu  Asn Ser Ala Phe Leu  Pro Ala Val
    2735                 2740                 2745

Leu Ala  Asn Asp Ser Glu Ala  Asn
    2750                 2755
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<212> PRT
<213> Shewanella putrefaciens

<400> 8

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Met Pro Leu Arg Ile Ala Leu Ile Leu Leu Pro Thr Pro Gln Phe Glu
1               5                  10                  15

Val Asn Ser Val Asp Gln Ser Val Leu Ala Ser Tyr Gln Thr Leu Gln
            20                  25                  30

Pro Glu Leu Asn Ala Leu Leu Asn Ser Ala Pro Thr Pro Glu Met Leu
        35                  40                  45

Ser Ile Thr Ile Ser Asp Asp Ser Asp Ala Asn Ser Phe Glu Ser Gln
    50                  55                  60

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

Ala Thr Ala Thr His Ala Leu Leu Met Leu Pro Ala Leu Lys Ala Ala
                85                  90                  95

Gln Met Arg Ile His Pro His Ala Gln Leu Ala Ala Met Gln Gln Ala
            100                 105                 110

Lys Ser Thr Pro Met Ser Gln Val Ser Gly Glu Leu Lys Leu Gly Ala
        115                 120                 125
```

```
Asn Ala Leu Ser Leu Ala Gln Thr Asn Ala Leu Ser His Ala Leu Ser
    130                 135                 140

Gln Ala Lys Arg Asn Leu Thr Asp Val Ser Val Asn Glu Cys Phe Glu
145                 150                 155                 160

Asn Leu Lys Ser Glu Gln Gln Phe Thr Glu Val Tyr Ser Leu Ile Gln
                165                 170                 175

Gln Leu Ala Ser Arg Thr His Val Arg Lys Glu Val Asn Gln Gly Val
            180                 185                 190

Glu Leu Gly Pro Lys Gln Ala Lys Ser His Tyr Trp Phe Ser Glu Phe
        195                 200                 205

His Gln Asn Arg Val Ala Ala Ile Asn Phe Ile Asn Gly Gln Gln Ala
    210                 215                 220

Thr Ser Tyr Val Leu Thr Gln Gly Ser Gly Leu Leu Ala Ala Lys Ser
225                 230                 235                 240

Met Leu Asn Gln Gln Arg Leu Met Phe Ile Leu Pro Gly Asn Ser Gln
                245                 250                 255

Gln Gln Ile Thr Ala Ser Ile Thr Gln Leu Met Gln Gln Leu Glu Arg
            260                 265                 270

Leu Gln Val Thr Glu Val Asn Glu Leu Ser Leu Glu Cys Gln Leu Glu
        275                 280                 285

Leu Leu Ser Ile Met Tyr Asp Asn Leu Val Asn Ala Asp Lys Leu Thr
    290                 295                 300

Thr Arg Asp Ser Lys Pro Ala Tyr Gln Ala Val Ile Gln Ala Ser Ser
305                 310                 315                 320

Val Ser Ala Ala Lys Gln Glu Leu Ser Ala Leu Asn Asp Ala Leu Thr
                325                 330                 335

Ala Leu Phe Ala Glu Gln Thr Asn Ala Thr Ser Thr Asn Lys Gly Leu
```

340 345 350

Ile Gln Tyr Lys Thr Pro Ala Gly Ser Tyr Leu Thr Leu Thr Pro Leu
355 360 365

Gly Ser Asn Asn Asp Asn Ala Gln Ala Gly Leu Ala Phe Val Tyr Pro
370 375 380

Gly Val Gly Thr Val Tyr Ala Asp Met Leu Asn Glu Leu His Gln Tyr
385 390 395 400

Phe Pro Ala Leu Tyr Ala Lys Leu Glu Arg Glu Gly Asp Leu Lys Ala
405 410 415

Met Leu Gln Ala Glu Asp Ile Tyr His Leu Asp Pro Lys His Ala Ala
420 425 430

Gln Met Ser Leu Gly Asp Leu Ala Ile Ala Gly Val Gly Ser Ser Tyr
435 440 445

Leu Leu Thr Gln Leu Leu Thr Asp Glu Phe Asn Ile Lys Pro Asn Phe
450 455 460

Ala Leu Gly Tyr Ser Met Gly Glu Ala Ser Met Trp Ala Ser Leu Gly
465 470 475 480

Val Trp Gln Asn Pro His Ala Leu Ile Ser Lys Thr Gln Thr Asp Pro
485 490 495

Leu Phe Thr Ser Ala Ile Ser Gly Lys Leu Thr Ala Val Arg Gln Ala
500 505 510

Trp Gln Leu Asp Asp Thr Ala Ala Glu Ile Gln Trp Asn Ser Phe Val
515 520 525

Val Arg Ser Glu Ala Ala Pro Ile Glu Ala Leu Leu Lys Asp Tyr Pro
530 535 540

His Ala Tyr Leu Ala Ile Ile Gln Gly Asp Thr Cys Val Ile Ala Gly
545 550 555 560

Cys Glu Ile Gln Cys Lys Ala Leu Leu Ala Ala Leu Gly Lys Arg Gly
565 570 575

Ile Ala Ala Asn Arg Val Thr Ala Met His Thr Gln Pro Ala Met Gln
580 585 590

Glu His Gln Asn Val Met Asp Phe Tyr Leu Gln Pro Leu Lys Ala Glu
595 600 605

Leu Pro Ser Glu Ile Ser Phe Ile Ser Ala Ala Asp Leu Thr Ala Lys
610 615 620

Gln Thr Val Ser Glu Gln Ala Leu Ser Ser Gln Val Val Ala Gln Ser
625 630 635 640

Ile Ala Asp Thr Phe Cys Gln Thr Leu Asp Phe Thr Ala Leu Val His
645 650 655

His Ala Gln His Gln Gly Ala Lys Leu Phe Val Glu Ile Gly Ala Asp
660 665 670

Arg Gln Asn Cys Thr Leu Ile Asp Lys Ile Val Lys Gln Asp Gly Ala
675 680 685

Ser Ser Val Gln His Gln Pro Cys Cys Thr Val Pro Met Asn Ala Lys
690 695 700

Gly Ser Gln Asp Ile Thr Ser Val Ile Lys Ala Leu Gly Gln Leu Ile
705 710 715 720

Ser His Gln Val Pro Leu Ser Val Gln Pro Phe Ile Asp Gly Leu Lys
725 730 735

Arg Glu Leu Thr Leu Cys Gln Leu Thr Ser Gln Gln Leu Ala Ala His
740 745 750

Ala Asn Val Asp Ser Lys Phe Glu Ser Asn Gln Asp His Leu Leu Gln
755 760 765

Gly Glu Val

770

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<211> 2004
<212> PRT
<213> Shewanella putrefaciens

<400> 9

Met Ser Leu Pro Asp Asn Ala Ser Asn His Leu Ser Ala Asn Gln Lys
1 5 10 15

Gly Ala Ser Gln Ala Ser Lys Thr Ser Lys Gln Ser Lys Ile Ala Ile
20 25 30

Val Gly Leu Ala Thr Leu Tyr Pro Asp Ala Lys Thr Pro Gln Glu Phe
35 40 45

Trp Gln Asn Leu Leu Asp Lys Arg Asp Ser Arg Ser Thr Leu Thr Asn
50 55 60

Glu Lys Leu Gly Ala Asn Ser Gln Asp Tyr Gln Gly Val Gln Gly Gln
65 70 75 80

Ser Asp Arg Phe Tyr Cys Asn Lys Gly Gly Tyr Ile Glu Asn Phe Ser
85 90 95

Phe Asn Ala Ala Gly Tyr Lys Leu Pro Glu Gln Ser Leu Asn Gly Leu
100 105 110

Asp Asp Ser Phe Leu Trp Ala Leu Asp Thr Ser Arg Asn Ala Leu Ile
115 120 125

Asp Ala Gly Ile Asp Ile Asn Gly Ala Asp Leu Ser Arg Ala Gly Val
130 135 140

Val Met Gly Ala Leu Ser Phe Pro Thr Thr Arg Ser Asn Asp Leu Phe
145 150 155 160

Leu Pro Ile Tyr His Ser Ala Val Glu Lys Ala Leu Gln Asp Lys Leu
165 170 175

```
Gly Val Lys Ala Phe Lys Leu Ser Pro Thr Asn Ala His Thr Ala Arg
            180                 185                 190

Ala Ala Asn Glu Ser Ser Leu Asn Ala Ala Asn Gly Ala Ile Ala His
        195                 200                 205

Asn Ser Ser Lys Val Val Ala Asp Ala Leu Gly Leu Gly Gly Ala Gln
    210                 215                 220

Leu Ser Leu Asp Ala Ala Cys Ala Ser Ser Val Tyr Ser Leu Lys Leu
225                 230                 235                 240

Ala Cys Asp Tyr Leu Ser Thr Gly Lys Ala Asp Ile Met Leu Ala Gly
                245                 250                 255

Ala Val Ser Gly Ala Asp Pro Phe Phe Ile Asn Met Gly Phe Ser Ile
            260                 265                 270

Phe His Ala Tyr Pro Asp His Gly Ile Ser Val Pro Phe Asp Ala Ser
        275                 280                 285

Ser Lys Gly Leu Phe Ala Gly Glu Gly Ala Gly Val Leu Val Leu Lys
    290                 295                 300

Arg Leu Glu Asp Ala Glu Arg Asp Asn Asp Lys Ile Tyr Ala Val Val
305                 310                 315                 320

Ser Gly Val Gly Leu Ser Asn Asp Gly Lys Gly Gln Phe Val Leu Ser
                325                 330                 335

Pro Asn Pro Lys Gly Gln Val Lys Ala Phe Glu Arg Ala Tyr Ala Ala
            340                 345                 350

Ser Asp Ile Glu Pro Lys Asp Ile Glu Val Ile Glu Cys His Ala Thr
        355                 360                 365

Gly Thr Pro Leu Gly Asp Lys Ile Glu Leu Thr Ser Met Glu Thr Phe
    370                 375                 380

Phe Glu Asp Lys Leu Gln Gly Thr Asp Ala Pro Leu Ile Gly Ser Ala
385                 390                 395                 400
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Lys Ser Asn Leu Gly His Leu Leu Thr Ala Ala His Ala Gly Ile Met
405 410 415

Lys Met Ile Phe Ala Met Lys Glu Gly Tyr Leu Pro Pro Ser Ile Asn
420 425 430

Ile Ser Asp Ala Ile Ala Ser Pro Lys Lys Leu Phe Gly Lys Pro Thr
435 440 445

Leu Pro Ser Met Val Gln Gly Trp Pro Asp Lys Pro Ser Asn Asn His
450 455 460

Phe Gly Val Arg Thr Arg His Ala Gly Val Ser Val Phe Gly Phe Gly
465 470 475 480

Gly Cys Asn Ala His Leu Leu Leu Glu Ser Tyr Asn Gly Lys Gly Thr
485 490 495

Val Lys Ala Glu Ala Thr Gln Val Pro Arg Gln Ala Glu Pro Leu Lys
500 505 510

Val Val Gly Leu Ala Ser His Phe Gly Pro Leu Ser Ser Ile Asn Ala
515 520 525

Leu Asn Asn Ala Val Thr Gln Asp Gly Asn Gly Phe Ile Glu Leu Pro
530 535 540

Lys Lys Arg Trp Lys Gly Leu Glu Lys His Ser Glu Leu Leu Ala Glu
545 550 555 560

Phe Gly Leu Ala Ser Ala Pro Lys Gly Ala Tyr Val Asp Asn Phe Glu
565 570 575

Leu Asp Phe Leu Arg Phe Lys Leu Pro Pro Asn Glu Asp Asp Arg Leu
580 585 590

Ile Ser Gln Gln Leu Met Leu Met Arg Val Thr Asp Glu Ala Ile Arg
595 600 605

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Asp Ala Lys Leu Glu Pro Gly Gln Lys Val Ala Val Leu Val Ala Met
    610                 615                 620

Glu Thr Glu Leu Glu Leu His Gln Phe Arg Gly Arg Val Asn Leu His
625                 630                 635                 640

Thr Gln Leu Ala Gln Ser Leu Ala Ala Met Gly Val Ser Leu Ser Thr
                645                 650                 655

Asp Glu Tyr Gln Ala Leu Glu Ala Ile Ala Met Asp Ser Val Leu Asp
            660                 665                 670

Ala Ala Lys Leu Asn Gln Tyr Thr Ser Phe Ile Gly Asn Ile Met Ala
        675                 680                 685

Ser Arg Val Ala Ser Leu Trp Asp Phe Asn Gly Pro Ala Phe Thr Ile
    690                 695                 700

Ser Ala Ala Glu Gln Ser Val Ser Arg Cys Ile Asp Val Ala Gln Asn
705                 710                 715                 720

Leu Ile Met Glu Asp Asn Leu Asp Ala Val Val Ile Ala Ala Val Asp
                725                 730                 735

Leu Ser Gly Ser Phe Glu Gln Val Ile Leu Lys Asn Ala Ile Ala Pro
            740                 745                 750

Val Ala Ile Glu Pro Asn Leu Glu Ala Ser Leu Asn Pro Thr Ser Ala
        755                 760                 765

Ser Trp Asn Val Gly Glu Gly Ala Gly Ala Val Val Leu Val Lys Asn
    770                 775                 780

Glu Ala Thr Ser Gly Cys Ser Tyr Gly Gln Ile Asp Ala Leu Gly Phe
785                 790                 795                 800

Ala Lys Thr Ala Glu Thr Ala Leu Ala Thr Asp Lys Leu Leu Ser Gln
                805                 810                 815

Thr Ala Thr Asp Phe Asn Lys Val Lys Val Ile Glu Thr Met Ala Ala
            820                 825                 830
```

```
Pro Ala Ser Gln Ile Gln Leu Ala Pro Ile Val Ser Ser Gln Val Thr
        835                 840                 845

His Thr Ala Ala Glu Gln Arg Val Gly His Cys Phe Ala Ala Ala Gly
    850                 855                 860

Met Ala Ser Leu Leu His Gly Leu Leu Asn Leu Asn Thr Val Ala Gln
865                 870                 875                 880

Thr Asn Lys Ala Asn Cys Ala Leu Ile Asn Asn Ile Ser Glu Asn Gln
                885                 890                 895

Leu Ser Gln Leu Leu Ile Ser Gln Thr Ala Ser Glu Gln Gln Ala Leu
            900                 905                 910

Thr Ala Arg Leu Ser Asn Glu Leu Lys Ser Asp Ala Lys His Gln Leu
        915                 920                 925

Val Lys Gln Val Thr Leu Gly Gly Arg Asp Ile Tyr Gln His Ile Val
    930                 935                 940

Asp Thr Pro Leu Ala Ser Leu Glu Ser Ile Thr Gln Lys Leu Ala Gln
945                 950                 955                 960

Ala Thr Ala Ser Thr Val Val Asn Gln Val Lys Pro Ile Lys Ala Ala
                965                 970                 975

Gly Ser Val Glu Met Ala Asn Ser Phe Glu Thr Glu Ser Ser Ala Glu
            980                 985                 990

Pro Gln Ile Thr Ile Ala Ala Gln  Gln Thr Ala Asn Ile  Gly Val Thr
        995                 1000                1005

Ala Gln  Ala Thr Lys Arg Glu  Leu Gly Thr Pro Pro  Met Thr Thr
    1010                1015                1020

Asn Thr  Ile Ala Asn Thr Ala  Asn Asn Leu Asp Lys  Thr Leu Glu
    1025                1030                1035
```

```
Thr Val  Ala Gly Asn Thr Val  Ala Ser Lys Val Gly  Ser Gly Asp
    1040                1045                1050

Ile Val  Asn Phe Gln Gln Asn  Gln Gln Leu Ala Gln  Gln Ala His
    1055                1060                1065

Leu Ala  Phe Leu Glu Ser Arg  Ser Ala Gly Met Lys  Val Ala Asp
    1070                1075                1080

Ala Leu  Leu Lys Gln Gln Leu  Ala Gln Val Thr Gly  Gln Thr Ile
    1085                1090                1095

Asp Asn  Gln Ala Leu Asp Thr  Gln Ala Val Asp Thr  Gln Thr Ser
    1100                1105                1110

Glu Asn  Val Ala Ile Ala Ala  Glu Ser Pro Val Gln  Val Thr Thr
    1115                1120                1125

Pro Val  Gln Val Thr Thr Pro  Val Gln Ile Ser Val  Val Glu Leu
    1130                1135                1140

Lys Pro  Asp His Ala Asn Val  Pro Pro Tyr Thr Pro  Pro Val Pro
    1145                1150                1155

Ala Leu  Lys Pro Cys Ile Trp  Asn Tyr Ala Asp Leu  Val Glu Tyr
    1160                1165                1170

Ala Glu  Gly Asp Ile Ala Lys  Val Phe Gly Ser Asp  Tyr Ala Ile
    1175                1180                1185

Ile Asp  Ser Tyr Ser Arg Arg  Val Arg Leu Pro Thr  Thr Asp Tyr
    1190                1195                1200

Leu Leu  Val Ser Arg Val Thr  Lys Leu Asp Ala Thr  Ile Asn Gln
    1205                1210                1215

Phe Lys  Pro Cys Ser Met Thr  Thr Glu Tyr Asp Ile  Pro Val Asp
    1220                1225                1230

Ala Pro  Tyr Leu Val Asp Gly  Gln Ile Pro Trp Ala  Val Ala Val
    1235                1240                1245
```

```
Glu Ser  Gly Gln Cys Asp Leu  Met Leu Ile Ser Tyr  Leu Gly Ile
    1250                 1255                 1260

Asp Phe  Glu Asn Lys Gly Glu  Arg Val Tyr Arg Leu  Leu Asp Cys
    1265                 1270                 1275

Thr Leu  Thr Phe Leu Gly Asp  Leu Pro Arg Gly Gly  Asp Thr Leu
    1280                 1285                 1290

Arg Tyr  Asp Ile Lys Ile Asn  Asn Tyr Ala Arg Asn  Gly Asp Thr
    1295                 1300                 1305

Leu Leu  Phe Phe Phe Ser Tyr  Glu Cys Phe Val Gly  Asp Lys Met
    1310                 1315                 1320

Ile Leu  Lys Met Asp Gly Gly  Cys Ala Gly Phe Phe  Thr Asp Glu
    1325                 1330                 1335

Glu Leu  Ala Asp Gly Lys Gly  Val Ile Arg Thr Glu  Glu Glu Ile
    1340                 1345                 1350

Lys Ala  Arg Ser Leu Val Gln  Lys Gln Arg Phe Asn  Pro Leu Leu
    1355                 1360                 1365

Asp Cys  Pro Lys Thr Gln Phe  Ser Tyr Gly Asp Ile  His Lys Leu
    1370                 1375                 1380

Leu Thr  Ala Asp Ile Glu Gly  Cys Phe Gly Pro Ser  His Ser Gly
    1385                 1390                 1395

Val His  Gln Pro Ser Leu Cys  Phe Ala Ser Glu Lys  Phe Leu Met
    1400                 1405                 1410

Ile Glu  Gln Val Ser Lys Val  Asp Arg Thr Gly Gly  Thr Trp Gly
    1415                 1420                 1425

Leu Gly  Leu Ile Glu Gly His  Lys Gln Leu Glu Ala  Asp His Trp
    1430                 1435                 1440
```

```
Tyr Phe  Pro Cys His Phe Lys  Gly Asp Gln Val Met  Ala Gly Ser
    1445                 1450                 1455

Leu Met  Ala Glu Gly Cys Gly  Gln Leu Leu Gln Phe  Tyr Met Leu
    1460                 1465                 1470

His Leu  Gly Met His Thr Gln  Thr Lys Asn Gly Arg  Phe Gln Pro
    1475                 1480                 1485

Leu Glu  Asn Ala Ser Gln Gln  Val Arg Cys Arg Gly  Gln Val Leu
    1490                 1495                 1500

Pro Gln  Ser Gly Val Leu Thr  Tyr Arg Met Glu Val  Thr Glu Ile
    1505                 1510                 1515

Gly Phe  Ser Pro Arg Pro Tyr  Ala Lys Ala Asn Ile  Asp Ile Leu
    1520                 1525                 1530

Leu Asn  Gly Lys Ala Val Val  Asp Phe Gln Asn Leu  Gly Val Met
    1535                 1540                 1545

Ile Lys  Glu Glu Asp Glu Cys  Thr Arg Tyr Pro Leu  Leu Thr Glu
    1550                 1555                 1560

Ser Thr  Thr Ala Ser Thr Ala  Gln Val Asn Ala Gln  Thr Ser Ala
    1565                 1570                 1575

Lys Lys  Val Tyr Lys Pro Ala  Ser Val Asn Ala Pro  Leu Met Ala
    1580                 1585                 1590

Gln Ile  Pro Asp Leu Thr Lys  Glu Pro Asn Lys Gly  Val Ile Pro
    1595                 1600                 1605

Ile Ser  His Val Glu Ala Pro  Ile Thr Pro Asp Tyr  Pro Asn Arg
    1610                 1615                 1620

Val Pro  Asp Thr Val Pro Phe  Thr Pro Tyr His Met  Phe Glu Phe
    1625                 1630                 1635

Ala Thr  Gly Asn Ile Glu Asn  Cys Phe Gly Pro Glu  Phe Ser Ile
    1640                 1645                 1650
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Tyr Arg  Gly Met Ile Pro Pro  Arg Thr Pro Cys Gly  Asp Leu Gln
    1655                 1660                 1665

Val Thr  Thr Arg Val Ile Glu  Val Asn Gly Lys Arg  Gly Asp Phe
    1670                 1675                 1680

Lys Lys  Pro Ser Ser Cys Ile  Ala Glu Tyr Glu Val  Pro Ala Asp
    1685                 1690                 1695

Ala Trp  Tyr Phe Asp Lys Asn  Ser His Gly Ala Val  Met Pro Tyr
    1700                 1705                 1710

Ser Ile  Leu Met Glu Ile Ser  Leu Gln Pro Asn Gly  Phe Ile Ser
    1715                 1720                 1725

Gly Tyr  Met Gly Thr Thr Leu  Gly Phe Pro Gly Leu  Glu Leu Phe
    1730                 1735                 1740

Phe Arg  Asn Leu Asp Gly Ser  Gly Glu Leu Leu Arg  Glu Val Asp
    1745                 1750                 1755

Leu Arg  Gly Lys Thr Ile Arg  Asn Asp Ser Arg Leu  Leu Ser Thr
    1760                 1765                 1770

Val Met  Ala Gly Thr Asn Ile  Ile Gln Ser Phe Ser  Phe Glu Leu
    1775                 1780                 1785

Ser Thr  Asp Gly Glu Pro Phe  Tyr Arg Gly Thr Ala  Val Phe Gly
    1790                 1795                 1800

Tyr Phe  Lys Gly Asp Ala Leu  Lys Asp Gln Leu Gly  Leu Asp Asn
    1805                 1810                 1815

Gly Lys  Val Thr Gln Pro Trp  His Val Ala Asn Gly  Val Ala Ala
    1820                 1825                 1830

Ser Thr  Lys Val Asn Leu Leu  Asp Lys Ser Cys Arg  His Phe Asn
    1835                 1840                 1845
```

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Ala Pro  Ala Asn Gln Pro His  Tyr Arg Leu Ala Gly  Gly Gln Leu
    1850                 1855                 1860

Asn Phe  Ile Asp Ser Val Glu  Ile Val Asp Asn Gly  Gly Thr Glu
    1865                 1870                 1875

Gly Leu  Gly Tyr Leu Tyr Ala  Glu Arg Thr Ile Asp  Pro Ser Asp
    1880                 1885                 1890

Trp Phe  Phe Gln Phe His Phe  His Gln Asp Pro Val  Met Pro Gly
    1895                 1900                 1905

Ser Leu  Gly Val Glu Ala Ile  Ile Glu Thr Met Gln  Ala Tyr Ala
    1910                 1915                 1920

Ile Ser  Lys Asp Leu Gly Ala  Asp Phe Lys Asn Pro  Lys Phe Gly
    1925                 1930                 1935

Gln Ile  Leu Ser Asn Ile Lys  Trp Lys Tyr Arg Gly  Gln Ile Asn
    1940                 1945                 1950

Pro Leu  Asn Lys Gln Met Ser  Met Asp Val Ser Ile  Thr Ser Ile
    1955                 1960                 1965

Lys Asp  Glu Asp Gly Lys Lys  Val Ile Thr Gly Asn  Ala Ser Leu
    1970                 1975                 1980

Ser Lys  Asp Gly Leu Arg Ile  Tyr Glu Val Phe Asp  Ile Ala Ile
    1985                 1990                 1995

Ser Ile  Glu Glu Ser Val
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Val Thr Glu Ser Asn Ile Ser Phe Asp Val Gln Val Met Glu Gln Gln
20 25 30

Leu Lys Asp Phe Ser Arg Ala Cys Tyr Val Val Asn His Ala Asp His
35 40 45

Gly Phe Gly Ile Ala Gln Thr Ala Asp Ile Val Thr Glu Gln Ala Ala
50 55 60

Asn Ser Thr Asp Leu Pro Val Ser Ala Phe Thr Pro Ala Leu Gly Thr
65 70 75 80

Glu Ser Leu Gly Asp Asn Asn Phe Arg Arg Val His Gly Val Lys Tyr
85 90 95

Ala Tyr Tyr Ala Gly Ala Met Ala Asn Gly Ile Ser Ser Glu Glu Leu
100 105 110

Val Ile Ala Leu Gly Gln Ala Gly Ile Leu Cys Gly Ser Phe Gly Ala
115 120 125

Ala Gly Leu Ile Pro Ser Arg Val Glu Ala Ala Ile Asn Arg Ile Gln
130 135 140

Ala Ala Leu Pro Asn Gly Pro Tyr Met Phe Asn Leu Ile His Ser Pro
145 150 155 160

Ser Glu Pro Ala Leu Glu Arg Gly Ser Val Glu Leu Phe Leu Lys His
165 170 175

Lys Val Arg Thr Val Glu Ala Ser Ala Phe Leu Gly Leu Thr Pro Gln
180 185 190

Ile Val Tyr Tyr Arg Ala Ala Gly Leu Ser Arg Asp Ala Gln Gly Lys
195 200 205

Val Val Val Gly Asn Lys Val Ile Ala Lys Val Ser Arg Thr Glu Val
210 215 220

Ala Glu Lys Phe Met Met Pro Ala Pro Ala Lys Met Leu Gln Lys Leu

225 230 235 240

Val Asp Asp Gly Ser Ile Thr Ala Glu Gln Met Glu Leu Ala Gln Leu
245 250 255

Val Pro Met Ala Asp Asp Ile Thr Ala Glu Ala Asp Ser Gly Gly His
260 265 270

Thr Asp Asn Arg Pro Leu Val Thr Leu Leu Pro Thr Ile Leu Ala Leu
275 280 285

Lys Glu Glu Ile Gln Ala Lys Tyr Gln Tyr Asp Thr Pro Ile Arg Val
290 295 300

Gly Cys Gly Gly Gly Val Gly Thr Pro Asp Ala Ala Leu Ala Thr Phe
305 310 315 320

Asn Met Gly Ala Ala Tyr Ile Val Thr Gly Ser Ile Asn Gln Ala Cys
325 330 335

Val Glu Ala Gly Ala Ser Asp His Thr Arg Lys Leu Leu Ala Thr Thr
340 345 350

Glu Met Ala Asp Val Thr Met Ala Pro Ala Ala Asp Met Phe Glu Met
355 360 365

Gly Val Lys Leu Gln Val Val Lys Arg Gly Thr Leu Phe Pro Met Arg
370 375 380

Ala Asn Lys Leu Tyr Glu Ile Tyr Thr Arg Tyr Asp Ser Ile Glu Ala
385 390 395 400

Ile Pro Leu Asp Glu Arg Glu Lys Leu Glu Lys Gln Val Phe Arg Ser
405 410 415

Ser Leu Asp Glu Ile Trp Ala Gly Thr Val Ala His Phe Asn Glu Arg
420 425 430

Asp Pro Lys Gln Ile Glu Arg Ala Glu Gly Asn Pro Lys Arg Lys Met
435 440 445

Ala Leu Ile Phe Arg Trp Tyr Leu Gly Leu Ser Ser Arg Trp Ser Asn
450 455 460

Ser Gly Glu Val Gly Arg Glu Met Asp Tyr Gln Ile Trp Ala Gly Pro
465 470 475 480

Ala Leu Gly Ala Phe Asn Gln Trp Ala Lys Gly Ser Tyr Leu Asp Asn
485 490 495

Tyr Gln Asp Arg Asn Ala Val Asp Leu Ala Lys His Leu Met Tyr Gly
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Ala Ala Tyr Leu Asn Arg Ile Asn Ser Leu Thr Ala Gln Gly Val Lys
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Val Pro Ala Gln Leu Leu Arg Trp Lys Pro Asn Gln Arg Met Ala
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Arg Thr Tyr Ser Tyr Met Lys Ser Asn Ser Ala Ser Ala Lys Arg Tyr
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Tyr Glu Lys His Glu Tyr Pro Asp Asp Thr Phe Lys Ser Leu Lys Val
35 40 45

Asp Gly Val Phe Ile Phe Asn Arg Thr Asn Gln Pro Val Phe Ser Lys
50 55 60

Gly Phe Asn His Arg Asn Asp Ile Pro Leu Val Phe Glu Leu Thr Asp
65 70 75 80

Phe Lys Gln His Pro Gln Asn Ile Ala Leu Ser Pro Gln Thr Lys Gln
85 90 95

```
Ala His Pro Pro Ala Ser Lys Pro Leu Asp Ser Pro Asp Asp Val Pro
           100                 105                 110

Ser Thr His Gly Val Ile Ala Thr Arg Tyr Gly Pro Ala Ile Tyr Tyr
       115                 120                 125

Ser Ser Thr Ser Ile Leu Lys Ser Asp Arg Ser Gly Ser Gln Leu Gly
   130                 135                 140

Tyr Leu Val Phe Ile Arg Leu Ile Asp Glu Trp Phe Ile Ala Glu Leu
145                 150                 155                 160

Ser Gln Tyr Thr Ala Ala Gly Val Glu Ile Ala Met Ala Asp Ala Ala
                165                 170                 175

Asp Ala Gln Leu Ala Arg Leu Gly Ala Asn Thr Lys Leu Asn Lys Val
           180                 185                 190

Thr Ala Thr Ser Glu Arg Leu Ile Thr Asn Val Asp Gly Lys Pro Leu
       195                 200                 205

Leu Lys Leu Val Leu Tyr His Thr Asn Asn Gln Pro Pro Pro Met Leu
   210                 215                 220

Asp Tyr Ser Ile Ile Ile Leu Leu Val Glu Met Ser Phe Leu Leu Ile
225                 230                 235                 240

Leu Ala Tyr Phe Leu Tyr Ser Tyr Phe Leu Val Arg Pro Val Arg Lys
                245                 250                 255

Leu Ala Ser Asp Ile Lys Lys Met Asp Lys Ser Arg Glu Ile Lys Lys
           260                 265                 270

Leu Arg Tyr His Tyr Pro Ile Thr Glu Leu Val Lys Val Ala Thr His
       275                 280                 285

Phe Asn Ala Leu Met Gly Thr Ile Gln Glu Gln Thr Lys Gln Leu Asn
   290                 295                 300
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Glu Gln Val Phe Ile Asp Lys Leu Thr Asn Ile Pro Asn Arg Arg Ala
305 310 315 320

Phe Glu Gln Arg Leu Glu Thr Tyr Cys Gln Leu Leu Ala Arg Gln Gln
325 330 335

Ile Gly Phe Thr Leu Ile Ile Ala Asp Val Asp His Phe Lys Glu Tyr
340 345 350

Asn Asp Thr Leu Gly His Leu Ala Gly Asp Glu Ala Leu Ile Lys Val
355 360 365

Ala Gln Thr Leu Ser Gln Gln Phe Tyr Arg Ala Glu Asp Ile Cys Ala
370 375 380

Arg Phe Gly Gly Glu Glu Phe Ile Met Leu Phe Arg Asp Ile Pro Asp
385 390 395 400

Glu Pro Leu Gln Arg Lys Leu Asp Ala Met Leu His Ser Phe Ala Glu
405 410 415

Leu Asn Leu Pro His Pro Asn Ser Ser Thr Ala Asn Tyr Val Thr Val
420 425 430

Ser Leu Gly Val Cys Thr Val Val Ala Val Asp Asp Phe Glu Phe Lys
435 440 445

Ser Glu Ser His Ile Ile Gly Ser Gln Ala Ala Leu Ile Ala Asp Lys
450 455 460

Ala Leu Tyr His Ala Lys Ala Cys Gly Arg Asn Gln Ala Leu Ser Lys
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tcaagctgaa ttaccaaatg gcccttatgc ggttaacttg atccatgcac cagcagaaga 18000

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agttggtcgc cgctttatgg aacctgcacc gcaaaaatta ctggataagt tattagaaca 18240

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tactggggaa gcggattctg gtggtcatac agataaccgt ccgtttttaa cattattacc 18360

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attgcaaggt gttagcttaa gtacagaatt ggcaagttat cgtacgagtg attaatgtta 19140

cttgatgata tgtgaattaa ttaaagcgcc tgagggcgct ttttttggtt tttaactcag 19200

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<210> 14
<211> 217
<212> DNA
<213> Shewanella putrefaciens

<400> 14

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acagagttgg ttaagtcatg gctgcctgaa gatgagttaa ttaaggttaa tcgctacatt 180

aaacaagaag ctaaaactca aggtttaatg gtaagag 217

<210> 15
<211> 72
<212> PRT
<213> Shewanella putrefaciens

<400> 15

Ile Gly Lys Asn Arg Gly Tyr Val Cys Cys Phe Lys Glu Cys Pro Glu
1 5 10 15

Lys Leu Leu Thr Ser Arg Leu Ile Ser Leu Tyr Phe Cys Pro Leu Thr
20 25 30

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

Pro Glu Asp Glu Leu Ile Lys Val Asn Arg Tyr Ile Lys Gln Glu Ala
50 55 60

Lys Thr Gln Gly Leu Met Val Arg
65 70

<210> 16
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<212> DNA
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<223> n is a, c, g, or t

<220>
<221> misc_feature
<222> (466)..(466)
<223> n is a, c, g, or t

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tgaactgtgt cgttgatgca gcatgtgcag gccctcttgc tgcattgcgt atggcattaa 180

gcgagcttgt tgaaggccgc agcgaaatga tgattacagg tggtgtgtgt accgataact 240

caccaaccat gtacatgagc ttctctaaaa caccggcatt cacgacaaac gaaacaattc 300

aaccattcga tattgactcg aaaggtatga tgattggtga aggtatcggt atgattgcgc 360

ttaaacgtct tgaagacgca gagcgtgatg gcgaccgtat ctattccgtg attaaaggtg 420

ttgggtgcat cttcagacgg taatttatta agagtantta tgcgcntcgt cctgaaggtc 480

aggctaaggc acttaaacgt gcttacgacg atgcaggttt cgcaccgcac acacttggct 540

tacttgaagc ccacggcaca ggcacagcag caggtgatgt ggcagaattc agtggtctta 600

actctgtatt cagtgaaggc aatgacgaaa agcaacacat cgcattaggt tcagtgaaat 660

cacagattgg tcacactaaa tcaacagcgg gtactgcggg tctaatcaaa gcgtctttag 720

cactgcacca taaagtactg ccgccaacaa tcaatgtaac cagccctaac cctaaactga 780

atattgaaga ctcgcctttc tacctcaata cacagacgcg tccatggatg caacgtgtcg 840

atggtacacc gcgtcgtgct ggtattagct catttggttt tggtg 885

<210> 17
<211> 409
<212> DNA
<213> Shewanella putrefaciens

<400> 17
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tctaattgaa ggccatggta cgggtaccaa agcgggtgat gccgcagaat ttgctggctt 120

gaccaaacac tttggcgccg ccagtgatga aaagcaatat atcgccttag gctcagttaa 180

atcgcaaatt ggtcatacta aatctgcggc tggctctgcg ggtatgatta aggcggcatt 240

agcgctgcat cataaaatct tacctgcaac gatccatatc gataaaccaa gtgaagcctt 300

ggatatcaaa aacagcccgt tatacctaaa cagcgaaacg cgtccttgga tgccacgtga 360

agatggtatt ccacgtcgtg caggtattag ctcatttggt tttggtggc 409

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<211> 81
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<213> Artificial Sequence

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<223> SYNTHETIC

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tctaattgaa ggccatggta c 81

<210> 19
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<223> SYNTHETIC

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tctaattgaa ggccatggta c 81

<210> 20
<211> 43
<212> DNA
<213> Artificial Sequence

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<223> SYNTHETIC

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<210> 21
<211> 43
<212> DNA
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<220>
<223> SYNTHETIC

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<210> 22
<211> 55
<212> DNA
<213> Artificial Sequence

<220>
<223> SYNTHETIC

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<210> 23
<211> 55
<212> DNA
<213> Artificial Sequence

<220>
<223> SYNTHETIC

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<210> 24
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> SYNTHETIC

<400> 24
cggcttcgat tttggcggca tgaacggtg 29

<210> 25
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> SYNTHETIC

<400> 25
cgcgtatgat taaggcggca ttagcgctg 29

<210> 26
<211> 28
<212> DNA
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<220>
<223> SYNTHETIC

<400> 26
gcactgctgc aagcatgaac gcgtcgtt 28

<210> 27
<211> 28
<212> DNA
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<220>
<223> SYNTHETIC

<400> 27
gctctgcggc tatcattaac gcggcatt 28

<210> 28
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<210> 29
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<220>
<223> SYNTHETIC

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<210> 30
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cgcgccgcgc gggtattagc tcatttggtt ttggtggc 98

<210> 31
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<213> Artificial Sequence

<220>
<223> SYNTHETIC

<400> 31
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cacgtcgtgc aggtattagc tcatttggtt ttggtggc 98

<210> 32
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<220>
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<400> 32

Asp Xaa Ala Cys
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<210> 33
<211> 4
<212> PRT
<213> Shewanella putrefaciens

<400> 33

Gly Phe Gly Gly
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<210> 34
<211> 5
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<213> Shewanella putrefaciens

<220>
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<222> (4)..(4)
<223> Xaa can be any naturally occurring amino acid

<400> 34

Gly His Ser Xaa Gly
1 5

<210> 35
<211> 6
<212> PRT
<213> Shewanella putrefaciens

<220>
<221> misc_feature
<222> (3)..(3)
<223> Xaa can be any naturally occurring amino acid

<400> 35

Leu Gly Xaa Asp Ser Leu
1 5

<210> 36
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<212> PRT
<213> Shewanella putrefaciens

<220>
<221> misc_feature
<222> (3)..(3)
<223> Xaa can be any naturally occurring amino acid

<400> 36

Leu Gly Xaa Asp Ser Ile
1 5

<210> 37
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<212> PRT
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<220>
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<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (4)..(5)
<223> Xaa can be any naturally occurring amino acid

<400> 37

Gly Xaa Gly Xaa Xaa Gly
1 5

<210> 38
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<222> (4)..(5)
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<400> 38

Gly Xaa Gly Xaa Xaa Ala
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<210> 39
<211> 6
<212> PRT
<213> 'Axial Seamount' polynoid polychaete

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<220>
<221> misc_feature
<222> (4)..(5)
<223> Xaa can be any naturally occurring amino acid

<400> 39

Gly Xaa Gly Xaa Xaa Pro
1 5

<210> 40
<211> 5
<212> PRT
<213> Shewanella putrefaciens

<220>
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<223> Xaa can be any naturally occurring amino acid

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<221> misc_feature
<222> (4)..(4)
<223> Xaa can be any naturally occurring amino acid

<400> 40

Gly Xaa Ser Xaa Gly
1 5

<210> 41
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> SYNTHETIC

<400> 41
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<210> 42
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> SYNTHETIC

<400> 42
cacacacaac agcgaaatgc ttatcaag 28

<210> 43
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> SYNTHETIC

<400> 43
cacacacagc gaccaaaacc aaatgagcta atac 34

<210> 44
<211> 12

<212> DNA
<213> Artificial Sequence

<220>
<223> SYNTHETIC

<400> 44
aagcccgggc tt 12

<210> 45
<211> 20
<212> DNA
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<220>
<223> SYNTHETIC

<400> 45
gtacaagccc gggcttagct 20

<210> 46
<211> 56
<212> DNA
<213> Artificial Sequence

<220>
<223> SYNTHETIC

<400> 46
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<210> 47
<211> 41
<212> DNA
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<220>
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<210> 48
<211> 37
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<210> 50
<211> 37
<212> DNA
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<210> 51
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<210> 52
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<400> 52
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<210> 53
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<212> DNA
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gaattcgtcg acacaatgtc attaccagac aatgcttct 39

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<211> 38
<212> DNA
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<400> 54
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<210> 55
<211> 39
<212> DNA
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<400> 55
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<210> 56
<211> 37
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<223> SYNTHETIC

<400> 56
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<210> 57
<211> 39
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<220>
<223> SYNTHETIC

<400> 57
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<210> 58
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<400> 58
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<210> 59
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<400> 59
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<210> 60
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<223> SYNTHETIC

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<210> 62
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<400> 65
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<210> 66
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<400> 66
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<400> 67
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<210> 68
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<400> 68
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<210> 69
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<400> 69
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atggaggtcc tcgccgccaa gactggctac gagactgaca tgatcgagtc cgacatggag 180

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gccatgctca acgtcgaggc caaggacgtc gacgctctca gccgcactcg cactgtgggt 300

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Leu Glu Lys Ala Glu Thr Val Val Met Glu Val Leu Ala Ala Lys Thr
35 40 45

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

Leu Gly Ile Asp Ser Ile Lys Arg Val Glu Ile Leu Ser Glu Val Gln
65 70 75 80

Ala Met Leu Asn Val Glu Ala Lys Asp Val Asp Ala Leu Ser Arg Thr
85 90 95

```
Arg Thr Val Gly Glu Val Val Asn Ala Met Lys Ala Glu Ile Ala Gly
            100                 105                 110

Gly Ser Ala Pro Ala Pro Ala Ala Ala Ala Pro Gly Pro Ala Ala Ala
        115                 120                 125

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

Val Val Met Glu Val Leu Ala Ala Lys Thr Gly Tyr Glu Thr Asp Met
145                 150                 155                 160

Ile Glu Ser Asp Met Glu Leu Glu Thr Glu Leu Gly Ile Asp Ser Ile
                165                 170                 175

Lys Arg Val Glu Ile Leu Ser Glu Val Gln Ala Met Leu Asn Val Glu
            180                 185                 190

Ala Lys Asp Val Asp Ala Leu Ser Arg Thr Arg Thr Val Gly Glu Val
        195                 200                 205

Val Asp Ala Met Lys Ala Glu Ile Ala Gly Ser Ser Ala Ser Ala Pro
    210                 215                 220

Ala Ala Ala Ala Pro Ala Pro Ala Ala Ala Ala Pro Ala Pro Ala Ala
225                 230                 235                 240

Ala Ala Pro Ala Val Ser Asn Glu Leu Leu Glu Lys Ala Glu Thr Val
                245                 250                 255

Val Met Glu Val Leu Ala Ala Lys Thr Gly Tyr Glu Thr Asp Met Ile
            260                 265                 270

Glu Ser Asp Met Glu Leu Glu Thr Glu Leu Gly Ile Asp Ser Ile Lys
        275                 280                 285

Arg Val Glu Ile Leu Ser Glu Val Gln Ala Met Leu Asn Val Glu Ala
    290                 295                 300

Lys Asp Val Asp Ala Leu Ser Arg Thr Arg Thr Val Gly Glu Val Val
305                 310                 315                 320
```

```
Asp Ala Met Lys Ala Glu Ile Ala Gly Gly Ser Ala Pro Ala Pro Ala
                325                 330                 335

Ala Ala Ala Pro Ala Pro Ala Ala Ala Ala Pro Ala Val Ser Asn Glu
            340                 345                 350

Leu Leu Glu Lys Ala Glu Thr Val Val Met Glu Val Leu Ala Ala Lys
        355                 360                 365

Thr Gly Tyr Glu Thr Asp Met Ile Glu Ser Asp Met Glu Leu Glu Thr
    370                 375                 380

Glu Leu Gly Ile Asp Ser Ile Lys Arg Val Glu Ile Leu Ser Glu Val
385                 390                 395                 400

Gln Ala Met Leu Asn Val Glu Ala Lys Asp Val Asp Ala Leu Ser Arg
                405                 410                 415

Thr Arg Thr Val Gly Glu Val Val Asp Ala Met Lys Ala Glu Ile Ala
            420                 425                 430

Gly Ser Ser Ala Pro Ala Pro Ala Ala Ala Ala Pro Ala Pro Ala Ala
        435                 440                 445

Ala Ala Pro Ala Pro Ala Ala Ala Ala Pro Ala Val Ser Ser Glu Leu
    450                 455                 460

Leu Glu Lys Ala Glu Thr Val Val Met Glu Val Leu Ala Ala Lys Thr
465                 470                 475                 480

Gly Tyr Glu Thr Asp Met Ile Glu Ser Asp Met Glu Leu Glu Thr Glu
                485                 490                 495

Leu Gly Ile Asp Ser Ile Lys Arg Val Glu Ile Leu Ser Glu Val Gln
            500                 505                 510

Ala Met Leu Asn Val Glu Ala Lys Asp Val Asp Ala Leu Ser Arg Thr
        515                 520                 525
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Arg Thr Val Gly Glu Val Val Asp Ala Met Lys Ala Glu Ile Ala Gly
    530                 535                 540

Gly Ser Ala Pro Ala Pro Ala Ala Ala Ala Pro Ala Pro Ala Ala Ala
545                 550                 555                 560

Ala Pro Ala Val Ser Asn Glu Leu Leu Glu Lys Ala Glu Thr Val Val
                565                 570                 575

Met Glu Val Leu Ala Ala Lys Thr Gly Tyr Glu Thr Asp Met Ile Glu
            580                 585                 590

Ser Asp Met Glu Leu Glu Thr Glu Leu Gly Ile Asp Ser Ile Lys Arg
        595                 600                 605

Val Glu Ile Leu Ser Glu Val Gln Ala Met Leu Asn Val Glu Ala Lys
    610                 615                 620

Asp Val Asp Ala Leu Ser Arg Thr Arg Thr Val Gly Glu Val Val Asp
625                 630                 635                 640

Ala Met Lys Ala Glu Ile Ala Gly Gly Ser Ala Pro Ala Pro Ala Ala
                645                 650                 655

Ala Ala Pro Ala Ser Ala Gly Ala Ala Pro Ala Val Lys Ile Asp Ser
            660                 665                 670

Val His Gly Ala Asp Cys Asp Asp Leu Ser Leu Met His Ala Lys Val
        675                 680                 685

Val Asp Ile Arg Arg Pro Asp Glu Leu Ile Leu Glu Arg Pro Glu Asn
    690                 695                 700

Arg Pro Val Leu Val Val Asp Asp Gly Ser Glu Leu Thr Leu Ala Leu
705                 710                 715                 720

Val Arg Val Leu Gly Ala Cys Ala Val Val Leu Thr Phe Glu Gly Leu
                725                 730                 735

Gln Leu Ala Gln Arg Ala Gly Ala Ala Ala Ile Arg His Val Leu Ala
            740                 745                 750
```

```
Lys Asp Leu Ser Ala Glu Ser Ala Glu Lys Ala Ile Lys Glu Ala Glu
        755                 760                 765

Gln Arg Phe Gly Ala Leu Gly Gly Phe Ile Ser Gln Gln Ala Glu Arg
    770                 775                 780

Phe Glu Pro Ala Glu Ile Leu Gly Phe Thr Leu Met Cys Ala Lys Phe
785                 790                 795                 800

Ala Lys Ala Ser Leu Cys Thr Ala Val Ala Gly Gly Arg Pro Ala Phe
                805                 810                 815

Ile Gly Val Ala Arg Leu Asp Gly Arg Leu Gly Phe Thr Ser Gln Gly
            820                 825                 830

Thr Ser Asp Ala Leu Lys Arg Ala Gln Arg Gly Ala Ile Phe Gly Leu
        835                 840                 845

Cys Lys Thr Ile Gly Leu Glu Trp Ser Glu Ser Asp Val Phe Ser Arg
    850                 855                 860

Gly Val Asp Ile Ala Gln Gly Met His Pro Glu Asp Ala Ala Val Ala
865                 870                 875                 880

Ile Val Arg Glu Met Ala Cys Ala Asp Ile Arg Ile Arg Glu Val Gly
                885                 890                 895

Ile Gly Ala Asn Gln Gln Arg Cys Thr Ile Arg Ala Ala Lys Leu Glu
            900                 905                 910

Thr Gly Asn Pro Gln Arg Gln Ile Ala Lys Asp Asp Val Leu Leu Val
        915                 920                 925

Ser Gly Gly Ala Arg Gly Ile Thr Pro Leu Cys Ile Arg Glu Ile Thr
    930                 935                 940

Arg Gln Ile Ala Gly Gly Lys Tyr Ile Leu Leu Gly Arg Ser Lys Val
945                 950                 955                 960
```

```
Ser Ala Ser Glu Pro Ala Trp Cys Ala Gly Ile Thr Asp Glu Lys Ala
                965                 970                 975

Val Gln Lys Ala Ala Thr Gln Glu Leu Lys Arg Ala Phe Ser Ala Gly
            980                 985                 990

Glu Gly Pro Lys Pro Thr Pro Arg  Ala Val Thr Lys Leu  Val Gly Ser
        995                1000                1005

Val Leu  Gly Ala Arg Glu Val  Arg Ser Ser Ile Ala  Ala Ile Glu
    1010                1015                1020

Ala Leu  Gly Gly Lys Ala Ile  Tyr Ser Ser Cys Asp  Val Asn Ser
    1025                1030                1035

Ala Ala  Asp Val Ala Lys Ala  Val Arg Asp Ala Glu  Ser Gln Leu
    1040                1045                1050

Gly Ala  Arg Val Ser Gly Ile  Val His Ala Ser Gly  Val Leu Arg
    1055                1060                1065

Asp Arg  Leu Ile Glu Lys Lys  Leu Pro Asp Glu Phe  Asp Ala Val
    1070                1075                1080

Phe Gly  Thr Lys Val Thr Gly  Leu Glu Asn Leu Leu  Ala Ala Val
    1085                1090                1095

Asp Arg  Ala Asn Leu Lys His  Met Val Leu Phe Ser  Ser Leu Ala
    1100                1105                1110

Gly Phe  His Gly Asn Val Gly  Gln Ser Asp Tyr Ala  Met Ala Asn
    1115                1120                1125

Glu Ala  Leu Asn Lys Met Gly  Leu Glu Leu Ala Lys  Asp Val Ser
    1130                1135                1140

Val Lys  Ser Ile Cys Phe Gly  Pro Trp Asp Gly Gly  Met Val Thr
    1145                1150                1155

Pro Gln  Leu Lys Lys Gln Phe  Gln Glu Met Gly Val  Gln Ile Ile
    1160                1165                1170
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```
Pro Arg  Glu Gly Gly Ala Asp  Thr Val Ala Arg Ile  Val Leu Gly
    1175                 1180                 1185

Ser Ser  Pro Ala Glu Ile Leu  Val Gly Asn Trp Arg  Thr Pro Ser
    1190                 1195                 1200

Lys Lys  Val Gly Ser Asp Thr  Ile Thr Leu His Arg  Lys Ile Ser
    1205                 1210                 1215

Ala Lys  Ser Asn Pro Phe Leu  Glu Asp His Val Ile  Gln Gly Arg
    1220                 1225                 1230

Arg Val  Leu Pro Met Thr Leu  Ala Ile Gly Ser Leu  Ala Glu Thr
    1235                 1240                 1245

Cys Leu  Gly Leu Phe Pro Gly  Tyr Ser Leu Trp Ala  Ile Asp Asp
    1250                 1255                 1260

Ala Gln  Leu Phe Lys Gly Val  Thr Val Asp Gly Asp  Val Asn Cys
    1265                 1270                 1275

Glu Val  Thr Leu Thr Pro Ser  Thr Ala Pro Ser Gly  Arg Val Asn
    1280                 1285                 1290

Val Gln  Ala Thr Leu Lys Thr  Phe Ser Ser Gly Lys  Leu Val Pro
    1295                 1300                 1305

Ala Tyr  Arg Ala Val Ile Val  Leu Ser Asn Gln Gly  Ala Pro Pro
    1310                 1315                 1320

Ala Asn  Ala Thr Met Gln Pro  Pro Ser Leu Asp Ala  Asp Pro Ala
    1325                 1330                 1335

Leu Gln  Gly Ser Val Tyr Asp  Gly Lys Thr Leu Phe  His Gly Pro
    1340                 1345                 1350

Ala Phe  Arg Gly Ile Asp Asp  Val Leu Ser Cys Thr  Lys Ser Gln
    1355                 1360                 1365
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Leu Val Ala Lys Cys Ser Ala Val Pro Gly Ser Asp Ala Ala Arg
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Gly Glu Phe Ala Thr Asp Thr Asp Ala His Asp Pro Phe Val Asn
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Asp Leu Ala Phe Gln Ala Met Leu Val Trp Val Arg Arg Thr Leu
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Gly Gln Ala Ala Leu Pro Asn Ser Ile Gln Arg Ile Val Gln His
1415 1420 1425

Arg Pro Val Pro Gln Asp Lys Pro Phe Tyr Ile Thr Leu Arg Ser
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Asn Gln Ser Gly Gly His Ser Gln His Lys His Ala Leu Gln Phe
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His Asn Glu Gln Gly Asp Leu Phe Ile Asp Val Gln Ala Ser Val
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Arg Ile Ala Ile Thr Gly Met Asp Ala Thr Phe Gly Ala Leu Lys Gly
35 40 45

Leu Asp Ala Phe Glu Arg Ala Ile Tyr Thr Gly Ala His Gly Ala Ile
50 55 60

Pro Leu Pro Glu Lys Arg Trp Arg Phe Leu Gly Lys Asp Lys Asp Phe
65 70 75 80

Leu Asp Leu Cys Gly Val Lys Ala Thr Pro His Gly Cys Tyr Ile Glu
85 90 95

Asp Val Glu Val Asp Phe Gln Arg Leu Arg Thr Pro Met Thr Pro Glu
100 105 110

Asp Met Leu Leu Pro Gln Gln Leu Leu Ala Val Thr Thr Ile Asp Arg
115 120 125

Ala Ile Leu Asp Ser Gly Met Lys Lys Gly Gly Asn Val Ala Val Phe
130 135 140

Val Gly Leu Gly Thr Asp Leu Glu Leu Tyr Arg His Arg Ala Arg Val
145 150 155 160

Ala Leu Lys Glu Arg Val Arg Pro Glu Ala Ser Lys Lys Leu Asn Asp
165 170 175

Met Met Gln Tyr Ile Asn Asp Cys Gly Thr Ser Thr Ser Tyr Thr Ser
180 185 190

Tyr Ile Gly Asn Leu Val Ala Thr Arg Val Ser Ser Gln Trp Gly Phe
195 200 205

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Thr Gly Pro Ser Phe Thr Ile Thr Glu Gly Asn Asn Ser Val Tyr Arg
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Cys Ala Glu Leu Gly Lys Tyr Leu Leu Glu Thr Gly Glu Val Asp Gly
225                 230                 235                 240

Val Val Val Ala Gly Val Asp Leu Cys Gly Ser Ala Glu Asn Leu Tyr
                245                 250                 255

Val Lys Ser Arg Arg Phe Lys Val Ser Thr Ser Asp Thr Pro Arg Ala
            260                 265                 270

Ser Phe Asp Ala Ala Ala Asp Gly Tyr Phe Val Gly Glu Gly Cys Gly
        275                 280                 285

Ala Phe Val Leu Lys Arg Glu Thr Ser Cys Thr Lys Asp Asp Arg Ile
    290                 295                 300

Tyr Ala Cys Met Asp Ala Ile Val Pro Gly Asn Val Pro Ser Ala Cys
305                 310                 315                 320

Leu Arg Glu Ala Leu Asp Gln Ala Arg Val Lys Pro Gly Asp Ile Glu
                325                 330                 335

Met Leu Glu Leu Ser Ala Asp Ser Ala Arg His Leu Lys Asp Pro Ser
            340                 345                 350

Val Leu Pro Lys Glu Leu Thr Ala Glu Glu Glu Ile Gly Gly Leu Gln
        355                 360                 365

Thr Ile Leu Arg Asp Asp Asp Lys Leu Pro Arg Asn Val Ala Thr Gly
    370                 375                 380

Ser Val Lys Ala Thr Val Gly Asp Thr Gly Tyr Ala Ser Gly Ala Ala
385                 390                 395                 400

Ser Leu Ile Lys Ala Ala Leu Cys Ile Tyr Asn Arg Tyr Leu Pro Ser
                405                 410                 415
```

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Asn Gly Asp Asp Trp Asp Glu Pro Ala Pro Glu Ala Pro Trp Asp Ser
            420                 425                 430

Thr Leu Phe Ala Cys Gln Thr Ser Arg Ala Trp Leu Lys Asn Pro Gly
        435                 440                 445

Glu Arg Arg Tyr Ala Ala Val Ser Gly Val Ser Glu Thr Arg Ser Cys
    450                 455                 460

Tyr Ser Val Leu Leu Ser Glu Ala Glu Gly His Tyr Glu Arg Glu Asn
465                 470                 475                 480

Arg Ile Ser Leu Asp Glu Glu Ala Pro Lys Leu Ile Val Leu Arg Ala
                485                 490                 495

Asp Ser His Glu Glu Ile Leu Gly Arg Leu Asp Lys Ile Arg Glu Arg
            500                 505                 510

Phe Leu Gln Pro Thr Gly Ala Ala Pro Arg Glu Ser Glu Leu Lys Ala
        515                 520                 525

Gln Ala Arg Arg Ile Phe Leu Glu Leu Leu Gly Glu Thr Leu Ala Gln
    530                 535                 540

Asp Ala Ala Ser Ser Gly Ser Gln Lys Pro Leu Ala Leu Ser Leu Val
545                 550                 555                 560

Ser Thr Pro Ser Lys Leu Gln Arg Glu Val Glu Leu Ala Ala Lys Gly
                565                 570                 575

Ile Pro Arg Cys Leu Lys Met Arg Arg Asp Trp Ser Ser Pro Ala Gly
            580                 585                 590

Ser Arg Tyr Ala Pro Glu Pro Leu Ala Ser Asp Arg Val Ala Phe Met
        595                 600                 605

Tyr Gly Glu Gly Arg Ser Pro Tyr Tyr Gly Ile Thr Gln Asp Ile His
    610                 615                 620

Arg Ile Trp Pro Glu Leu His Glu Val Ile Asn Glu Lys Thr Asn Arg
625                 630                 635                 640
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Leu Trp Ala Glu Gly Asp Arg Trp Val Met Pro Arg Ala Ser Phe Lys
                645                 650                 655

Ser Glu Leu Glu Ser Gln Gln Gln Glu Phe Asp Arg Asn Met Ile Glu
            660                 665                 670

Met Phe Arg Leu Gly Ile Leu Thr Ser Ile Ala Phe Thr Asn Leu Ala
        675                 680                 685

Arg Asp Val Leu Asn Ile Thr Pro Lys Ala Ala Phe Gly Leu Ser Leu
    690                 695                 700

Gly Glu Ile Ser Met Ile Phe Ala Phe Ser Lys Lys Asn Gly Leu Ile
705                 710                 715                 720

Ser Asp Gln Leu Thr Lys Asp Leu Arg Glu Ser Asp Val Trp Asn Lys
                725                 730                 735

Ala Leu Ala Val Glu Phe Asn Ala Leu Arg Glu Ala Trp Gly Ile Pro
            740                 745                 750

Gln Ser Val Pro Lys Asp Glu Phe Trp Gln Gly Tyr Ile Val Arg Gly
        755                 760                 765

Thr Lys Gln Asp Ile Glu Ala Ala Ile Ala Pro Asp Ser Lys Tyr Val
    770                 775                 780

Arg Leu Thr Ile Ile Asn Asp Ala Asn Thr Ala Leu Ile Ser Gly Lys
785                 790                 795                 800

Pro Asp Ala Cys Lys Ala Ala Ile Ala Arg Leu Gly Gly Asn Ile Pro
                805                 810                 815

Ala Leu Pro Val Thr Gln Gly Met Cys Gly His Cys Pro Glu Val Gly
            820                 825                 830

Pro Tyr Thr Lys Asp Ile Ala Lys Ile His Ala Asn Leu Glu Phe Pro
        835                 840                 845
```

```
Val Val Asp Gly Leu Asp Leu Trp Thr Thr Ile Asn Gln Lys Arg Leu
    850                 855                 860

Val Pro Arg Ala Thr Gly Ala Lys Asp Glu Trp Ala Pro Ser Ser Phe
865                 870                 875                 880

Gly Glu Tyr Ala Gly Gln Leu Tyr Glu Lys Gln Ala Asn Phe Pro Gln
                885                 890                 895

Ile Val Glu Thr Ile Tyr Lys Gln Asn Tyr Asp Val Phe Val Glu Val
            900                 905                 910

Gly Pro Asn Asn His Arg Ser Thr Ala Val Arg Thr Thr Leu Gly Pro
        915                 920                 925

Gln Arg Asn His Leu Ala Gly Ala Ile Asp Lys Gln Asn Glu Asp Ala
    930                 935                 940

Trp Thr Thr Ile Val Lys Leu Val Ala Ser Leu Lys Ala His Leu Val
945                 950                 955                 960

Pro Gly Val Thr Ile Ser Pro Leu Tyr His Ser Lys Leu Val Ala Glu
                965                 970                 975

Ala Gln Ala Cys Tyr Ala Ala Leu Cys Lys Gly Glu Lys Pro Lys Lys
            980                 985                 990

Asn Lys Phe Val Arg Lys Ile Gln  Leu Asn Gly Arg Phe  Asn Ser Lys
        995                 1000                1005

Ala Asp  Pro Ile Ser Ser Ala  Asp Leu Ala Ser Phe  Pro Pro Ala
    1010                1015                1020

Asp Pro  Ala Ile Glu Ala Ala  Ile Ser Ser Arg Ile  Met Lys Pro
    1025                1030                1035

Val Ala  Pro Lys Phe Tyr Ala  Arg Leu Asn Ile Asp  Glu Gln Asp
    1040                1045                1050

Glu Thr  Arg Asp Pro Ile Leu  Asn Lys Asp Asn Ala  Pro Ser Ser
    1055                1060                1065
```

```
Ser Ser  Ser Ser Ser Ser Ser  Ser Ser Ser Ser Ser  Ser Pro Ser
    1070                 1075                 1080

Pro Ala  Pro Ser Ala Pro Val  Gln Lys Lys Ala Ala  Pro Ala Ala
    1085                 1090                 1095

Glu Thr  Lys Ala Val Ala Ser  Ala Asp Ala Leu Arg  Ser Ala Leu
    1100                 1105                 1110

Leu Asp  Leu Asp Ser Met Leu  Ala Leu Ser Ser Ala  Ser Ala Ser
    1115                 1120                 1125

Gly Asn  Leu Val Glu Thr Ala  Pro Ser Asp Ala Ser  Val Ile Val
    1130                 1135                 1140

Pro Pro  Cys Asn Ile Ala Asp  Leu Gly Ser Arg Ala  Phe Met Lys
    1145                 1150                 1155

Thr Tyr  Gly Val Ser Ala Pro  Leu Tyr Thr Gly Ala  Met Ala Lys
    1160                 1165                 1170

Gly Ile  Ala Ser Ala Asp Leu  Val Ile Ala Ala Gly  Arg Gln Gly
    1175                 1180                 1185

Ile Leu  Ala Ser Phe Gly Ala  Gly Gly Leu Pro Met  Gln Val Val
    1190                 1195                 1200

Arg Glu  Ser Ile Glu Lys Ile  Gln Ala Ala Leu Pro  Asn Gly Pro
    1205                 1210                 1215

Tyr Ala  Val Asn Leu Ile His  Ser Pro Phe Asp Ser  Asn Leu Glu
    1220                 1225                 1230

Lys Gly  Asn Val Asp Leu Phe  Leu Glu Lys Gly Val  Thr Phe Val
    1235                 1240                 1245

Glu Ala  Ser Ala Phe Met Thr  Leu Thr Pro Gln Val  Val Arg Tyr
    1250                 1255                 1260
```

```
Arg Ala  Ala Gly Leu Thr Arg  Asn Ala Asp Gly Ser  Val Asn Ile
    1265                 1270                 1275

Arg Asn  Arg Ile Ile Gly Lys  Val Ser Arg Thr Glu  Leu Ala Glu
    1280                 1285                 1290

Met Phe  Met Arg Pro Ala Pro  Glu His Leu Leu Gln  Lys Leu Ile
    1295                 1300                 1305

Ala Ser  Gly Glu Ile Asn Gln  Glu Gln Ala Glu Leu  Ala Arg Arg
    1310                 1315                 1320

Val Pro  Val Ala Asp Asp Ile  Ala Val Glu Ala Asp  Ser Gly Gly
    1325                 1330                 1335

His Thr  Asp Asn Arg Pro Ile  His Val Ile Leu Pro  Leu Ile Ile
    1340                 1345                 1350

Asn Leu  Arg Asp Arg Leu His  Arg Glu Cys Gly Tyr  Pro Ala Asn
    1355                 1360                 1365

Leu Arg  Val Arg Val Gly Ala  Gly Gly Gly Ile Gly  Cys Pro Gln
    1370                 1375                 1380

Ala Ala  Leu Ala Thr Phe Asn  Met Gly Ala Ser Phe  Ile Val Thr
    1385                 1390                 1395

Gly Thr  Val Asn Gln Val Ala  Lys Gln Ser Gly Thr  Cys Asp Asn
    1400                 1405                 1410

Val Arg  Lys Gln Leu Ala Lys  Ala Thr Tyr Ser Asp  Val Cys Met
    1415                 1420                 1425

Ala Pro  Ala Ala Asp Met Phe  Glu Glu Gly Val Lys  Leu Gln Val
    1430                 1435                 1440

Leu Lys  Lys Gly Thr Met Phe  Pro Ser Arg Ala Asn  Lys Leu Tyr
    1445                 1450                 1455

Glu Leu  Phe Cys Lys Tyr Asp  Ser Phe Glu Ser Met  Pro Pro Ala
    1460                 1465                 1470
```

```
Glu Leu  Ala Arg Val Glu Lys  Arg Ile Phe Ser Arg  Ala Leu Glu
    1475                 1480                 1485

Glu Val  Trp Asp Glu Thr Lys  Asn Phe Tyr Ile Asn  Arg Leu His
    1490                 1495                 1500

Asn Pro  Glu Lys Ile Gln Arg  Ala Glu Arg Asp Pro  Lys Leu Lys
    1505                 1510                 1515

Met Ser  Leu Cys Phe Arg Trp  Tyr Leu Ser Leu Ala  Ser Arg Trp
    1520                 1525                 1530

Ala Asn  Thr Gly Ala Ser Asp  Arg Val Met Asp Tyr  Gln Val Trp
    1535                 1540                 1545

Cys Gly  Pro Ala Ile Gly Ser  Phe Asn Asp Phe Ile  Lys Gly Thr
    1550                 1555                 1560

Tyr Leu  Asp Pro Ala Val Ala  Asn Glu Tyr Pro Cys  Val Val Gln
    1565                 1570                 1575

Ile Asn  Lys Gln Ile Leu Arg  Gly Ala Cys Phe Leu  Arg Arg Leu
    1580                 1585                 1590

Glu Ile  Leu Arg Asn Ala Arg  Leu Ser Asp Gly Ala  Ala Ala Leu
    1595                 1600                 1605

Val Ala  Ser Ile Asp Asp Thr  Tyr Val Pro Ala Glu  Lys Leu
    1610                 1615                 1620
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Thr Ala Ala Glu Ser Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln
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Gln Gln Gln Gln Pro Arg Glu Gly Asp Lys Glu Lys Ala Ala Glu Thr
35 40 45

Met Ala Leu Arg Val Lys Thr Asn Lys Lys Pro Cys Trp Glu Met Thr
50 55 60

Lys Glu Glu Leu Thr Ser Gly Lys Thr Glu Val Phe Asn Tyr Glu Glu
65 70 75 80

Leu Leu Glu Phe Ala Glu Gly Asp Ile Ala Lys Val Phe Gly Pro Glu
85 90 95

Phe Ala Val Ile Asp Lys Tyr Pro Arg Arg Val Arg Leu Pro Ala Arg
100 105 110

Glu Tyr Leu Leu Val Thr Arg Val Thr Leu Met Asp Ala Glu Val Asn
115 120 125

Asn Tyr Arg Val Gly Ala Arg Met Val Thr Glu Tyr Asp Leu Pro Val
130 135 140

Asn Gly Glu Leu Ser Glu Gly Gly Asp Cys Pro Trp Ala Val Leu Val
145 150 155 160

Glu Ser Gly Gln Cys Asp Leu Met Leu Ile Ser Tyr Met Gly Ile Asp
165 170 175

Phe Gln Asn Gln Gly Asp Arg Val Tyr Arg Leu Leu Asn Thr Thr Leu
180 185 190

Thr Phe Tyr Gly Val Ala His Glu Gly Glu Thr Leu Glu Tyr Asp Ile
195 200 205

Arg Val Thr Gly Phe Ala Lys Arg Leu Asp Gly Gly Ile Ser Met Phe
210 215 220

Phe Phe Glu Tyr Asp Cys Tyr Val Asn Gly Arg Leu Leu Ile Glu Met
225 230 235 240

```
Arg Asp Gly Cys Ala Gly Phe Phe Thr Asn Glu Glu Leu Asp Ala Gly
                245                 250                 255

Lys Gly Val Val Phe Thr Arg Gly Asp Leu Ala Ala Arg Ala Lys Ile
            260                 265                 270

Pro Lys Gln Asp Val Ser Pro Tyr Ala Val Ala Pro Cys Leu His Lys
        275                 280                 285

Thr Lys Leu Asn Glu Lys Glu Met Gln Thr Leu Val Asp Lys Asp Trp
    290                 295                 300

Ala Ser Val Phe Gly Ser Lys Asn Gly Met Pro Glu Ile Asn Tyr Lys
305                 310                 315                 320

Leu Cys Ala Arg Lys Met Leu Met Ile Asp Arg Val Thr Ser Ile Asp
                325                 330                 335

His Lys Gly Gly Val Tyr Gly Leu Gly Gln Leu Val Gly Glu Lys Ile
            340                 345                 350

Leu Glu Arg Asp His Trp Tyr Phe Pro Cys His Phe Val Lys Asp Gln
        355                 360                 365

Val Met Ala Gly Ser Leu Val Ser Asp Gly Cys Ser Gln Met Leu Lys
    370                 375                 380

Met Tyr Met Ile Trp Leu Gly Leu His Leu Thr Thr Gly Pro Phe Asp
385                 390                 395                 400

Phe Arg Pro Val Asn Gly His Pro Asn Lys Val Arg Cys Arg Gly Gln
                405                 410                 415

Ile Ser Pro His Lys Gly Lys Leu Val Tyr Val Met Glu Ile Lys Glu
            420                 425                 430

Met Gly Phe Asp Glu Asp Asn Asp Pro Tyr Ala Ile Ala Asp Val Asn
        435                 440                 445

Ile Ile Asp Val Asp Phe Glu Lys Gly Gln Asp Phe Ser Leu Asp Arg
```

```
    450                 455                 460

Ile Ser Asp Tyr Gly Lys Gly Asp Leu Asn Lys Lys Ile Val Val Asp
465                 470                 475                 480

Phe Lys Gly Ile Ala Leu Lys Met Gln Lys Arg Ser Thr Asn Lys Asn
                485                 490                 495

Pro Ser Lys Val Gln Pro Val Phe Ala Asn Gly Ala Ala Thr Val Gly
            500                 505                 510

Pro Glu Ala Ser Lys Ala Ser Ser Gly Ala Ser Ala Ser Ala Ser Ala
        515                 520                 525

Ala Pro Ala Lys Pro Ala Phe Ser Ala Asp Val Leu Ala Pro Lys Pro
    530                 535                 540

Val Ala Leu Pro Glu His Ile Leu Lys Gly Asp Ala Leu Ala Pro Lys
545                 550                 555                 560

Glu Met Ser Trp His Pro Met Ala Arg Ile Pro Gly Asn Pro Thr Pro
                565                 570                 575

Ser Phe Ala Pro Ser Ala Tyr Lys Pro Arg Asn Ile Ala Phe Thr Pro
            580                 585                 590

Phe Pro Gly Asn Pro Asn Asp Asn Asp His Thr Pro Gly Lys Met Pro
        595                 600                 605

Leu Thr Trp Phe Asn Met Ala Glu Phe Met Ala Gly Lys Val Ser Met
    610                 615                 620

Cys Leu Gly Pro Glu Phe Ala Lys Phe Asp Asp Ser Asn Thr Ser Arg
625                 630                 635                 640

Ser Pro Ala Trp Asp Leu Ala Leu Val Thr Arg Ala Val Ser Val Ser
                645                 650                 655

Asp Leu Lys His Val Asn Tyr Arg Asn Ile Asp Leu Asp Pro Ser Lys
            660                 665                 670
```

```
Gly Thr Met Val Gly Glu Phe Asp Cys Pro Ala Asp Ala Trp Phe Tyr
        675                 680                 685

Lys Gly Ala Cys Asn Asp Ala His Met Pro Tyr Ser Ile Leu Met Glu
    690                 695                 700

Ile Ala Leu Gln Thr Ser Gly Val Leu Thr Ser Val Leu Lys Ala Pro
705                 710                 715                 720

Leu Thr Met Glu Lys Asp Asp Ile Leu Phe Arg Asn Leu Asp Ala Asn
                725                 730                 735

Ala Glu Phe Val Arg Ala Asp Leu Asp Tyr Arg Gly Lys Thr Ile Arg
            740                 745                 750

Asn Val Thr Lys Cys Thr Gly Tyr Ser Met Leu Gly Glu Met Gly Val
        755                 760                 765

His Arg Phe Thr Phe Glu Leu Tyr Val Asp Asp Val Leu Phe Tyr Lys
    770                 775                 780

Gly Ser Thr Ser Phe Gly Trp Phe Val Pro Glu Val Phe Ala Ala Gln
785                 790                 795                 800

Ala Gly Leu Asp Asn Gly Arg Lys Ser Glu Pro Trp Phe Ile Glu Asn
                805                 810                 815

Lys Val Pro Ala Ser Gln Val Ser Ser Phe Asp Val Arg Pro Asn Gly
            820                 825                 830

Ser Gly Arg Thr Ala Ile Phe Ala Asn Ala Pro Ser Gly Ala Gln Leu
        835                 840                 845

Asn Arg Arg Thr Asp Gln Gly Gln Tyr Leu Asp Ala Val Asp Ile Val
    850                 855                 860

Ser Gly Ser Gly Lys Lys Ser Leu Gly Tyr Ala His Gly Ser Lys Thr
865                 870                 875                 880

Val Asn Pro Asn Asp Trp Phe Phe Ser Cys His Phe Trp Phe Asp Ser
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885 890 895

Val Met Pro Gly Ser Leu Gly Val Glu Ser Met Phe Gln Leu Val Glu
900 905 910

Ala Ile Ala Ala His Glu Asp Leu Ala Gly Lys Ala Arg His Cys Gln
915 920 925

Pro His Leu Cys Ala Arg Pro Arg Ala Arg Ser Ser Trp Lys Tyr Arg
930 935 940

Gly Gln Leu Thr Pro Lys Ser Lys Lys Met Asp Ser Glu Val His Ile
945 950 955 960

Val Ser Val Asp Ala His Asp Gly Val Val Asp Leu Val Ala Asp Gly
965 970 975

Phe Leu Trp Ala Asp Ser Leu Arg Val Tyr Ser Val Ser Asn Ile Arg
980 985 990

Val Arg Ile Ala Ser Gly Glu Ala Pro Ala Ala Ala Ser Ser Ala Ala
995 1000 1005

Ser Val Gly Ser Ser Ala Ser Ser Val Glu Arg Thr Arg Ser Ser
1010 1015 1020

Pro Ala Val Ala Ser Gly Pro Ala Gln Thr Ile Asp Leu Lys Gln
1025 1030 1035

Leu Lys Thr Glu Leu Leu Glu Leu Asp Ala Pro Leu Tyr Leu Ser
1040 1045 1050

Gln Asp Pro Thr Ser Gly Gln Leu Lys Lys His Thr Asp Val Ala
1055 1060 1065

Ser Gly Gln Ala Thr Ile Val Gln Pro Cys Thr Leu Gly Asp Leu
1070 1075 1080

Gly Asp Arg Ser Phe Met Glu Thr Tyr Gly Val Val Ala Pro Leu
1085 1090 1095

```
Tyr Thr  Gly Ala Met Ala Lys  Gly Ile Ala Ser Ala  Asp Leu Val
    1100                 1105                 1110

Ile Ala  Ala Gly Lys Arg Lys  Ile Leu Gly Ser Phe  Gly Ala Gly
    1115                 1120                 1125

Gly Leu  Pro Met His His Val  Arg Ala Ala Leu Glu  Lys Ile Gln
    1130                 1135                 1140

Ala Ala  Leu Pro Gln Gly Pro  Tyr Ala Val Asn Leu  Ile His Ser
    1145                 1150                 1155

Pro Phe  Asp Ser Asn Leu Glu  Lys Gly Asn Val Asp  Leu Phe Leu
    1160                 1165                 1170

Glu Lys  Gly Val Thr Val Val  Glu Ala Ser Ala Phe  Met Thr Leu
    1175                 1180                 1185

Thr Pro  Gln Val Val Arg Tyr  Arg Ala Ala Gly Leu  Ser Arg Asn
    1190                 1195                 1200

Ala Asp  Gly Ser Val Asn Ile  Arg Asn Arg Ile Ile  Gly Lys Val
    1205                 1210                 1215

Ser Arg  Thr Glu Leu Ala Glu  Met Phe Ile Arg Pro  Ala Pro Glu
    1220                 1225                 1230

His Leu  Leu Glu Lys Leu Ile  Ala Ser Gly Glu Ile  Thr Gln Glu
    1235                 1240                 1245

Gln Ala  Glu Leu Ala Arg Arg  Val Pro Val Ala Asp  Asp Ile Ala
    1250                 1255                 1260

Val Glu  Ala Asp Ser Gly Gly  His Thr Asp Asn Arg  Pro Ile His
    1265                 1270                 1275

Val Ile  Leu Pro Leu Ile Ile  Asn Leu Arg Asn Arg  Leu His Arg
    1280                 1285                 1290

Glu Cys  Gly Tyr Pro Ala His  Leu Arg Val Arg Val  Gly Ala Gly
```

1295 1300 1305

Gly Gly Val Gly Cys Pro Gln Ala Ala Ala Ala Ala Leu Thr Met
1310 1315 1320

Gly Ala Ala Phe Ile Val Thr Gly Thr Val Asn Gln Val Ala Lys
1325 1330 1335

Gln Ser Gly Thr Cys Asp Asn Val Arg Lys Gln Leu Ser Gln Ala
1340 1345 1350

Thr Tyr Ser Asp Ile Cys Met Ala Pro Ala Ala Asp Met Phe Glu
1355 1360 1365

Glu Gly Val Lys Leu Gln Val Leu Lys Lys Gly Thr Met Phe Pro
1370 1375 1380

Ser Arg Ala Asn Lys Leu Tyr Glu Leu Phe Cys Lys Tyr Asp Ser
1385 1390 1395

Phe Asp Ser Met Pro Pro Ala Glu Leu Glu Arg Ile Glu Lys Arg
1400 1405 1410

Ile Phe Lys Arg Ala Leu Gln Glu Val Trp Glu Glu Thr Lys Asp
1415 1420 1425

Phe Tyr Ile Asn Gly Leu Lys Asn Pro Glu Lys Ile Gln Arg Ala
1430 1435 1440

Glu His Asp Pro Lys Leu Lys Met Ser Leu Cys Phe Arg Trp Tyr
1445 1450 1455

Leu Gly Leu Ala Ser Arg Trp Ala Asn Met Gly Ala Pro Asp Arg
1460 1465 1470

Val Met Asp Tyr Gln Val Trp Cys Gly Pro Ala Ile Gly Ala Phe
1475 1480 1485

Asn Asp Phe Ile Lys Gly Thr Tyr Leu Asp Pro Ala Val Ser Asn
1490 1495 1500

Glu Tyr Pro Cys Val Val Gln Ile Asn Leu Gln Ile Leu Arg Gly
1505 1510 1515

Ala Cys Tyr Leu Arg Arg Leu Asn Ala Leu Arg Asn Asp Pro Arg
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Ile Asp Leu Glu Thr Glu Asp Ala Ala Phe Val Tyr Glu Pro Thr
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gagggtaacc ctaagcgtaa aatggcattg attttccgtt ggtacttagg tctttctagt 1380

cgctggtcaa actcaggcga agtgggtcgt gaaatggatt atcaaatttg ggctggccct 1440

gctctcggtg catttaacca atgggcaaaa ggcagttact tagataacta tcaagaccga 1500

aatgccgtcg atttggcaaa gcacttaatg tacggcgcgg cttacttaaa tcgtattaac 1560

tcgctaacgg ctcaaggcgt taaagtgcca gcacagttac ttcgctggaa gccaaaccaa 1620

agaatggcc 1629

THE EMBODIMENTS OF THE INVENTION FOR WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. An oligonucleotide probe or primer consisting of at least 50 consecutive nucleotides of SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:76, or the complement thereof.

2. An oligonucleotide probe or primer consisting of at least 75 consecutive nucleotides of SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:76, or the complement thereof.

3. An oligonucleotide probe or primer consisting of at least 100 consecutive nucleotides of SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:76, or the complement thereof.

4. The oligonucleotide probe or primer of any one of claims 1 to 3, wherein the probe or primer is a degenerate probe or primer.

5. A method of identifying a nucleotide sequence having homology to a PKS-like gene, comprising:

   a) screening a nucleotide sample obtained from an organism with an oligonucleotide probe of any one of claims 1 to 4 under hybridization conditions;

   b) isolating a nucleotide sequence that binds to the oligonucleotide probe;

   c) sequencing the nucleotide sequence; and

   d) determining the homology of the nucleotide sequence to a known PKS-like gene.

6. The method of claim 5, wherein the method further identifies an organism comprising a PKS-like gene.

7. An isolated nucleic acid molecule comprising:

   a) a nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO:72; or

b) a nucleic acid sequence encoding an amino acid sequence that is at least 80% identical to SEQ ID NO:72, wherein said nucleic acid sequence encodes a protein having chain length factor activity and acyl transferase activity.

8. The isolated nucleic acid molecule of claim 7, wherein said nucleic acid molecule comprises a nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO:72.

9. The isolated nucleic acid molecule of claim 7 or 8, wherein said nucleic acid molecule comprises the sequence as set forth in SEQ ID NO:71.

10. The isolated nucleic acid molecule of any one of claims 7 to 9, wherein said nucleic acid molecule is from *Schizochytrium*.

11. A recombinant nucleic acid molecule comprising the isolated nucleic acid molecule of any one of claims 7 to 10, operably linked to a promoter.

12. An isolated nucleic acid molecule comprising a nucleic acid sequence that is fully complementary to the full length of the nucleic acid sequence of any one of claims 7 to 9.

13. An isolated nucleic acid molecule comprising:

(a) a nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO:73; or

(b) a nucleic acid sequence encoding an amino acid sequence that is at least 80% identical to SEQ ID NO:73, wherein said nucleic acid sequence encodes a protein having dehydrase activity.

14. The isolated nucleic acid molecule of claim 13, wherein said nucleic acid molecule comprises a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:73.

15. The isolated nucleic acid molecule of claim 13 or claim 14, wherein said nucleic acid molecule comprises the sequence as set forth in SEQ ID NO:76.

16. The isolated nucleic acid molecule of any one of claims 13 to 15, wherein said nucleic acid molecule is from *Schizochytrium*.

17. The isolated nucleic acid molecule of any one of claims 13 to 16, wherein said nucleic acid molecule, when expressed by a host cell, modulates the production of a long chain polyunsaturated fatty acid.

18. The isolated nucleic acid molecule of any one of claims 13 to 17, wherein said nucleic acid molecule, when expressed by a host cell, modulates the production of docosahexaenoic acid.

19. The isolated nucleic acid molecule of any one of claims 13 to 18, wherein said nucleic acid molecule, when expressed by a host cell, modulates the production of eicosapentaenoic acid.

20. The isolated nucleic acid molecule of claim 13, wherein said nucleic acid sequence of (b) encodes an amino acid sequence that is at least 90% identical to SEQ ID NO:73.

21. The isolated nucleic acid molecule of claim 13, wherein said nucleic acid sequence of (b) encodes an amino acid sequence that is at least 95% identical to SEQ ID NO:73.

22. A recombinant nucleic acid molecule comprising the isolated nucleic acid molecule of any one of claims 13 to 21, operably linked to a promoter.

23. An isolated nucleic acid molecule comprising a nucleic acid sequence that is fully complementary to the full length of the nucleic acid sequence of any one of claims 13 to 15, 20, or 21.

24. A recombinant microbial cell comprising at least one copy of the nucleic acid molecule according to any one of claims 7 to 11 or 13 to 22.

25. The recombinant microbial cell of claim 24, wherein said microbial cell comprises a nucleic acid molecule derived from two or more polyketide synthase systems.

26. The recombinant microbial cell of claim 24 or 25, wherein said microbial cell is a eukaryotic or prokaryotic cell.

27. The recombinant microbial cell of claim 24 or 25, wherein said microbial cell is a fungal cell.

28. The recombinant microbial cell of claim 27, wherein said fungal cell is a yeast cell.

29. The recombinant microbial cell of claim 24 or 25, wherein said microbial cell is an algal cell.

30. The recombinant microbial cell of claim 29, wherein said algal cell is a marine algal cell.

31. The recombinant microbial cell of claim 24 or 25, wherein said cell is a bacterial cell or a cyanobacterial cell.

32. The recombinant microbial cell of claim 31, wherein said bacterial cell is a Lactobacillus cell.

33. The recombinant microbial cell of any one of claims 24 to 32, wherein said recombinant microbial cell is enriched for 22:6 fatty acids as compared to a non-recombinant microbial cell which is devoid of said isolated nucleic acid.

34. A method for production of a long chain polyunsaturated fatty acid in a microbial cell culture, said method comprising growing a microbial cell culture having a plurality of recombinant microbial cells as set forth in any one of claims 24 to 33 under conditions whereby a long chain polyunsaturated fatty acid is produced by said microbial cell culture.

35. A recombinant plant cell comprising at least one copy of the nucleic acid molecule according to any one of claims 7 to 11 or 13 to 22.

36. The recombinant plant cell of claim 35, wherein said recombinant plant cell is a recombinant seed cell.

37. The recombinant plant cell of claim 36, wherein said recombinant seed cell is a recombinant embryo cell.

38. The recombinant plant cell of any one of claims 35 to 37, wherein said recombinant plant cell is from a plant selected from the group consisting of Brassica, soybean, safflower, Arabidopsis, corn and sunflower.

39. A method for production of a long chain polyunsaturated fatty acid in a plant, said method comprising growing a plant having a plurality of recombinant plant cells as set forth in any one of claims 35 to 38 under conditions whereby a long chain polyunsaturated fatty acid is produced in said plant.

40. The method of claim 39, wherein said long chain polyunsaturated fatty acid produced in said plant is a 20:5 and 22:6 fatty acid.

41. The method of claim 39 or 40, wherein said long chain polyunsaturated fatty acid is eicosapentaenoic acid.

42. The method of claim 39 or 40, wherein said long chain polyunsaturated fatty acid is docosahexaenoic acid.

43. An isolated protein encoded by the nucleic acid molecule of any one of claims 7 to 11 or 13 to 22.

44. An expression cassette comprising the nucleic acid molecule of any one of claims 7 to 11 or 13 to 22.

45. A method to identify a nucleic acid sequence encoding a protein or fragment thereof from a polyketide synthase (PKS)-like system comprising screening a library constructed from an organism that produces at least one polyunsaturated fatty acid (PUFA) with a nucleic acid comprising a sequence which is the complement of the sequence encoding an amino acid sequence of SEQ ID NO:72, SEQ NO:73, or a fragment thereof.

46. The method of claim 45, wherein said organism produces an oil containing said at least one PUFA.

47. The method of claim 45 or 46, wherein said organism produces said at least one PUFA when cultured.

48. The method of any one of claims 45 to 47, wherein PUFA production in said organism is inhibited by thiolactomycin.

49. The method of any one of claims 45 to 48, wherein said organism is an algae.

50. The method of any one of claims 45 to 48, wherein said organism is a *Thraustochytrium.*

51. The method of any one of claims 45 to 48, wherein said organism is a *Schizochytrium.*

52. The method of any one of claims 45 to 51, further comprising detecting whether nucleic acids identified by said method encode proteins which, when substituted for the corresponding sequence from a *Schizochytrium* PKS system in a functional PKS system, have similar biological activity as proteins encoded by said corresponding sequence from said *Schizochytrium* PKS system.

53. The method of any one of claims 45 to 52, comprising screening the library with a nucleic acid sequence comprising SEQ ID NO:71 or SEQ ID NO:76.

54. The isolated nucleic acid molecule of claim 7, wherein said nucleic acid sequence of (b) encodes an amino acid sequence that is at least 90% identical to SEQ ID NO:72.

55. The isolated nucleic acid molecule of claim 7, wherein said nucleic acid sequence of (b) encodes an amino acid sequence that is at least 95% identical to SEQ ID NO:72.

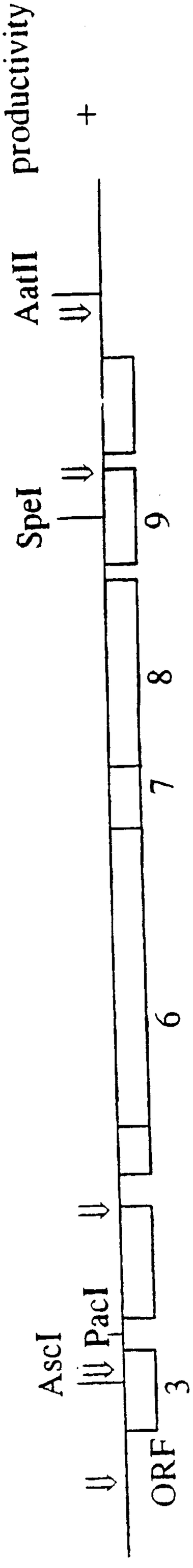


FIG. 1A

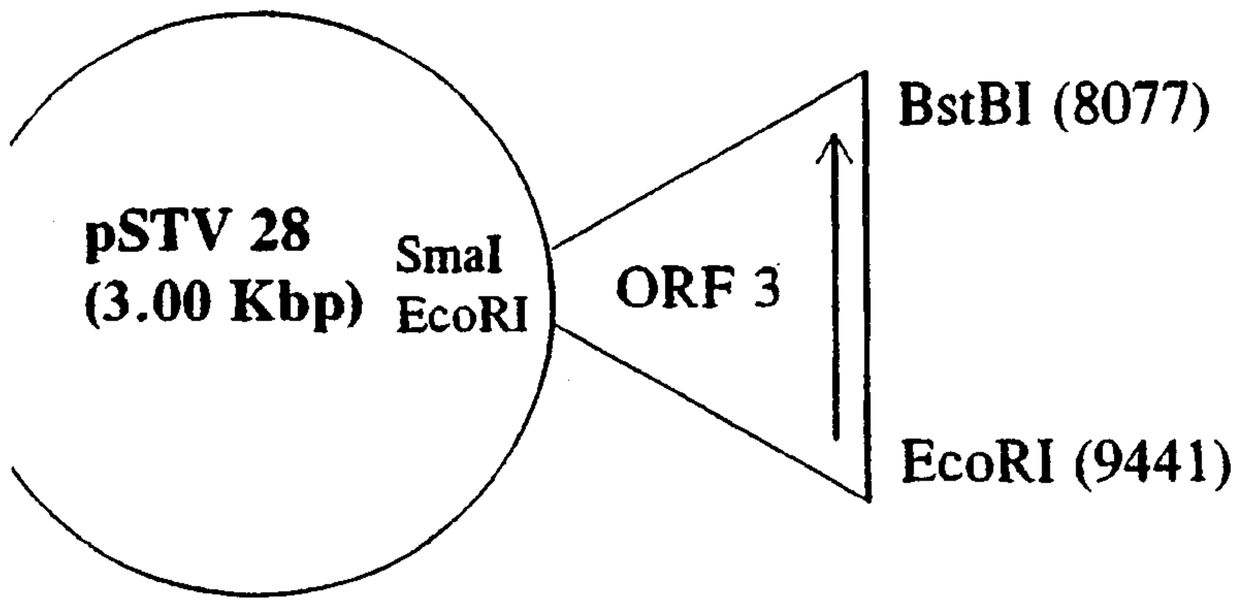
EPA
productivity

pAA-NEB ——— AscI-AatII/NEB +

pPA-NEB (Δ2,3) ——— PacI-AatII/NEB

Single ORF clones

ORF3 / pSTV 28



ORF 6 / pUC118

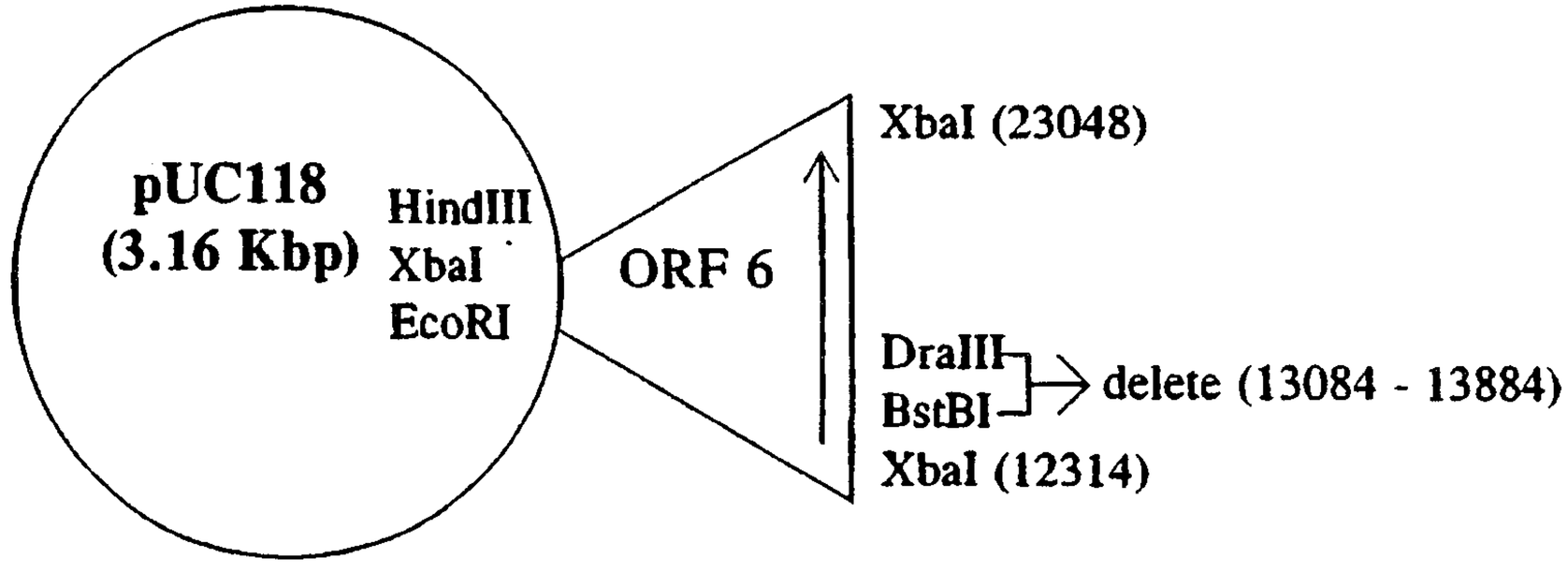
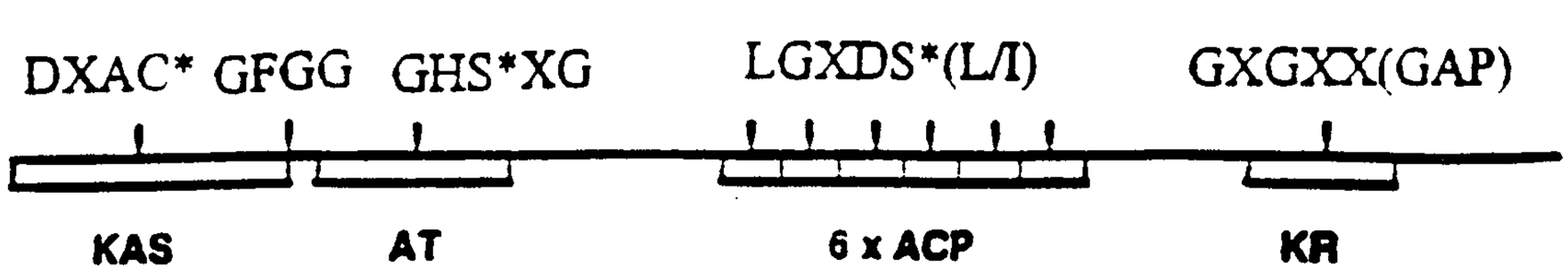


FIG. 1B

Orf6 8.3 KB - 293 kD



Acetate-like

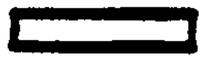
FIG. 2A

Orf7 2.3 KB - 84 kD

HgI C (C-1/2)

FIG. 2B

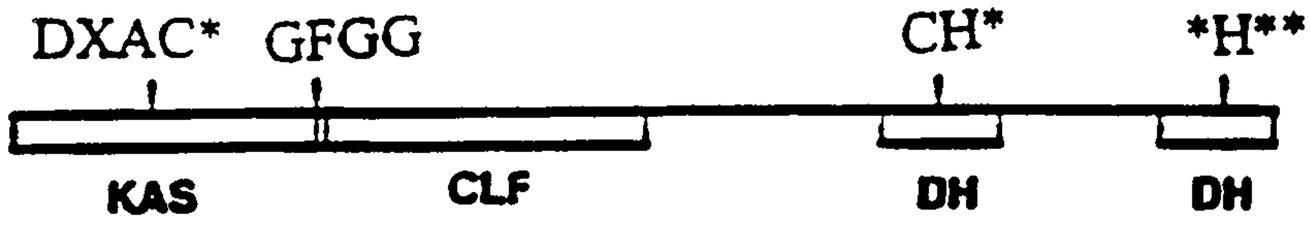
Orf3 0.8 KB - 30 kD



Het I- pantetheine transferase

FIG. 2E

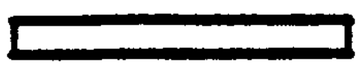
Orf8 6.0 KB - 217 kD



HgI D HgI C (N-1/2) FabA Faba/(Z)

FIG. 2C

Orf9 1.6 KB - 59 kD



Anabeana - Orf552 homolog

FIG. 2D

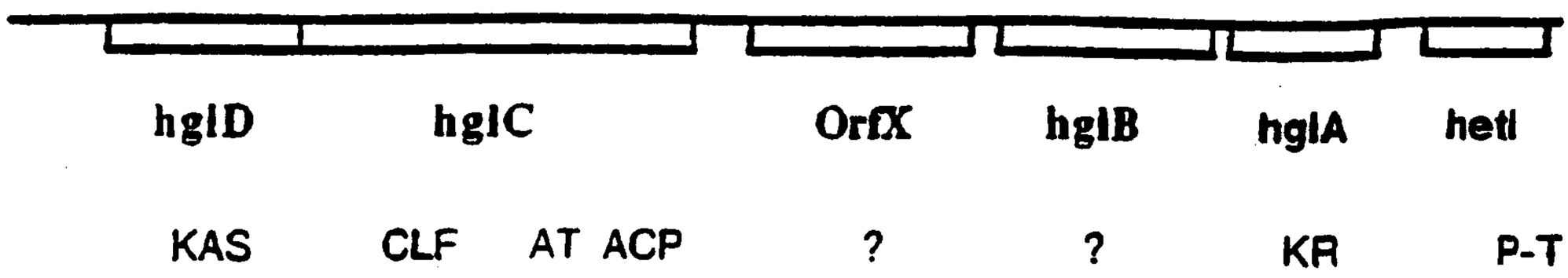


FIG. 2F

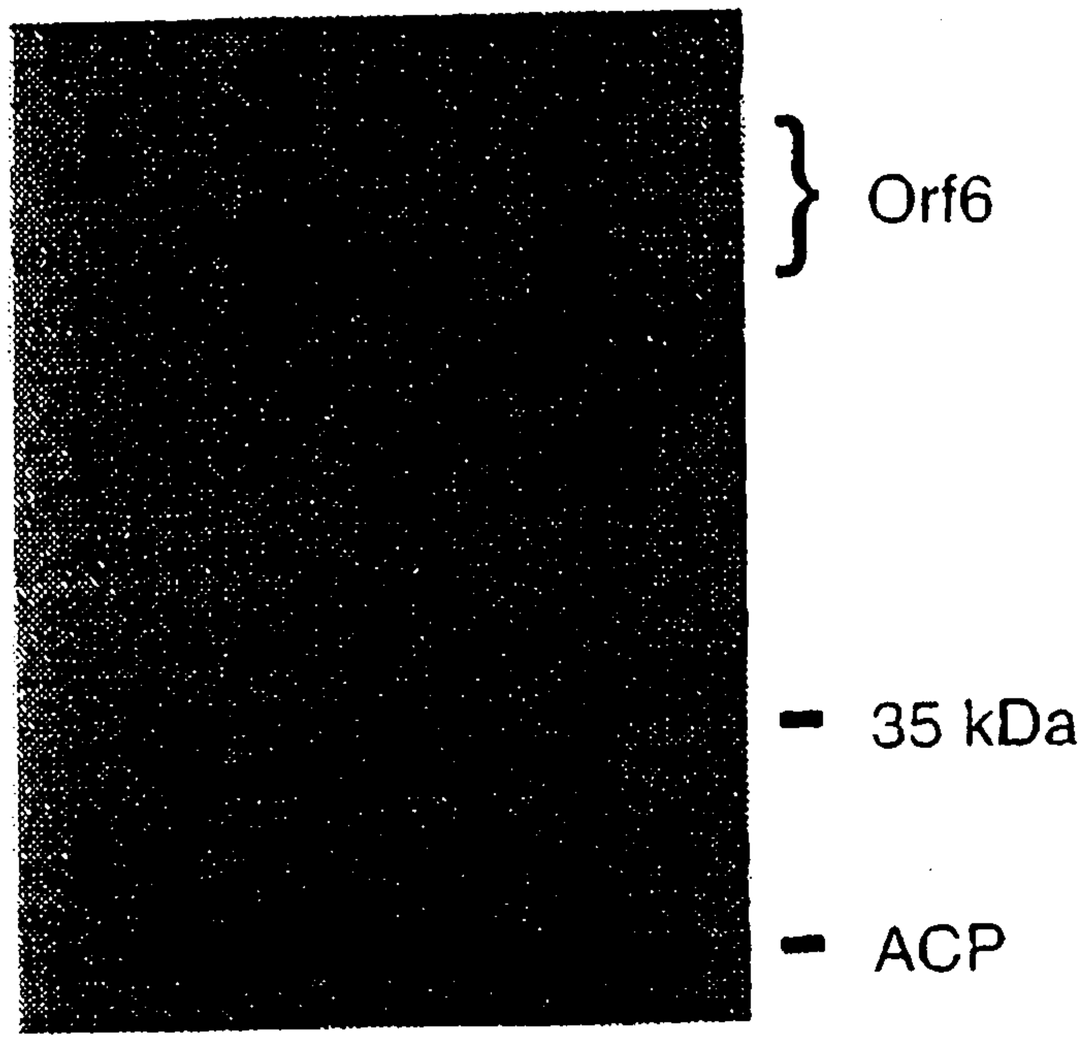


FIG. 3

GATCTCTTAC AAAGAAACTA TCTCAATGTG AATTTAACCT TAATTCCGTT TAATTACGGC 60

CTGATAGAGC ATCACCCAAT CAGCCATAAA ACTGTAAAGT GGGTACTCAA AGGTGGCTGG 120

GCGATTCTTC TCAAATACAA AGTGCCCAAC CCAAGCAAAT CCATATCCGA TAACAGGTAA 180

AAGTAGCAAT AAACCCCAGC GCTGAGTTAG TAATACATAA GCGAATAATA GGATCACTAA 240

ACTACTGCCG AAATAGTGTA ATATTCGACA GTTTCTATGC TGATGTTGAG ATAAATAAAA 300

AGGGTAAAAT TCAGCAAAAG AACGATAGCG CTTACTCATT ACTCACACCT CGGTAAAAAA 360

GCAACTCGCC ATTAACTTGG CCAATCGTCA GTTGTTCTAT CGTCTCAAAG TTATGCCGAC 420

TAAATAACTC TATATGTGCA TTATGATTAG CAAAAACTCC GATACCATCA AGATGAAGTT 480

GTTCATCACA CCAACTCAAA ACTGCGTCGA TAAGCTTACT GCCATAGCCC TTGCCTTGCT 540

CCACATTTGC GATAGCAATA AACTGTAAAA TGCCACATTG GCCACTTGGT AAGCTCTCTA 600

TAATCTGATT TTCTTTGTTA ATAAGTGCCT GAGTTGAATA CCAACCAGTA CTTAACAACA 660

TCTTTAAACG CCAATGCCAA AAACGCGCTT CACCTAAGGG AACCTGCTGA GTCACTATGC 720

AGGCTACGCC TATCAATCTA TCCCCAACGA ACATACCAAT AAGTGCTTGC TCCTGTTGCC 780

AGAGCTCATT GAGTTCTTCT CGAATAGCCC CGCGAAGCTT TTGCTCATAC TGCGCTTGAT 840

CACCACTAAA AAGTGTTTCG ATAAAAAAGG GATCATCATG ATAGGCGTTA TAGAGAATAG 900

AGGCTGCTAT GCGTAAATCT TCTGCCGTGA GATAAACTGC ACGACACTCT TCCATGGCTT 960

GATCTTCCAT TGTTATTGTC CTTGACCTTG ATCACACAAC ACCAATGTAA CAAGACTGTA 1020

FIG. 4A-1

TAGAAGTGCA ATTAATAATC AATTCGTGCA TTAAGCAGGT CAGCATTTCT TTGCTAAACA 1080

AGCTTTATTG GCTTTGACAA AACTTTGCCT AGACTTTAAC GATAGAAATC ATAATGAAAG 1140

AGAAAAGCTA CAACCTAGAG GGGAATAATC AAACAACTGC TAAGATCTAG ATAATGTAAT 1200

AAACACCGAG TTTATCGACC ATACTTAGAT AGAGTCATAG CAACGAGAAT AGTTATGGAT 1260

ACAACGCCGC AAGATCTATC ACACCTGTTT TTACAGCTAG GATTAGCAAA TGATCAACCC 1320

GCAATTGAAC AGTTTATCAA TGACCATCAA TTAGCGGACA ATATATTGCT ACATCAAGCA 1380

AGCTTTTGGA GCCCATCGCA AAAGCACTTC TTAATTGAGT CATTTAATGA AGATGCCCAG 1440

TGGACCGAAG TCATCGACCA CTTAGACACC TTATTAAGAA AAAACTAACC ATTACAACAG 1500

CAACTTTAAA TTTTGCCGTA AGCCATCTCC CCCCACCCCA CAACAGCGTT GTTGCTTATG 1560

ACCACTGGAG TACATTCGTC TTTAGTCGTT TTACCATCAC CATGGGTACG TTGAGTGCGA 1620

TAAAAAAGCA CATAAACTTC TTTATCGGCC TGAATATAGG CTTCGTTAAA ATCAGCTGTT 1680

CCCATTAAAG TAACCACTTG CTCTTTACTC ATGCCTAGAG ATATCTTTGT CAAATTGTCA 1740

CGGTTTTTAT CTTGAGTTTT CTCCCAAGCA CCGTGATTAT CCCAGTCAGA TTCCCCATCA 1800

CCAACATTGA CCACACAGCC CGTTAGCCCT AAGCTTGCAA TCCCAAAACA TGCTAAACCT 1860

AATAATTTAT TTTTCATTTT AACTTCCTGT TATGACATTA TTTTTGCTTA GAAGAAAAGC 1920

AACTTACATG CCAAAACACA AGCTGTTGTT TTAAATGACT TTATTTATTA TTAGCCTTTT 1980

AGGATATGCC TAGAGCAATA ATAATTACCA ATGTTTAAGG AATTTGACTA ACTATGAGTC 2040

FIG. 4A-2

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CGATTGAGCA AGTGCTAACA GCTGCTAAAA AAATCAATGA ACAAGGTAGA GAACCAACAT 2100
TAGCATTGAT TAAAACCAAA CTTGGTAATA GCATCCCAAT GCGCGAGTTA ATCCAAGGTT 2160
TGCAACAGTT TAAGTCTATG AGTGCAGAAG AAAGACAAGC AATACCTAGC AGCTTAGCAA 2220
CAGCAAAAGA AACTCAATAT GGTCAATCAA GCTTATCTCA ATCTGAACAA GCTGATAGGA 2280
TCCTCCAGCT AGAAAACGCC CTCAATGAAT TAAGAAACGA ATTTAATGGG CTAAAAAGTC 2340
AATTTGATAA CTTACAACAA AACCTGATGA ATAAAGAGCC TGACACCAAA TGCATGTAAT 2400
TGAACTACGA TTTGAATGTT TTGATAACAC CACGATTACT GCAGCAGAAA AAGCCATTAA 2460
TGGTTTGCTT GAAGCTTATC GAGCCAATGG CCAGGTTCTA GGTCGTGAAT TTGCCGTTGC 2520
ATTTAACGAT GGTGAGTTTA AAGCACGCAT GTTAACCCCA GAAAAAAGCA GCTTATCTAA 2580
ACGCTTTAAT AGTCCTTGGG TAAATAGTGC ACTCGAAGAG CTAACCGAAG CCAAATTGCT 2640
TGCGCCACGT GAAAAGTATA TTGGCCAAGA TATTAATTCT GAAGCATCTA GCCAAGACAC 2700
ACCAAGTTGG CAGCTACTTT ACACAAGTTA TGTGCACATG TGCTCACCAC TAAGAAATGG 2760
CGACACCTTG CAGCCTATTC CACTGTATCA AATTCCAGCA ACTGCCAACG GCGATCATAA 2820
ACGAATGATC CGTTGGCAAA CAGAATGGCA AGCTTGTGAT GAATTGCAAA TGGCCGCAGC 2880
TACTAAAGCT GAATTTGCCG CACTTGAAGA GCTAACCAGT CATCAGAGTG ATCTATTTAG 2940
GCGTGGTTGG GACTTACGTG GCAGAGTCGA ATACTTGACG AAAATTCCGA CCTATTACTA 3000
TTTATACCGT GTTGGCGGTG AAAGCTTAGC AGTAGAAAAG CAGCGCTCTT GTCCTAAGTG 3060
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FIG. 4A-3

TGGCAGTCAA GAATGGCTGC TCGATAAACC ATTATTGGAT ATGTTCCATT TTCGCTGTGA 3120
CACCTGCCGC ATCGTATCTA ATATCTCTTG GGACCATTTA TAACTCTTCC GAGTCTTATC 3180
ACACTAGAGT TTAGTCAGCA TAAAAATGGC GCTTATATTT CAATTAAAAG AAATATAAGC 3240
GCCATTTTCA TCGATACTAT ATATCAGCAG ACTATTTTCC GCGTAAATTA GCCCACATTA 3300
ATTTCATTCT TTGCCAGATC CCTGGATGAT CTAGTTGTGG CATCGACTCT TCAATAGGTT 3360
TAACCGCAGG TGTAACCCTT GGAGTCAATT CGTTTATAAA CTCGTTTAAA CTGTCACTTA 3420
ATTTAACGCT TTGTACTTCA CCTGGAATTT CAATCCATAC GCTGCCATCA CTATTATTAA 3480
CCGTCAACAT TTTATCTTCA TCATCAAGAA TACCAATAAA CCAAGTCGGC TCTTGCTTAA 3540
GCTTTCTCTT CATCATTAAA TGACCAATGA TGTTTTGTTG TAAGTATTCA AAATCAGTTT 3600
GATCCCACAC TTGGATTAGC TCACCTTGGC CCCATTGTGA GTCAAAAAAT AGCGGTGCAG 3660
AAAAATGACT GCCAAAAAAT GGATTAATTT CTGCAGATAA TGTCATTTCA AGTGCTGTTT 3720
CAACATTAGC AAATTCACCA GGTTGTTGAC GTACAACCGA TTGCCAAAAC ACTGCGCCAT 3780
CGGAGCCCGC TTCGGCGACA ACACACTCAG ACTTTTGTCC TTGCGCATAA TATCTTGGCT 3840
GTTCACCAAG CTTATCCATG TAGGCTTGTT GATATTTAGA TAAAAAAAGA TCTAAAGCAG 3900
GTAAAGAAGA CACTTAAGCC AGTTCCAAAA TCAGTTATAA TAGGGGTCTA TTTTGACATG 3960
GAAACCGTAT TGATGACACA ACATCATGAT CCCTACAGTA ACGCCCCCGA ACTTTCTGAA 4020
TTAACTTTAG GAAAGTCGAC CGGTTATCAA GAGCAGTATG ATGCATCTTT ACTACAAGCG 4080

FIG. 4A-4

TGCCGCGTAA ATTAAACCGT GATGCTATCG GTCTAACCAA TGAGCTACCT TTTCATGGCT 4140

GTGATATTTG GACTGGCTAC GAACTGTCTT GGCTAAATGC TAAAGGCAAG CCAATGATTG 4200

CTATTGCAGA CTTTAACCTA AGTTTTGATA GTAAAAATCT GATCGAGTCT AAGTCGTTTA 4260

AGCTGTATTT AAACAGCTAT AACCAAACAC GATTTGATAG CGTTCAAGCG GTTCAAGAAC 4320

GTTTAACTGA AGACTTAAGC GCCTGTGCCC AAGGCACAGT TACGGTAAAA GTGATTGAAC 4380

CTAAGCAATT TAACCACCTG AGAGTGGTTG ATATGCCAGG TACCTGCATT GACGATTTAG 4440

ATATTGAAGT TGATGACTAT AGCTTTAACT CTGACTATCT CACCGACAGT GTTGATGACA 4500

AAGTCATGGT TGCTGAAACG CTAACGTCAA ACTTATTGAA ATCAAACTGC CTAATCACTT 4560

CTCAGCCTGA CTGGGGTACA GTGATGATCC GTTATCAAGG GCCTAAGATA GACCGTGAAA 4620

AGCTACTTAG ATATCTGATT TCATTTAGAC AGCACAATGA ATTTCATGAG CAGTGTGTTG 4680

AGCGTATATT TGTTGATTTA AAGCACTATT GCCAATGTGC CAAACTTACT GTCTATGCAC 4740

GTTATACCCG CCGTGGTGGT TTAGATATCA ACCCATATCG TAGCGACTTT GAAAACCCTG 4800

CAGAAAATCA GCGCCTAGCG AGACAGTAAT TGATTGCAGT ACCTACAAAA AACAATGCCT 4860

ATAAGCCAAG CTTATGGGCA TTTTTATATT ATCAACTTGT CATCAAACCT CAGCCGCCAA 4920

GCCTTTTAGT TTTATCGCTA AATTAAGCCG CTCTCTCAGC CAAATATTTG CAGGATTTTG 4980

CTGTAATTTA TGGCTCCACA CCATGAAATA CTCTATCGGC TCTACCGCAA AAGGTAAGTC 5040

AAATACCTGT AAGCCAAACA GCTTGGCATA TTCGTCAGTG TGGGCTTTTG ACGCGATAGC 5100

FIG. 4A-5

TAACGCATCA CTTTTTGAGG CAACCGACAT CATACTTAAT ATTGATGATT GCTCGCTGTG 5160
CATTTGCCTT GCCGGTAACA CCTGTTTAGT CAGCAAGTCG GCAACACTTA AATTGTAGCG 5220
GCGCATCTTA AAAATAATAT GCTTTTCATT AAAGTATTGC TCTTGCGTCA ACCCACCTTG 5280
GATCCTTGGG TGAGCATTTC GTGCCACACA AACTAATTTA TCCTGCATTA CTTTTTGACT 5340
CTTAAATGCC GCAGATTCTG GCAGCCAAAT ATCTAAGGCT AAATCCACCT TTTCTAGTTG 5400
TAGGTCCATC TGCAACTCTT CTTCAATGAG CGGCGGCTCA CGAAATACAA TATTAATTGC 5460
AGTGCCCTGT AACACTTGCT CAATTTGATC TTGCAAGAGT TGTATTGCCG ACTCGCTGGC 5520
ATACACATAA AAAGTTCGCT CACTTGAAGT GGGGTCAAAT GCTTCAAAGC TAGTCGCAAC 5580
TTGCTCAATT GTTGACATAG CGCCCGCGAG CTGTTGATAA AGCGTCATCG CACTTGCGGT 5640
AGGTTTAACT CCCCTACCCA CTCGAGTAAA CAACTCTTCT CCAACAATAC TTTTTAGCCT 5700
CGAAATCGCA TTACTAACCG ACGACTGAGT CAAATCCAGC TCTTCTGCCG CCCGGCTAAA 5760
AGATGAGGTG CGATACACCG CAGTAAAAAC GCGAAATAAA TTAAGATCAA AAGCTTTTTG 5820
CTGCGACATA AATCAGCTAT CTCCTTATCC TTATCCTTAT CCTTATAAAA AGTTAGCTCC 5880
AGAGCACTCT AGCTCAAAAA CAACTCAGCG TATTAAGCCA ATATTTTGGG AACTCAATTA 5940
ATATTCATAA TAAAAGTATT CATAATATAA ATACCAAGTC ATAATTTAGC CCTAATTATT 6000
AATCAATTCA AGTTACCTAT ACTGGCCTCA ATTAAGCAAA TGTCTCATCA GTCTCCCTGC 6060
AACTAAATGC AATATTGAGA CATAAAGCTT TGAACTGATT CAATCTTACG AGGGTAACTT 6120

FIG. 4A-6

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ATGAAACAGA CTCTAATGGC TATCTCAATC ATGTCGCTTT TTTCATTCAA TGCGCTAGCA 6180
GCGCAACATG AACATGACCA CATCACTGTT GATTACGAAG GGAAAGCCGC AACAGAACAC 6240
ACCATAGCTC ACAACCAAGC TGTAGCTAAA ACACTTAACT TTGCCGACAC GCGTGCATTT 6300
GAGCAATCGT CTAAAAATCT AGTCGCCAAG TTTGATAAAG CAACTGCCGA TATATTACGT 6360
GCCGAATTTG CTTTTATTAG CGATGAAATC CCTGACTCGG TTAACCCGTC TCTCTACCGT 6420
CAGGCTCAGC TTAATATGGT GCCTAATGGT CTGTATAAAG TGAGCGATGG CATTTACCAG 6480
GTCCGCGGTA CCGACTTATC TAACCTTACA CTTATCCGCA GTGATAACGG TTGGATAGCA 6540
TACGATGTTT TGTTAACCAA AGAAGCAGCA AAAGCCTCAC TACAATTTGC GTTAAAGAAT 6600
CTACCTAAAG ATGGCGATTT ACCCGTTGTT GCGATGATTT ACTCCCATAG CCATGCGGAC 6660
CACTTTGGCG GAGCTCGCGG TGTTCAAGAG ATGTTCCCTG ATGTCAAAGT CTACGGCTCA 6720
GATAACATCA CTAAAGAAAT TGTCGATGAG AACGTACTTG CCGGTAACGC CATGAGCCGC 6780
CGCGCAGCTT ATCAATACGG CGCAACACTG GGCAAACATG ACCACGGTAT TGTTGATGCT 6840
GCGCTAGGTA AAGGTCTATC AAAAGGTGAA ATCACTTACG TCGCCCCAGA CTACACCTTA 6900
AACAGTGAAG GCAAATGGGA AACGCTGACG ATTGATGGTC TAGAGATGGT GTTTATGGAT 6960
GCCTCGGGCA CCGAAGCTGA GTCAGAAATG ATCACTTATA TTCCCTCTAA AAAAGCGCTC 7020
TGGACGGCGG AGCTTACCTA TCAAGGTATG CACAACATTT ATACGCTGCG CGGCGCTAAA 7080
GTACGTGATG CGCTCAAGTG GTCAAAAGAT ATCAACGAAA TGATCAATGC CTTTGGTCAA 7140
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FIG. 4A-7

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GATGTCGAAG TGCTGTTTGC CTCGCACTCT GCGCCAGTGT GGGGTAACCA AGCGATCAAC 7200
GATTTCTTAC GCCTACAGCG TGATAACTAC GGCCTAGTGC ACAATCAAAC CTTGAGACTT 7260
GCCAACGATG GTGTCGGTAT ACAAGATATT GGCGATGCGA TTCAAGACAC GATTCCAGAG 7320
TCTATCTACA AGACGTGGCA TACCAATGGT TACCACGGCA CTTATAGCCA TAACGCTAAA 7380
GCGGTTTATA ACAAGTATCT AGGCTACTTC GATATGAACC CAGCCAACCT TAATCCGCTG 7440
CCAACCAAGC AAGAATCTGC CAAGTTTGTC GAATACATGG GCGGCGCAGA TGCCGCAATT 7500
AAGCGCGCTA AAGATGATTA CGCTCAAGGT GAATACCGCT TTGTTGCAAC GGCATTAAAT 7560
AAGGTGGTGA TGGCCGAGCC AGAAAATGAC TCCGCTCGTC AATTGCTAGC CGATACCTAT 7620
GAGCAACTTG GTTATCAAGC AGAAGGGGCT GGCTGGAGAA ACATTTACTT AACTGGCGCA 7680
CAAGAGCTAC GAGTAGGTAT TCAAGCTGGC GCGCCTAAAA CCGCATCGGC AGATGTCATC 7740
AGTGAAATGG ACATGCCGAC TCTATTTGAC TTCCTCGCGG TGAAGATTGA TAGTCAACAG 7800
GCGGCTAAGC ACGGCTTAGT TAAGATGAAT GTTATCACCC CTGATACTAA AGATATTCTC 7860
TATATTGAGC TAAGCAACGG TAACTTAAGC AACGCAGTGG TCGACAAAGA GCAAGCAGCT 7920
GACGCAAACC TTATGGTTAA TAAAGCTGAC GTTAACCGCA TCTTACTTGG CCAAGTAACC 7980
CTAAAAGCGT TATTAGCCAG CGGCGATGCC AAGCTCACTG GTGATAAAAC GGCATTTAGT 8040
AAAATAGCCG ATAGCATGGT CGAGTTTACA CCTGACTTCG AAATCGTACC AACGCCTGTT 8100
AAATGAGGCA TTAATCTCAA CAAGTGCAAG CTAGACATAA AAATGGGGCG ATTAGACGCC 8160
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FIG. 4A-8

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CCATTTTTTA TGCAATTTTG AACTAGCTAG TCTTAGCTGA AGCTCGAACA ACAGCTTTAA 8220
AATTCACTTC TTCTGCTGCA ATACTTATTT GCTGACACTG ACCAATACTC AGTGCAAAAC 8280
GATAACTATC ATCAAGATGG CCCAGTAAAC AATGCCAATT ATCAGCAGCG TTCATTTGCT 8340
GTTCTTTAGC CTCAATCAAA CCTAAACCAG ACTTTTGTGG CTCAGCGTTA GGCTTATTAG 8400
AACTCGACTC TAGTAAAGCA AGACCAATAT CTTGTTTTAA CAAAACCTGT CGCTGATTAA 8460
GTTGATGCTC AACCTTGTGA TCCGCAATAG CATCGGAAAT ATCAACACAA TGGCTCAAGC 8520
TTTTAGGTGC ATTAACTCCA AGAAAAGTTT CGCTCAGTGC AGAGAAGTCA AACGCAAAAG 8580
ATTTTAGCGA TAATGCCAGC CCAAGTCCTT TCGCTTTAAT GTAAGACTCC TTGAGCGCCC 8640
ACAAATCAAA AAAGCGGTCT CGCTGCAAGG CCTCTGGTAA CGCTAACAAG GCTCGCTTTT 8700
CTGATTCAGA GAAATAATGA CTAAGAATAG AGTGGATATT GGTGCTGTTA CGGCAACGCT 8760
CAATGTCGAC GCCAAACTCA ATACTAGCAG AGTCAGTTTC CTCCTTGCTT GCCTGACTGG 8820
CGCCTTTATT ATCAGCAGTG CAAATGCCTA CTAATAGCCA ATCTCCACTA TGACTCACAT 8880
TAAAGTGGAC CCCGGTTTGA GCAAATTGCG CATCACTCAA TCTAGGCTTA CCTTTGTCGC 8940
CATATTCAAA GCGCCATTCA TTGGGGCGTA TTTCACTATG TTGTGACAAT AAAGCGCGCA 9000
AATAGCCTCT TACCATTAAA CCTTGAGTTT TAGCTTCTTG TTTAATGTAG CGATTAACCT 9060
TAATTAACTC ATCTTCAGGC AGCCATGACT TAACCAACTC TGTAGTCTGG TTATCGCACT 9120
CTTGTATTGT TAACGGACAG AAGTATAAGG AAATCAATCG AGAAGTTAGC AATTTTTCAG 9180
```

FIG. 4A-9

GACACTCTTT AAAGCAACAA ACATAACCCC TATTTTTACC AATTTAAGAT CAAAACTAAA 9240
GCCAAAACTA ATTGAGAATA GTGTCAAACT AGCTTTAAAG GAAAAAAATA TAAAAAGAAC 9300
ATTATACTTG TATAAATTAT TTTACACACC AAAGCCATGA TCTTCACAAA ATTAGCTCCC 9360
TCTCCCTAAA ACAAGATTGA ATAAAAAAAT AAACCTTAAC TTTCATATAG ATAAAACAAA 9420
CCAATGGGAT AAAGTATATT GAATTCATTT TTAAGGAAAA ATTCAAATTG AATTCAAGCT 9480
CTTCAGTAAA AGCATATTTT GCCGTTAGTG TGAAAAAAAA CAAATTTAAA AACCAACATA 9540
GAACAAATAA GCAGACAATA AAACCAAGGC GCAACACAAA CAACGCGCTT ACAATTTTCA 9600
CAAAAAAGCA ACAAGAGTAA CGTTTAGTAT TTGGATATGG TTATTGTAAT TGAGAATTTT 9660
ATAACAATTA TATTAAGGGA ATGAGTATGT TTTTAAATTC AAAACTTTCG CGCTCAGTCA 9720
AACTTGCCAT ATCCGCAGGC TTAACAGCCT CGCTAGCTAT GCCTGTTTTT GCAGAAGAAA 9780
CTGCTGCTGA AGAACAAATA GAAAGAGTCG CAGTGACCGG ATCGCGAATC GCTAAAGCAG 9840
AGCTAACTCA ACCAGCTCCA GTCGTCAGCC TTTCAGCCGA AGAACTGACA AAATTTGGTA 9900
ATCAAGATTT AGGTAGCGTA CTAGCAGAAT TACCTGCTAT TGGTGCAACC AACACTATTA 9960
TTGGTAATAA CAATAGCAAC TCAAGCGCAG GTGTTAGCTC AGCAGACTTG CGTCGTCTAG 10020
GTGCTAACAG AACCTTAGTA TTAGTCAACG GTAAGCGCTA CGTTGCCGGC CAACCGGGCT 10080
CAGCTGAGGT AGATTTGTCA ACTATACCAA CTAGCATGAT CTCGCGAGTT GAGATTGTAA 10140
CCGGCGGTGC TTCAGCAATT TATGGTTCGG ACGCTGTATC AGGTGTTATC AACGTTATCC 10200

FIG. 4A-10

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TTAAAGAAGA CTTTGAAGGC TTTGAGTTTA ACGCACGTAC TAGCGGTTCT ACTGAAAGTG 10260
TAGGCACTCA AGAGCACTCT TTTGACATTT TGGGTGGTGC AAACGTTGCA GATGGACGTG 10320
GTAATGTAAC CTTCTACGCA GGTTATGAAC GTACAAAAGA AGTCATGGCT ACCGACATTC 10380
GCCAATTCGA TGCTTGGGGA ACAATTAAAA ACGAAGCCGA TGGTGGTGAA GATGATGGTA 10440
TTCCAGACAG ACTACGTGTA CCACGAGTTT ATTCTGAAAT GATTAATGCT ACCGGTGTTA 10500
TCAATGCATT TGGTGGTGGA ATTGGTCGCT CAACCTTTGA CAGTAACGGC AATCCTATTG 10560
CACAACAAGA ACGTGATGGG ACTAACAGCT TTGCATTTGG TTCATTCCCT AATGGCTGTG 10620
ACACATGTTT CAACACTGAA GCATACGAAA ACTATATTCC AGGGGTAGAA AGAATAAACG 10680
TTGGCTCATC ATTCAACTTT GATTTTACCG ATAACATTCA ATTTTACACT GACTTCAGAT 10740
ATGTAAAGTC AGATATTCAG CAACAATTTC AGCCTTCATT CCGTTTTGGT AACATTAATA 10800
TCAATGTTGA AGATAACGCC TTTTTGAATG ACGACTTGCG TCAGCAAATG CTCGATGCGG 10860
GTCAAACCAA TGCTAGTTTT GCCAAGTTTT TTGATGAATT AGGAAATCGC TCAGCAGAAA 10920
ATAAACGCGA ACTTTTCCGT TACGTAGGTG GCTTTAAAGG TGGCTTTGAT ATTAGCGAAA 10980
CCATATTTGA TTACGACCTT TACTATGTTT ATGGCGAGAC TAATAACCGT CGTAAAACCC 11040
TTAATGACCT AATTCCTGAT AACTTTGTCG CAGCTGTCGA CTCTGTTATT GATCCTGATA 11100
CTGGCTTAGC AGCGTGTCGC TCACAAGTAG CAAGCGCTCA AGGCGATGAC TATACAGATC 11160
CCGCGTCTGT AAATGGTAGC GACTGTGTTG CTTATAACCC ATTTGGCATG GGTCAAGCTT 11220
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FIG. 4A-11

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CAGCAGAAGC CCGCGACTGG GTTTCTGCTG ATGTGACTCG TGAAGACAAA ATAACTCAAC 11280
AAGTGATTGG TGGTACTCTC GGTACCGATT CTGAAGAACT ATTTGAGCTT CAAGGTGGTG 11340
CAATCGCTAT GGTTGTTGGT TTTGAATACC GTGAAGAAAC GTCTGGTTCA ACAACCGATG 11400
AATTTACTAA AGCAGGTTTC TTGACAAGCG CTGCAACGCC AGATTCTTAT GGCGAATACG 11460
ACGTGACTGA GTATTTTGTT GAGGTGAACA TCCCAGTACT AAAAGAATTA CCTTTTGCAC 11520
ATGAGTTGAG CTTTGACGGT GCATACCGTA ATGCTGATTA CTCACATGCC GGTAAGACTG 11580
AAGCATGGAA AGCTGGTATG TTCTACTCAC CATTAGAGCA ACTTGCATTA CGTGGTACGG 11640
TAGGTGAAGC AGTACGAGCA CCAAACATTG CAGAAGCCTT TAGTCCACGC TCTCCTGGTT 11700
TTGGCCGCGT TTCAGATCCA TGTGATGCAG ATAACATTAA TGACGATCCG GATCGCGTGT 11760
CAAACTGTGC AGCATTGGGG ATCCCTCCAG GATTCCAAGC TAATGATAAC GTCAGTGTAG 11820
ATACCTTATC TGGTGGTAAC CCAGATCTAA AACCTGAAAC ATCAACATCC TTTACAGGTG 11880
GTCTTGTTTG GACACCAACG TTTGCTGACA ATCTATCATT CACTGTCGAT TATTATGATA 11940
TTCAAATTGA GGATGCTATT TTGTCAGTAG CCACCCAGAC TGTGGCTGAT AACTGTGTTG 12000
ACTCAACTGG CGGACCTGAC ACCGACTTCT GTAGTCAAGT TGATCGTAAT CCAACGACCT 12060
ATGATATTGA ACTTGTTCGC TCTGGTTATC TAAATGCCGC GGCATTGAAT ACCAAAGGTA 12120
TTGAATTTCA AGCTGCATAC TCATTAGATC TAGAGTCTTT CAACGCGCCT GGTGAACTAC 12180
GCTTCAACCT ATTGGGGAAC CAATTACTTG AACTAGAACG TCTTGAATTC CAAAATCGTC 12240
```

FIG. 4A-12

CTGATGAGAT TAATGATGAA AAAGGCGAAG TAGGTGATCC AGAGCTGCAG TTCCGCCTAG 12300
GCATCGATTA CCGTCTAGAT GATCTAAGTG TTAGCTGGAA CACGCGTTAT ATTGATAGCG 12360
TAGTAACTTA TGATGTCTCT GAAAATGGTG GCTCTCCTGA AGATTTATAT CCAGGCCACA 12420
TAGGCTCAAT GACAACTCAT GACTTGAGCG CTACATACTA CATCAATGAG AACTTCATGA 12480
TTAACGGTGG TGTACGTAAC CTATTTGACG CACTTCCACC TGGATACACT AACGATGCGC 12540
TATATGATCT AGTTGGTCGC CGTGCATTCC TAGGTATTAA GGTAATGATG TAATTAATTA 12600
TTACGCCTCT AACTAATAAA AATGCAATCT CTTCGTAGAG ATTGCATTTT TTTATGAAAT 12660
CCAATCTTAA ACTGGTTCTC CGAGCATCTT ACGCCTTAAA AACCCCGCCC CTCAATGTAA 12720
CGCCAAAGTT AATTGCTTAC ACGCACTTAC ACAAACGAAC AATTTCATTA ACACGAGACA 12780
CAGCTCACGC TTTTTATTTT ACCCTTGATT TTACTACATA AAATTGCGTT TTAGCGCACA 12840
AGTGTTCTCC CAAGCTGGTC GTATCTGTAA TTATTCAGTC CCAGGTGATT GTATTGACCC 12900
ATAAGCTCAG GTAGTCTGCT CTGCCATTAG CTAAACAATA TTGACAAAAT GGCGATAAAA 12960
TGTGGCTTAG CGCTAAGTTC ACCGTAAGTT TTATCGGCAT TAAGTCCCAA CAGATTATTA 13020
ACGGAAACCC GCTAAACTGA TGGCAAAAAT AAATAGTGAA CACTTGGATG AAGCTACTAT 13080
TACTTCGAAT AAGTGTACGC AAACAGAGAC TGAGGCTCGG CATAGAAATG CCACTACAAC 13140
ACCTGAGATG CGCCGATTCA TACAAGAGTC GGATCTCAGT GTTAGCCAAC TGTCTAAAAT 13200
ATTAAATATC AGTGAAGCTA CCGTACGTAA GTGGCGCAAG CGTGACTCTG TCGAAAACTG 13260

FIG. 4A-13

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TCCTAATACC CCGCACCATC TCAATACCAC GCTAACCCCT TTGCAAGAAT ATGTGGTTGT 13320
GGGCCTGCGT TATCAATTGA AAATGCCATT AGACAGATTG CTCAAAGCAA CCCAAGAGTT 13380
TATCAATCCA AACGTGTCGC GCTCAGGTTT AGCAAGATGT TTGAAGCGTT ATGGCGTTTC 13440
ACGGGTGAGT GATATCCAAA GCCCACACGT ACCAATGCGC TACTTTAATC AAATTCCAGT 13500
CACTCAAGGC AGCGATGTGC AAACCTACAC CCTGCACTAT GAAACGCTGG CAAAAACCTT 13560
AGCCTTACCT AGTACCGATG GTGACAATGT GGTGCAAGTG GTGTCTCTCA CCATTCCACC 13620
AAAGTTAACC GAAGAAGCAC CCAGTTCAAT TTTGCTCGGC ATTGATCCTC ATAGCGACTG 13680
GATCTATCTC GACATATACC AAGATGGCAA TACACAAGCC ACGAATAGAT ATATGGCTTA 13740
TGTGCTAAAA CACGGGCCAT TCCATTTACG AAAGTTACTC GTGCGTAACT ATCACACCTT 13800
TTTACAGCGC TTTCCTGGAG CGACGCAAAA TCGCCGCCCC TCTAAAGATA TGCCTGAAAC 13860
AATCAACAAG ACGCCTGAAA CACAGGCACC CAGTGGAGAC TCATAATGAG CCAGACCTCT 13920
AAACCTACAA ACTCAGCAAC TGAGCAAGCA CAAGACTCAC AAGCTGACTC TCGTTTAAAT 13980
AAACGACTAA AAGATATGCC AATTGCTATT GTTGGCATGG CGAGTATTTT TGCAAACTCT 14040
CGCTATTTGA ATAAGTTTTG GGACTTAATC AGCGAAAAAA TTGATGCGAT TACTGAATTA 14100
CCATCAACTC ACTGGCAGCC TGAAGAATAT TACGACGCAG ATAAAACCGC AGCAGACAAA 14160
AGCTACTGTA AACGTGGTGG CTTTTTGCCA GATGTAGACT TCAACCCAAT GGAGTTTGGC 14220
CTGCCGCCAA ACATTTTGGA ACTGACCGAT TCATCGCAAC TATTATCACT CATCGTTGCT 14280
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FIG. 4A-14

```
AAAGAAGTGT TGGCTGATGC TAACTTACCT GAGAATTACG ACCGCGATAA AATTGGTATC 14340
ACCTTAGGTG TCGGCGGTGG TCAAAAAATT AGCCACAGCC TAACAGCGCG TCTGCAATAC 14400
CCAGTATTGA AGAAAGTATT CGCCAATAGC GGCATTAGTG ACACCGACAG CGAAATGCTT 14460
ATCAAGAAAT TCCAAGACCA ATATGTACAC TGGGAAGAAA ACTCGTTCCC AGGTTCACTT 14520
GGTAACGTTA TTGCGGGCCG TATCGCCAAC CGCTTCGATT TTGGCGGCAT GAACTGTGTG 14580
GTTGATGCTG CCTGTGCTGG ATCACTTGCT GCTATGCGTA TGGCGCTAAC AGAGCTAACT 14640
GAAGGTCGCT CTGAAATGAT GATCACCGGT GGTGTGTGTA CTGATAACTC ACCCTCTATG 14700
TATATGAGCT TTTCAAAAAC GCCCGCCTTT ACCACTAACG AAACCATTCA GCCATTTGAT 14760
ATCGACTCAA AAGGCATGAT GATTGGTGAA GGTATTGGCA TGGTGGCGCT AAAGCGTCTT 14820
GAAGATGCAG AGCGCGATGG CGACCGCATT TACTCTGTAA TTAAAGGTGT GGGTGCATCA 14880
TCTGACGGTA AGTTTAAATC AATCTATGCC CCTCGCCCAT CAGGCCAAGC TAAAGCACTT 14940
AACCGTGCCT ATGATGACGC AGGTTTTGCG CCGCATACCT TAGGTCTAAT TGAAGCTCAC 15000
GGAACAGGTA CTGCAGCAGG TGACGCGGCA GAGTTTGCCG GCCTTTGCTC AGTATTTGCT 15060
GAAGGCAACG ATACCAAGCA ACACATTGCG CTAGGTTCAG TTAAATCACA AATTGGTCAT 15120
ACTAAATCAA CTGCAGGTAC AGCAGGTTTA ATTAAAGCTG CTCTTGCTTT GCATCACAAG 15180
GTACTGCCGC CGACCATTAA CGTTAGTCAG CCAAGCCCTA AACTTGATAT CGAAAACTCA 15240
CCGTTTTATC TAAACACTGA GACTCGTCCA TGGTTACCAC GTGTTGATGG TACGCCGCGC 15300
```

FIG. 4A-15

CGCGCGGGTA TTAGCTCATT TGGTTTTGGT GGCACTAACT TCCATTTTGT ACTAGAAGAG 15360
TACAACCAAG AACACAGCCG TACTGATAGC GAAAAAGCTA AGTATCGTCA ACGCCAAGTG 15420
GCGCAAAGCT TCCTTGTTAG CGCAAGCGAT AAAGCATCGC TAATTAACGA GTTAAACGTA 15480
CTAGCAGCAT CTGCAAGCCA AGCTGAGTTT ATCCTCAAAG ATGCAGCAGC AAACTATGGC 15540
GTACGTGAGC TTGATAAAAA TGCACCACGG ATCGGTTTAG TTGCAAACAC AGCTGAAGAG 15600
TTAGCAGGCC TAATTAAGCA AGCACTTGCC AAACTAGCAG CTAGCGATGA TAACGCATGG 15660
CAGCTACCTG GTGGCACTAG CTACCGCGCC GCTGCAGTAG AAGGTAAAGT TGCCGCACTG 15720
TTTGCTGGCC AAGGTTCACA ATATCTCAAT ATGGGCCGTG ACCTTACTTG TTATTACCCA 15780
GAGATGCGTC AGCAATTTGT AACTGCAGAT AAAGTATTTG CCGCAAATGA TAAAACGCCG 15840
TTATCGCAAA CTCTGTATCC AAAGCCTGTA TTTAATAAAG ATGAATTAAA GGCTCAAGAA 15900
GCCATTTTGA CCAATACCGC CAATGCCCAA AGCGCAATTG GTGCGATTTC AATGGGTCAA 15960
TACGATTTGT TTACTGCGGC TGGCTTTAAT GCCGACATGG TTGCAGGCCA TAGCTTTGGT 16020
GAGCTAAGTG CACTGTGTGC TGCAGGTGTT ATTTCAGCTG ATGACTACTA CAAGCTGGCT 16080
TTTGCTCGTG GTGAGGCTAT GGCAACAAAA GCACCGGCTA AAGACGGCGT TGAAGCAGAT 16140
GCAGGAGCAA TGTTTGCAAT CATAACCAAG AGTGCTGCAG ACCTTGAAAC CGTTGAAGCC 16200
ACCATCGCTA AATTTGATGG GGTGAAAGTC GCTAACTATA ACGCGCCAAC GCAATCAGTA 16260
ATTGCAGGCC CAACAGCAAC TACCGCTGAT GCGGCTAAAG CGCTAACTGA GCTTGGTTAC 16320

FIG. 4A-16

```
AAAGCGATTA ACCTGCCAGT ATCAGGTGCA TTCCACACTG AACTTGTTGG TCACGCTCAA 16380
GCGCCATTTG CTAAAGCGAT TGACGCAGCC AAATTTACTA AAACAAGCCG AGCACTTTAC 16440
TCAAATGCAA CTGGCGGACT TTATGAAAGC ACTGCTGCAA AGATTAAAGC CTCGTTTAAG 16500
AAACATATGC TTCAATCAGT GCGCTTTACT AGCCAGCTAG AAGCCATGTA CAACGACGGC 16560
GCCCGTGTAT TTGTTGAATT TGGTCCAAAG AACATCTTAC AAAAATTAGT TCAAGGCACG 16620
CTTGTCAACA CTGAAAATGA AGTTTGCACT ATCTCTATCA ACCCTAATCC TAAAGTTGAT 16680
AGTGATCTGC AGCTTAAGCA AGCAGCAATG CAGCTAGCGG TTACTGGTGT GGTACTCAGT 16740
GAAATTGACC CATACCAAGC CGATATTGCC GCACCAGCGA AAAAGTCGCC AATGAGCATT 16800
TCGCTTAATG CTGCTAACCA TATCAGCAAA GCAACTCGCG CTAAGATGGC CAAGTCTTTA 16860
GAGACAGGTA TCGTCACCTC GCAAATAGAA CATGTTATTG AAGAAAAAAT CGTTGAAGTT 16920
GAGAAACTGG TTGAAGTCGA AAAGATCGTC GAAAAAGTGG TTGAAGTAGA GAAAGTTGTT 16980
GAGGTTGAAG CTCCTGTTAA TTCAGTGCAA GCCAATGCAA TTCAAACCCG TTCAGTTGTC 17040
GCTCCAGTAA TAGAGAACCA AGTCGTGTCT AAAAACAGTA AGCCAGCAGT CCAGAGCATT 17100
AGTGGTGATG CACTCAGCAA CTTTTTTGCT GCACAGCAGC AAACCGCACA GTTGCATCAG 17160
CAGTTCTTAG CTATTCCGCA GCAATATGGT GAGACGTTCA CTACGCTGAT GACCGAGCAA 17220
GCTAAACTGG CAAGTTCTGG TGTTGCAATT CCAGAGAGTC TGCAACGCTC AATGGAGCAA 17280
TTCCACCAAC TACAAGCGCA AACACTACAA AGCCACACCC AGTTCCTTGA GATGCAAGCG 17340
```

FIG. 4A-17

GGTAGCAACA TTGCAGCGTT AAACCTACTC AATAGCAGCC AAGCAACTTA CGCTCCAGCC 17400

ATTCACAATG AAGCGATTCA AAGCCAAGTG GTTCAAAGCC AAACTGCAGT CCAGCCAGTA 17460

ATTTCAACAC AAGTTAACCA TGTGTCAGAG CAGCCAACTC AAGCTCCAGC TCCAAAAGCG 17520

CAGCCAGCAC CTGTGACAAC TGCAGTTCAA ACTGCTCCGG CACAAGTTGT TCGTCAAGCC 17580

GCACCAGTTC AAGCCGCTAT TGAACCGATT AATACAAGTG TTGCGACTAC AACGCCTTCA 17640

GCCTTCAGCG CCGAAACAGC CCTGAGCGCA ACAAAAGTCC AAGCCACTAT GCTTGAAGTG 17700

GTTGCTGAGA AAACCGGTTA CCCAACTGAA ATGCTAGAGC TTGAAATGGA TATGGAAGCC 17760

GATTTAGGCA TCGATTCTAT CAAGCGTGTA GAAATTCTTG GCACAGTACA AGATGAGCTA 17820

CCGGGTCTAC CTGAGCTTAG CCCTGAAGAT CTAGCTGAGT GTCGAACGCT AGGCGAAATC 17880

GTTGACTATA TGGGCAGTAA ACTGCCGGCT GAAGGCTCTA TGAATTCTCA GCTGTCTACA 17940

GGTTCCGCAG CTGCGACTCC TGCAGCGAAT GGTCTTTCTG CGGAGAAAGT TCAAGCGACT 18000

ATGATGTCTG TGGTTGCCGA AAAGACTGGC TACCCAACTG AAATGCTAGA GCTTGAAATG 18060

GATATGGAAG CCGATTTAGG CATAGATTCT ATCAAGCGCG TTGAAATTCT TGGCACAGTA 18120

CAAGATGAGC TACCGGGTCT ACCTGAGCTT AGCCCTGAAG ATCTAGCTGA GTGTCGTACT 18180

CTAGGCGAAA TCGTTGACTA TATGAACTCT AAACTCGCTG ACGGCTCTAA GCTGCCGGCT 18240

GAAGGCTCTA TGAATTCTCA GCTGTCTACA AGTGCCGCAG CTGCGACTCC TGCAGCGAAT 18300

GGTCTCTCTG CGGAGAAAGT TCAAGCGACT ATGATGTCTG TGGTTGCCGA AAAGACTGGC 18360

FIG. 4A-18

```
TACCCAACTG AAATGCTAGA ACTTGAAATG GATATGGAAG CTGACCTTGG CATCGATTCA 18420
ATCAAGCGCG TTGAAATTCT TGGCACAGTA CAAGATGAGC TACCGGGTTT ACCTGAGCTA 18480
AATCCAGAAG ATTTGGCAGA GTGTCGTACT CTTGGCGAAA TCGTGACTTA TATGAACTCT 18540
AAACTCGCTG ACGGCTCTAA GCTGCCAGCT GAAGGCTCTA TGCACTATCA GCTGTCTACA 18600
AGTACCGCTG CTGCGACTCC TGTAGCGAAT GGTCTCTCTG CAGAAAAAGT TCAAGCGACC 18660
ATGATGTCTG TAGTTGCAGA TAAAACTGGC TACCCAACTG AAATGCTTGA ACTTGAAATG 18720
GATATGGAAG CCGATTTAGG TATCGATTCT ATCAAGCGCG TTGAAATTCT TGGCACAGTA 18780
CAAGATGAGC TACCGGGTTT ACCTGAGCTA AATCCAGAAG ATCTAGCAGA GTGTCGCACC 18840
CTAGGCGAAA TCGTTGACTA TATGGGCAGT AAACTGCCGG CTGAAGGCTC TGCTAATACA 18900
AGTGCCGCTG CGTCTCTTAA TGTTAGTGCC GTTGCGGCGC CTCAAGCTGC TGCGACTCCT 18960
GTATCGAACG GTCTCTCTGC AGAGAAAGTG CAAAGCACTA TGATGTCAGT AGTTGCAGAA 19020
AAGACCGGCT ACCCAACTGA AATGCTAGAA CTTGGCATGG ATATGGAAGC CGATTTAGGT 19080
ATCGACTCAA TTAAACGCGT TGAGATTCTT GGCACAGTAC AAGATGAGCT ACCGGGTCTA 19140
CCAGAGCTTA ATCCTGAAGA TTTAGCTGAG TGCCGTACGC TGGGCGAAAT CGTTGACTAT 19200
ATGAACTCTA AGCTGGCTGA CGGCTCTAAG CTTCCAGCTG AAGGCTCTGC TAATACAAGT 19260
GCCACTGCTG CGACTCCTGC AGTGAATGGT CTTTCTGCTG ACAAGGTACA GGCGACTATG 19320
ATGTCTGTAG TTGCTGAAAA GACCGGCTAC CCAACTGAAA TGCTAGAACT TGGCATGGAT 19380
```

FIG. 4A-19

ATGGAAGCAG ACCTTGGTAT TGATTCTATT AAGCGÇGTTG AAATTCTTGG CACAGTACAA 19440
GATGAGCTCC CAGGTTTACC TGAGCTTAAT CCTGAAGATC TCGCTGAGTG CCGCACGCTT 19500
GGCGAAATCG TTAGCTATAT GAACTCTCAA CTGGCTGATG GCTCTAAACT TTCTACAAGT 19560
GCGGCTGAAG GCTCTGCTGA TACAAGTGCT GCAAATGCTG CAAAGCCGGC AGCAATTTCG 19620
GCAGAACCAA GTGTTGAGCT TCCTCCTCAT AGCGAGGTAG CGCTAAAAAA GCTTAATGCG 19680
GCGAACAAGC TAGAAAATTG TTTCGCCGCA GACGCAAGTG TTGTGATTAA CGATGATGGT 19740
CACAACGCAG GCGTTTTAGC TGAGAAACTT ATTAAACAAG GCCTAAAAGT AGCCGTTGTG 19800
CGTTTACCGA AAGGTCAGCC TCAATCGCCA CTTTCAAGCG ATGTTGCTAG CTTTGAGCTT 19860
GCCTCAAGCC AAGAATCTGA GCTTGAAGCC AGTATCACTG CAGTTATCGC GCAGATTGAA 19920
ACTCAGGTTG GCGCTATTGG TGGCTTTATT CACTTGCAAC CAGAAGCGAA TACAGAAGAG 19980
CAAACGGCAG TAAACCTAGA TGCGCAAAGT TTTACTCACG TTAGCAATGC GTTCTTGTGG 20040
GCCAAATTAT TGCAACCAAA GCTCGTTGCT GGAGCAGATG CGCGTCGCTG TTTTGTAACA 20100
GTAAGCCGTA TCGACGGTGG CTTTGGTTAC CTAAATACTG ACGCCCTAAA AGATGCTGAG 20160
CTAAACCAAG CAGCATTAGC TGGTTTAACT AAAACCTTAA GCCATGAATG GCCACAAGTG 20220
TTCTGTCGCG CGCTAGATAT TGCAACAGAT GTTGATGCAA CCCATCTTGC TGATGCAATC 20280
ACCAGTGAAC TATTTGATAG CCAAGCTCAG CTACCTGAAG TGGGCTTAAG CTTAATTGAT 20340
GGCAAAGTTA ACCGCGTAAC TCTAGTTGCT GCTGAAGCTG CAGATAAAAC AGCAAAAGCA 20400

FIG. 4A-20

GAGCTTAACA GCACAGATAA AATCTTAGTG ACTGGTGGGG CAAAAGGGGT GACATTTGAA 20460
TGTGCACTGG CATTAGCATC TCGCAGCCAG TCTCACTTTA TCTTAGCTGG GCGCAGTGAA 20520
TTACAAGCTT TACCAAGCTG GGCTGAGGGT AAGCAAACTA GCGAGCTAAA ATCAGCTGCA 20580
ATCGCACATA TTATTTCTAC TGGTCAAAAG CCAACGCCTA AGCAAGTTGA AGCCGCTGTG 20640
TGGCCAGTGC AAAGCAGCAT TGAAATTAAT GCCGCCCTAG CCGCCTTTAA CAAAGTTGGC 20700
GCCTCAGCTG AATACGTCAG CATGGATGTT ACCGATAGCG CCGCAATCAC AGCAGCACTT 20760
AATGGTCGCT CAAATGAGAT CACCGGTCTT ATTCATGGCG CAGGTGTACT AGCCGACAAG 20820
CATATTCAAG ACAAGACTCT TGCTGAACTT GCTAAAGTTT ATGGCACTAA AGTCAACGGC 20880
CTAAAAGCGC TGCTCGCGGC ACTTGAGCCA AGCAAAATTA AATTACTTGC TATGTTCTCA 20940
TCTGCAGCAG GTTTTTACGG TAATATCGGC CAAAGCGATT ACGCGATGTC GAACGATATT 21000
CTTAACAAGG CAGCGCTGCA GTTCACCGCT CGCAACCCAC AAGCTAAAGT CATGAGCTTT 21060
AACTGGGGTC CTTGGGATGG CGGCATGGTT AACCCAGCGC TTAAAAAGAT GTTTACCGAG 21120
CGTGGTGTGT ACGTTATTCC ACTAAAAGCA GGTGCAGAGC TATTTGCCAC TCAGCTATTG 21180
GCTGAAACTG GCGTGCAGTT GCTCATTGGT ACGTCAATGC AAGGTGGCAG CGACACTAAA 21240
GCAACTGAGA CTGCTTCTGT AAAAAAGCTT AATGCGGGTG AGGTGCTAAG TGCATCGCAT 21300
CCGCGTGCTG GTGCACAAAA AACACCACTA CAAGCTGTCA CTGCAACGCG TCTGTTAACC 21360
CCAAGTGCCA TGGTCTTCAT TGAAGATCAC CGCATTGGCG GTAACAGTGT GTTGCCAACG 21420

FIG. 4A-21

GTATGCGCCA TCGACTGGAT GCGTGAAGCG GCAAGCGACA TGCTTGGCGC TCAAGTTAAG 21480
GTACTTGATT ACAAGCTATT AAAAGGCATT GTATTTGAGA CTGATGAGCC GCAAGAGTTA 21540
ACACTTGAGC TAACGCCAGA CGATTCAGAC GAAGCTACGC TACAAGCATT AATCAGCTGT 21600
AATGGGCGTC CGCAATACAA GGCGACGCTT ATCAGTGATA ATGCCGATAT TAAGCAACTT 21660
AACAAGCAGT TTGATTTAAG CGCTAAGGCG ATTACCACAG CAAAAGAGCT TTATAGCAAC 21720
GGCACCTTGT TCCACGGTCC GCGTCTACAA GGGATCCAAT CTGTAGTGCA GTTCGATGAT 21780
CAAGGCTTAA TTGCTAAAGT CGCTCTGCCT AAGGTTGAAC TTAGCGATTG TGGTGAGTTC 21840
TTGCCGCAAA CCCACATGGG TGGCAGTCAA CCTTTTGCTG AGGACTTGCT ATTACAAGCT 21900
ATGCTGGTTT GGGCTCGCCT TAAAACTGGC TCGGCAAGTT TGCCATCAAG CATTGGTGAG 21960
TTTACCTCAT ACCAACCAAT GGCCTTTGGT GAAACTGGTA CCATAGAGCT TGAAGTGATT 22020
AAGCACAACA AACGCTCACT TGAAGCGAAT GTTGCGCTAT ATCGTGACAA CGGCGAGTTA 22080
AGTGCCATGT TTAAGTCAGC TAAAATCACC ATTAGCAAAA GCTTAAATTC AGCATTTTTA 22140
CCTGCTGTCT TAGCAAACGA CAGTGAGGCG AATTAGTGGA ACAAACGCCT AAAGCTAGTG 22200
CGATGCCGCT GCGCATCGCA CTTATCTTAC TGCCAACACC GCAGTTTGAA GTTAACTCTG 22260
TCGACCAGTC AGTATTAGCC AGCTATCAAA CACTGCAGCC TGAGCTAAAT GCCCTGCTTA 22320
ATAGTGCGCC GACACCTGAA ATGCTCAGCA TCACTATCTC AGATGATAGC GATGCAAACA 22380
GCTTTGAGTC GCAGCTAAAT GCTGCGACCA ACGCAATTAA CAATGGCTAT ATCGTCAAGC 22440

FIG. 4A-22

TTGCTACGGC AACTCACGCT TTGTTAATGC TGCCTGCATT AAAAGCGGCG CAAATGCGGA 22500

TCCATCCTCA TGCGCAGCTT GCCGCTATGC AGCAAGCTAA ATCGACGCCA ATGAGTCAAG 22560

TATCTGGTGA GCTAAAGCTT GGCGCTAATG CGCTAAGCCT AGCTCAGACT AATGCGCTGT 22620

CTCATGCTTT AAGCCAAGCC AAGCGTAACT TAACTGATGT CAGCGTGAAT GAGTGTTTTG 22680

AGAACCTCAA AAGTGAACAG CAGTTCACAG AGGTTTATTC GCTTATTCAG CAACTTGCTA 22740

GCCGCACCCA TGTGAGAAAA GAGGTTAATC AAGGTGTGGA ACTTGGCCCT AAACAAGCCA 22800

AAAGCCACTA TTGGTTTAGC GAATTTCACC AAAACCGTGT TGCTGCCATC AACTTTATTA 22860

ATGGCCAACA AGCAACCAGC TATGTGCTTA CTCAAGGTTC AGGATTGTTA GCTGCGAAAT 22920

CAATGCTAAA CCAGCAAAGA TTAATGTTTA TCTTGCCGGG TAACAGTCAG CAACAAATAA 22980

CCGCATCAAT AACTCAGTTA ATGCAGCAAT TAGAGCGTTT GCAGGTAACT GAGGTTAATG 23040

AGCTTTCTCT AGAATGCCAA CTAGAGCTGC TCAGCATAAT GTATGACAAC TTAGTCAACG 23100

CAGACAAACT CACTACTCGC GATAGTAAGC CCGCTTATCA GGCTGTGATT CAAGCAAGCT 23160

CTGTTAGCGC TGCAAAGCAA GAGTTAAGCG CGCTTAACGA TGCACTCACA GCGCTGTTTG 23220

CTGAGCAAAC AAACGCCACA TCAACGAATA AAGGCTTAAT CCAATACAAA ACACCGGCGG 23280

GCAGTTACTT AACCCTAACA CCGCTTGGCA GCAACAATGA CAACGCCCAA GCGGGTCTTG 23340

CTTTTGTCTA TCCGGGTGTG GGAACGGTTT ACGCCGATAT GCTTAATGAG CTGCATCAGT 23400

ACTTCCCTGC GCTTTACGCC AAACTTGAGC GTGAAGGCGA TTTAAAGGCG ATGCTACAAG 23460

FIG. 4A-23

CAGAAGATAT CTATCATCTT GACCCTAAAC ATGCTGCCCA AATGAGCTTA GGTGACTTAG 23520
CCATTGCTGG CGTGGGGAGC AGCTACCTGT TAACTCAGCT GCTCACCGAT GAGTTTAATA 23580
TTAAGCCTAA TTTTGCATTA GGTTACTCAA TGGGTGAAGC ATCAATGTGG GCAAGCTTAG 23640
GCGTATGGCA AAACCCGCAT GCGCTGATCA GCAAAACCCA AACCGACCCG CTATTTACTT 23700
CTGCTATTTC CGGCAAATTG ACCGCGGTTA GACAAGCTTG GCAGCTTGAT GATACCGCAG 23760
CGGAAATCCA GTGGAATAGC TTTGTGGTTA GAAGTGAAGC AGCGCCGATT GAAGCCTTGC 23820
TAAAAGATTA CCCACACGCT TACCTCGCGA TTATTCAAGG GGATACCTGC GTAATCGCTG 23880
GCTGTGAAAT CCAATGTAAA GCGCTACTTG CAGCACTGGG TAAACGCGGT ATTGCAGCTA 23940
ATCGTGTAAC GGCGATGCAT ACGCAGCCTG CGATGCAAGA GCATCAAAAT GTGATGGATT 24000
TTTATCTGCA ACCGTTAAAA GCAGAGCTTC CTAGTGAAAT AAGCTTTATC AGCGCCGCTG 24060
ATTTAACTGC CAAGCAAACG GTGAGTGAGC AAGCACTTAG CAGCCAAGTC GTTGCTCAGT 24120
CTATTGCCGA CACCTTCTGC CAAACCTTGG ACTTTACCGC GCTAGTACAT CACGCCCAAC 24180
ATCAAGGCGC TAAGCTGTTT GTTGAAATTG GCGCGGATAG ACAAAACTGC ACCTTGATAG 24240
ACAAGATTGT TAAACAAGAT GGTGCCAGCA GTGTACAACA TCAACCTTGT TGCACAGTGC 24300
CTATGAACGC AAAAGGTAGC CAAGATATTA CCAGCGTGAT TAAAGCGCTT GGCCAATTAA 24360
TTAGCCATCA GGTGCCATTA TCGGTGCAAC CATTTATTGA TGGACTCAAG CGCGAGCTAA 24420
CACTTTGCCA ATTGACCAGC CAACAGCTGG CAGCACATGC AAATGTTGAC AGCAAGTTTG 24480

FIG. 4A-24

AGTCTAACCA AGACCATTTA CTTCAAGGGG AAGTCTAATG TCATTACCAG ACAATGCTTC 24540

TAACCACCTT TCTGCCAACC AGAAAGGCGC ATCTCAGGCA AGTAAAACCA GTAAGCAAAG 24600

CAAAATCGCC ATTGTCGGTT TAGCCACTCT GTATCCAGAC GCTAAAACCC CGCAAGAATT 24660

TTGGCAGAAT TTGCTGGATA AACGCGACTC TCGCAGCACC TTAACTAACG AAAAACTCGG 24720

CGCTAACAGC CAAGATTATC AAGGTGTGCA AGGCCAATCT GACCGTTTTT ATTGTAATAA 24780

AGGCGGCTAC ATTGAGAACT TCAGCTTTAA TGCTGCAGGC TACAAATTGC CGGAGCAAAG 24840

CTTAAATGGC TTGGACGACA GCTTCCTTTG GGCGCTCGAT ACTAGCCGTA ACGCACTAAT 24900

TGATGCTGGT ATTGATATCA ACGGCGCTGA TTTAAGCCGC GCAGGTGTAG TCATGGGCGC 24960

GCTGTCGTTC CCAACTACCC GCTCAAACGA TCTGTTTTTG CCAATTTATC ACAGCGCCGT 25020

TGAAAAAGCC CTGCAAGATA AACTAGGCGT AAAGGCATTT AAGCTAAGCC CAACTAATGC 25080

TCATACCGCT CGCGCGGCAA ATGAGAGCAG CCTAAATGCA GCCAATGGTG CCATTGCCCA 25140

TAACAGCTCA AAAGTGGTGG CCGATGCACT TGGCCTTGGC GGCGCACAAC TAAGCCTAGA 25200

TGCTGCCTGT GCTAGTTCGG TTTACTCATT AAAGCTTGCC TGCGATTACC TAAGCACTGG 25260

CAAAGCCGAT ATCATGCTAG CAGGCGCAGT ATCTGGCGCG GATCCTTTCT TTATTAATAT 25320

GGGATTCTCA ATCTTCCACG CCTACCCAGA CCATGGTATC TCAGTACCGT TTGATGCCAG 25380

CAGTAAAGGT TTGTTTGCTG GCGAAGGCGC TGGCGTATTA GTGCTTAAAC GTCTTGAAGA 25440

TGCCGAGCGC GACAATGACA AAATCTATGC GGTTGTTAGC GGCGTAGGTC TATCAAACGA 25500

FIG. 4A-25

CGGTAAAGGC CAGTTTGTAT TAAGCCCTAA TCCAAAAGGT CAGGTGAAGG CCTTTGAACG 25560
TGCTTATGCT GCCAGTGACA TTGAGCCAAA AGACATTGAA GTGATTGAGT GCCACGCAAC 25620
AGGCACACCG CTTGGCGATA AAATTGAGCT CACTTCAATG GAAACCTTCT TTGAAGACAA 25680
GCTGCAAGGC ACCGATGCAC CGTTAATTGG CTCAGCTAAG TCTAACTTAG GCCACCTATT 25740
AACTGCAGCG CATGCGGGGA TCATGAAGAT GATCTTCGCC ATGAAAGAAG GTTACCTGCC 25800
GCCAAGTATC AATATTAGTG ATGCTATCGC TTCGCCGAAA AAACTCTTCG GTAAACCAAC 25860
CCTGCCTAGC ATGGTTCAAG GCTGGCCAGA TAAGCCATCG AATAATCATT TTGGTGTAAG 25920
AACCCGTCAC GCAGGCGTAT CGGTATTTGG CTTTGGTGGC TGTAACGCCC ATCTGTTGCT 25980
TGAGTCATAC AACGGCAAAG GAACAGTAAA GGCAGAAGCC ACTCAAGTAC CGCGTCAAGC 26040
TGAGCCGCTA AAAGTGGTTG GCCTTGCCTC GCACTTTGGG CCTCTTAGCA GCATTAATGC 26100
ACTCAACAAT GCTGTGACCC AAGATGGGAA TGGCTTTATC GAACTGCCGA AAAAGCGCTG 26160
GAAAGGCCTT GAAAAGCACA GTGAACTGTT AGCTGAATTT GGCTTAGCAT CTGCGCCAAA 26220
AGGTGCTTAT GTTGATAACT TCGAGCTGGA CTTTTTACGC TTTAAACTGC CGCCAAACGA 26280
AGATGACCGT TTGATCTCAC AGCAGCTAAT GCTAATGCGA GTAACAGACG AAGCCATTCG 26340
TGATGCCAAG CTTGAGCCGG GGCAAAAAGT AGCTGTATTA GTGGCAATGG AAACTGAGCT 26400
TGAACTGCAT CAGTTCCGCG GCCGGGTTAA CTTGCATACT CAATTAGCGC AAAGTCTTGC 26460
CGCCATGGGC GTGAGTTTAT CAACGGATGA ATACCAAGCG CTTGAAGCCA TCGCCATGGA 26520

FIG. 4A-26

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CAGCGTGCTT GATGCTGCCA AGCTCAATCA GTACACCAGC TTTATTGGTA ATATTATGGC 26580
GTCACGCGTG GCGTCACTAT GGGACTTTAA TGGCCCAGCC TTCACTATTT CAGCAGCAGA 26640
GCAATCTGTG AGCCGCTGTA TCGATGTGGC GCAAAACCTC ATCATGGAGG ATAACCTAGA 26700
TGCGGTGGTG ATTGCAGCGG TCGATCTCTC TGGTAGCTTT GAGCAAGTCA TTCTTAAAAA 26760
TGCCATTGCA CCTGTAGCCA TTGAGCCAAA CCTCGAAGCA AGCCTTAATC CAACATCAGC 26820
AAGCTGGAAT GTCGGTGAAG GTGCTGGCGC GGTCGTGCTT GTTAAAAATG AAGCTACATC 26880
GGGCTGCTCA TACGGCCAAA TTGATGCACT TGGCTTTGCT AAAACTGCCG AAACAGCGTT 26940
GGCTACCGAC AAGCTACTGA GCCAAACTGC CACAGACTTT AATAAGGTTA AGTGATTGA 27000
AACTATGGCA GCGCCTGCTA GCCAAATTCA ATTAGCGCCA ATAGTTAGCT CTCAAGTGAC 27060
TCACACTGCT GCAGAGCAGC GTGTTGGTCA CTGCTTTGCT GCAGCGGGTA TGGCAAGCCT 27120
ATTACACGGC TTACTTAACT TAAATACTGT AGCCCAAACC AATAAAGCCA ATTGCGCGCT 27180
TATCAACAAT ATCAGTGAAA ACCAATTATC ACAGCTGTTG ATTAGCCAAA CAGCGAGCGA 27240
ACAACAAGCA TTAACCGCGC GTTTAAGCAA TGAGCTTAAA TCCGATGCTA AACACCAACT 27300
GGTTAAGCAA GTCACCTTAG GTGGCCGTGA TATCTACCAG CATATTGTTG ATACACCGCT 27360
TGCAAGCCTT GAAAGCATTA CTCAGAAATT GGCGCAAGCG ACAGCATCGA CAGTGGTCAA 27420
CCAAGTTAAA CCTATTAAGG CCGCTGGCTC AGTCGAAATG GCTAACTCAT TCGAAACGGA 27480
AAGCTCAGCA GAGCCACAAA TAACAATTGC AGCACAACAG ACTGCAAACA TTGGCGTCAC 27540
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FIG. 4A-27

CGCTCAGGCA ACCAAACGTG AATTAGGTAC CCCACCAATG ACAACAAATA CCATTGCTAA 27600

TACAGCAAAT AATTTAGACA AGACTCTTGA GACTGTTGCT GGCAATACTG TTGCTAGCAA 27660

GGTTGGCTCT GGCGACA1AG TCAATTTTCA ACAGAACCAA CAATTGGCTC AACAAGCTCA 27720

CCTCGCCTTT CTTGAAAGCC GCAGTGCGGG TATGAAGGTG GCTGATGCTT TATTGAAGCA 27780

ACAGCTAGCT CAAGTAACAG GCCAAACTAT CGATAATCAG GCCCTCGATA CTCAAGCCGT 27840

CGATACTCAA ACAAGCGAGA ATGTAGCGAT TGCCGCAGAA TCACCAGTTC AAGTTACAAC 27900

ACCTGTTCAA GTTACAACAC CTGTTCAAAT CAGTGTTGTG GAGTTAAAAC CAGATCACGC 27960

TAATGTGCCA CCATACACGC CGCCAGTGCC TGCATTAAAG CCGTGTATCT GGAACTATGC 28020

CGATTTAGTT GAGTACGCAG AAGGCGATAT CGCCAAGGTA TTTGGCAGTG ATTATGCCAT 28080

TATCGACAGC TACTCGCGCC GCGTACGTCT ACCGACCACT GACTACCTGT TGGTATCGCG 28140

CGTGACCAAA CTTGATGCGA CCATCAATCA ATTTAAGCCA TGCTCAATGA CCACTGAGTA 28200

CGACATCCCT GTTGATGCGC CGTACTTAGT AGACGGACAA ATCCCTTGGG CGGTAGCAGT 28260

AGAATCAGGC CAATGTGACT TGATGCTTAT TAGCTATCTC GGTATCGACT TTGAGAACAA 28320

AGGCGAGCGG GTTTATCGAC TACTCGATTG TACCCTCACC TTCCTAGGCG ACTTGCCACG 28380

TGGCGGAGAT ACCCTACGTT ACGACATTAA GATCAATAAC TATGCTCGCA ACGGCGACAC 28440

CCTGCTGTTC TTCTTCTCGT ATGAGTGTTT TGTTGGCGAC AAGATGATCC TCAAGATGGA 28500

TGGCGGCTGC GCTGGCTTCT TCACTGATGA AGAGCTTGCC GACGGTAAAG GCGTGATTCG 28560

FIG. 4A-28

CACAGAAGAA GAGATTAAAG CTCGCAGCCT AGTGCAAAAG CAACGCTTTA ATCCGTTACT 28620
AGATTGTCCT AAAACCCAAT TTAGTTATGG TGATATTCAT AAGCTATTAA CTGCTGATAT 28680
TGAGGGTTGT TTTGGCCCAA GCCACAGTGG CGTCCACCAG CCGTCACTTT GTTTCGCATC 28740
TGAAAAATTC TTGATGATTG AACAAGTCAG CAAGGTTGAT CGCACTGGCG GTACTTGGGG 28800
ACTTGGCTTA ATTGAGGGTC ATAAGCAGCT TGAAGCAGAC CACTGGTACT TCCCATGTCA 28860
TTTCAAGGGC GACCAAGTGA TGGCTGGCTC GCTAATGGCT GAAGGTTGTG GCCAGTTATT 28920
GCAGTTCTAT ATGCTGCACC TTGGTATGCA TACCCAAACT AAAAATGGTC GTTTCCAACC 28980
TCTTGAAAAC GCCTCACAGC AAGTACGCTG TCGCGGTCAA GTGCTGCCAC AATCAGGCGT 29040
GCTAACTTAC CGTATGGAAG TGACTGAAAT CGGTTTCAGT CCACGCCCAT ATGCTAAAGC 29100
TAACATCGAT ATCTTGCTTA ATGGCAAAGC GGTAGTGGAT TTCCAAAACC TAGGGGTGAT 29160
GATAAAAGAG GAAGATGAGT GTACTCGTTA TCCACTTTTG ACTGAATCAA CAACGGCTAG 29220
CACTGCACAA GTAAACGCTC AAACAAGTGC GAAAAAGGTA TACAAGCCAG CATCAGTCAA 29280
TGCGCCATTA ATGGCACAAA TTCCTGATCT GACTAAAGAG CCAAACAAGG GCGTTATTCC 29340
GATTTCCCAT GTTGAAGCAC CAATTACGCC AGACTACCCG AACCGTGTAC CTGATACAGT 29400
GCCATTCACG CCGTATCACA TGTTTGAGTT TGCTACAGGC AATATCGAAA ACTGTTTCGG 29460
GCCAGAGTTC TCAATCTATC GCGGCATGAT CCCACCACGT ACACCATGCG GTGACTTACA 29520
AGTGACCACA CGTGTGATTG AAGTTAACGG TAAGCGTGGC GACTTTAAAA AGCCATCATC 29580

FIG. 4A-29

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GTGTATCGCT GAATATGAAG TGCCTGCAGA TGCGTGGTAT TTCGATAAAA ACAGCCACGG 29640
CGCAGTGATG CCATATTCAA TTTTAATGGA GATCTCACTG CAACCTAACG GCTTTATCTC 29700
AGGTTACATG GGCACAACCC TAGGCTTCCC TGGCCTTGAG CTGTTCTTCC GTAACTTAGA 29760
CGGTAGCGGT GAGTTACTAC GTGAAGTAGA TTTACGTGGT AAAACCATCC GTAACGACTC 29820
ACGTTTATTA TCAACAGTGA TGGCCGGCAC TAACATCATC CAAAGCTTTA GCTTCGAGCT 29880
AAGCACTGAC GGTGAGCCTT TCTATCGCGG CACTGCGGTA TTTGGCTATT TTAAAGGTGA 29940
CGCACTTAAA GATCAGCTAG GCCTAGATAA CGGTAAAGTC ACTCAGCCAT GGCATGTAGC 30000
TAACGGCGTT GCTGCAAGCA CTAAGGTGAA CCTGCTTGAT AAGAGCTGCC GTCACTTTAA 30060
TGCGCCAGCT AACCAGCCAC ACTATCGTCT AGCCGGTGGT CAGCTGAACT TTATCGACAG 30120
TGTTGAAATT GTTGATAATG GCGGCACCGA AGGTTTAGGT TACTTGTATG CCGAGCGCAC 30180
CATTGACCCA AGTGATTGGT TCTTCCAGTT CCACTTCCAC CAAGATCCGG TTATGCCAGG 30240
CTCCTTAGGT GTTGAAGCAA TTATTGAAAC CATGCAAGCT TACGCTATTA GTAAAGACTT 30300
GGGCGCAGAT TTCAAAAATC CTAAGTTTGG TCAGATTTTA TCGAACATCA AGTGGAAGTA 30360
TCGCGGTCAA ATCAATCCGC TGAACAAGCA GATGTCTATG GATGTCAGCA TTACTTCAAT 30420
CAAAGATGAA GACGGTAAGA AAGTCATCAC AGGTAATGCC AGCTTGAGTA AAGATGGTCT 30480
GCGCATATAC GAGGTCTTCG ATATAGCTAT CAGCATCGAA GAATCTGTAT AAATCGGAGT 30540
GACTGTCTGG CTATTTTACT CAATTTCTGT GTCAAAAGTG CTCACCTATA TTCATAGGCT 30600
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FIG. 4A-30

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GCGCGCTTTT TTCTGGAAAT TGAGCAAAAG TATCTGCGTC CTAACTCGAT TTATAAGAAT 30660
GGTTTAATTG AAAAGAACAA CAGCTAAGAG CCGCAAGCTC AATATAAATA ATTAAGGGTC 30720
TTACAAATAA TGAATCCTAC AGCAACTAAC GAAATGCTTT CTCCGTGGCC ATGGGCTGTG 30780
ACAGAGTCAA ATATCAGTTT TGACGTGCAA GTGATGGAAC AACAACTTAA AGATTTTAGC 30840
CGGGCATGTT ACGTGGTCAA TCATGCCGAC CACGGCTTTG GTATTGCGCA AACTGCCGAT 30900
ATCGTGACTG AACAAGCGGC AAACAGCACA GATTTACCTG TTAGTGCTTT TACTCCTGCA 30960
TTAGGTACCG AAAGCCTAGG CGACAATAAT TTCCGCCGCG TTCACGGCGT TAAATACGCT 31020
TATTACGCAG GCGCTATGGC AAACGGTATT TCATCTGAAG AGCTAGTGAT TGCCCTAGGT 31080
CAAGCTGGCA TTTTGTGTGG TTCGTTTGGA GCAGCCGGTC TTATTCCAAG TCGCGTTGAA 31140
GCGGCAATTA ACCGTATTCA AGCAGCGCTG CCAAATGGCC CTTATATGTT TAACCTTATC 31200
CATAGTCCTA GCGAGCCAGC ATTAGAGCGT GGCAGCGTAG AGCTATTTTT AAAGCATAAG 31260
GTACGCACCG TTGAAGCATC AGCTTTCTTA GGTCTAACAC CACAAATCGT CTATTACCGT 31320
GCAGCAGGAT TGAGCCGAGA CGCACAAGGT AAAGTTGTGG TTGGTAACAA GGTTATCGCT 31380
AAAGTAAGTC GCACCGAAGT GGCTGAAAAG TTTATGATGC CAGCGCCCGC AAAAATGCTA 31440
CAAAAACTAG TTGATGACGG TTCAATTACC GCTGAGCAAA TGGAGCTGGC GCAACTTGTA 31500
CCTATGGCTG ACGACATCAC TGCAGAGGCC GATTCAGGTG GCCATACTGA TAACCGTCCA 31560
TTAGTAACAT TGCTGCCAAC CATTTTAGCG CTGAAAGAAG AAATTCAAGC TAAATACCAA 31620
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FIG. 4A-31

TACGACACTC CTATTCGTGT CGGTTGTGGT GGCGGTGTGG GTACGCCTGA TGCAGCGCTG 31680
GCAACGTTTA ACATGGGCGC GGCGTATATT GTTACCGGCT CTATCAACCA AGCTTGTGTT 31740
GAAGCGGGCG CAAGTGATCA CACTCGTAAA TTACTTGCCA CCACTGAAAT GGCCGATGTG 31800
ACTATGGCAC CAGCTGCAGA TATGTTCGAG ATGGGCGTAA AACTGCAGGT GGTTAAGCGC 31860
GGCACGCTAT TCCCAATGCG CGCTAACAAG CTATATGAGA TCTACACCCG TTACGATTCA 31920
ATCGAAGCGA TCCCATTAGA CGAGCGTGAA AAGCTTGAGA AACAAGTATT CCGCTCAAGC 31980
CTAGATGAAA TATGGGCAGG TACAGTGGCG CACTTTAACG AGCGCGACCC TAAGCAAATC 32040
GAACGCGCAG AGGGTAACCC TAAGCGTAAA ATGGCATTGA TTTTCCGTTG GTACTTAGGT 32100
CTTTCTAGTC GCTGGTCAAA CTCAGGCGAA GTGGGTCGTG AAATGGATTA TCAAATTTGG 32160
GCTGGCCCTG CTCTCGGTGC ATTTAACCAA TGGGCAAAAG GCAGTTACTT AGATAACTAT 32220
CAAGACCGAA ATGCCGTCGA TTTGGCAAAG CACTTAATGT ACGGCGCGGC TTACTTAAAT 32280
CGTATTAACT CGCTAACGGC TCAAGGCGTT AAAGTGCCAG CACAGTTACT TCGCTGGAAG 32340
CCAAACCAAA GAATGGCCTA ATACACTTAC AAAGCACCAG TCTAAAAAGC CACTAATCTT 32400
GATTAGTGGC TTTTTTTATT GTGGTCAATA TGAGGCTATT TAGCCTGTAA GCCTGAAAAT 32460
ATCAGCACTC TGACTTTACA AGCAAATTAT AATTAAGGCA GGGCTCTACT CATTTATACT 32520
GCTAGCAAAC AAGCAAGTTG CCCAGTAAAA CAACAAGGTA CCTGATTTAT ATCGTCATAA 32580
AAGTTGGCTA GAGATTCGTT ATTGATCTTT ACTGATTAGA GTCGCTCTGT TTGGAAAAAG 32640

FIG. 4A-32

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GTTTCTCGTT ATCATCAAAA TACACTCTCA AACCTTTAAT CAATTACAAC TTAGGCTTTC 32700
TGCGGGCATT TTTATCTTAT TTGCCACAGC TGTATTTGCC TTTAGGTTTT GGGTGCAACT 32760
ACCATTAATT GAGGCCTCAT TAGTTAAATT ATCTGAGCAA GAGCTCACCT CTTTAAATTA 32820
CGCTTTTCAG CAAATGAGAA AGCCACTACA AACCATTAAT TACGACTATG CGGTGTGGGA 32880
CAGAACCTAC AGCTATATGA AATCAAACTC AGCGAGCGCT AAAAGGTACT ATGAAAAACA 32940
TGAGTACCCA GATGATACGT TCAAGAGTTT AAAAGTCGAC GGAGTATTTA TATTCAACCG 33000
TACAAATCAG CCAGTTTTTA GTAAAGGTTT TAATCATAGA AATGATATAC CGCTGGTCTT 33060
TGAATTAACT GACTTTAAAC AACATCCACA AAACATCGCA TTATCTCCAC AAACCAAACA 33120
GGCACACCCA CCGGCAAGTA AGCCGTTAGA CTCCCCTGAT GATGTGCCTT CTACCCATGG 33180
GGTTATCGCC ACACGATACG GTCCAGCAAT TTATAGCTCT ACCAGCATTT TAAAATCTGA 33240
TCGTAGCGGC TCCCAACTTG GTTATTTAGT CTTCATTAGG TTAATTGATG AATGGTTCAT 33300
CGCTGAGCTA TCGCAATACA CTGCCGCAGG TGTTGAAATC GCTATGGCTG ATGCCGCAGA 33360
CGCACAATTA GCGAGATTAG GCGCAAACAC TAAGCTTAAT AAAGTAACCG CTACATCCGA 33420
ACGGTTAATA ACTAATGTCG ATGGTAAGCC TCTGTTGAAG TTAGTGCTTT ACCATACCAA 33480
TAACCAACCG CCGCCGATGC TAGATTACAG TATAATAATT CTATTAGTTG AGATGTCATT 33540
TTTACTGATC CTCGCTTATT TCCTTTACTC CTACTTCTTA GTCAGGCCAG TTAGAAAGCT 33600
GGCTTCAGAT ATTAAAAAAA TGGATAAAAG TCGTGAAATT AAAAAGCTAA GGTATCACTA 33660
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FIG. 4A-33

CCCTATTACT GAGCTAGTCA AAGTTGCGAC TCACTTCAAC GCCCTAATGG GGACGATTCA 33720

GGAACAAACT AAACAGCTTA ATGAACAAGT TTTTATTGAT AAATTAACCA ATATTCCCAA 33780

TCGTCGCGCT TTTGAGCAGC GACTTGAAAC CTATTGCCAA CTGCTAGCCC GGCAACAAAT 33840

TGGCTTTACT CTCATCATTG CCGATGTGGA TCATTTTAAA GAGTACAACG ATACTCTTGG 33900

GCACCTTGCT GGGGATGAAG CATTAATAAA AGTGGCACAA ACACTATCGC AACAGTTTTA 33960

CCGTGCAGAA GATATTTGTG CCCGTTTTGG TGGTGAAGAA TTTATTATGT TATTTCGAGA 34020

CATACCTGAT GAGCCCTTGC AGAGAAAGCT CGATGCGATG CTGCACTCTT TTGCAGAGCT 34080

CAACCTACCT CATCCAAACT CATCAACCGC TAATTACGTT ACTGTGAGCC TTGGGGTTTG 34140

CACAGTTGTT GCTGTTGATG ATTTTGAATT TAAAAGTGAG TCGCATATTA TTGGCAGTCA 34200

GGCTGCATTA ATCGCAGATA AGGCGCTTTA TCATGCTAAA GCCTGTGGTC GTAACCAGTT 34260

GTCAAAAACT ACTATTACTG TTGATGAGAT TGAGCAATTA GAAGCAAATA AAATCGGTCA 34320

TCAAGCCTAA ACTCGTTCGA GTACTTTCCC CTAAGTCAGA GCTATTTGCC ACTTCAAGAT 34380

GTGGCTACAA GGCTTACTCT TTCAAAACCT GCATCAATAG AACACAGCAA AATACAATAA 34440

TTTAAGTCAA TTTAGCCTAT TAAACAGAGT TAATGACAGC TCATGGTCGC AACTTATTAG 34500

CTATTTCTAG CAATATAAAA ACTTATCCAT TAGTAGTAAC CAATAAAAAA ACTAATATAT 34560

AAAACTATTT AATCATTATT TTACAGATGA TTAGCTACCA CCCACCTTAA GCTGGCTATA 34620

TTCGCACTAG TAAAAATAAA CATTAGATCG GGTTCAGATC AATTTACGAG TCTCGTATAA 34680

FIG. 4A-34

AATGTACAAT AATTCACTTA ATTTAATACT GCATATTTTT ACAAGTAGAG AGCGGTGATG 34740

AAACAAAATA CGAAAGGCTT TACATTAATT GAATTAGTCA TCGTGATTAT TATTCTCGGT 34800

ATACTTGCTG CTGTGGCACT GCCGAAATTC ATCAATGTTC AAGATGACGC TAGGATCTCT 34860

GCGATGAGCG GTCAGTTTTC ATCATTTGAA AGTGCCGTAA AACTATACCA TAGCGGTTGG 34920

TTAGCCAAAG GCTACAACAC TGCGGTTGAA AAGCTCTCAG GCTTTGGCCA AGGTAATGTT 34980

GCATCAAGTG ACACAGGTTT TCCGTACTCA ACATCAGGCA CGAGTACTGA TGTGCATAAA 35040

GCTTGTGGTG AACTATGGCA TGGCATTACC GATACAGACT TCACAATTGG TGCGGTTAGT 35100

GATGGCGATC TAATGACTGC AGATGTCGAT ATTGCTTACA CCTATCGTGG TGATATGTGT 35160

ATCTATCGCG ATCTGTATTT TATTCAGCGC TCATTACCTA CTAAGGTGAT GAACTACAAA 35220

TTTAAAACTG GTGAAATAGA AATTATTGAT GCTTTCTACA ACCCTGACGG CTCAACTGGT 35280

CAATTACCAT AAATTTGGCG CTTATCTAAG TTGTACTTGC TCTGACCGAC ACAAATAATG 35340

TCGTTTCTCA GCATATATCA AAATACACAG CAAAAATTTG GGGTTAGCTA TATAGCTAAC 35400

CCCAAATCAT ATCTAACTTT ACACTGCATC TAATTCCAAA CAGTATCCAG CCAAAAGCCT 35460

AAACTATTGT TGACTCAGCG CTAAAATATG CGATGCAACA AACAAGTCTT GGATCGCAAT 35520

ACCTGAGCTA TCAAAAATGG TCACCTCATC AGCACTTTGA CGTCCTGTTG CGGACTCGTT 35580

TATCACCTGA CCAATCTCAA TTATCGGCGT ATTTCTGCTA TGTTGAAACT CACCAATAAC 35640

AATAGATTGA GAAGCAAAGT CGCAAAACAA GCGAGCATGA CTATATAGGT CAGTTGGCAA 35700

FIG. 4A-35

CTCTTGCTTA CCCACTTTAT CAGCGCCCAT TGCAGAAATA TGCGTTCCTG CTTGTACCCA 35760

CTGCGCTTCA AATAAAGGCG CTTGAGCTGT GGTTGCTGTG ATAATAATAT CTGCTTGTTC 35820

ACAAGCAGCT TGTGCATCAC AAGCTTCGGC ATTAATGCCT TTTTCTAATA AACGCTTAAC 35880

CAAGTTTTCA GTTTTGCTAG CACTACGGCC AACTACCAAT ACCTTAGTTA ATGAACGAAC 35940

CTTGCTCACT GCTAGCACTT CATATTCAGC CTGATGACCG GTACCAAAAA CAGTTAATAC 36000

CGTAGCATCT TCTCTCGCGA GGTAACTCAC TGCTACTGCA TCGGCAGCAC CAGTGCGGTA 36060

AGCATTAACG GTAGTGGCAG CAATCACCGN CTGCAACATA CCGGTTAATG GATCGAGTAA 36120

AAATACGTTA GTGCCGTGGC ATGGTAAACC ATGTTTATGG TTATCAGGCC AATAGCTGCC 36180

TGTTTTCCAG CCGACAAGGT TTGGCGTTGA AGCCGACTTT AATGAGAACA TTTCATTAAG 36240

GTTCGCGCCC TGTGCATTAA CTACCGGGAA CAAGGTTGCT TTATCATCTA CGGCAGCGAC 36300

AAACGCTTCT TTAACAGCGA TATAAGCCAG CTCATGGGAG ATGAGCTTTG ATGTTTGCGC 36360

TTCAGTTAAA TAGATCATAT TACCACCCCT GCACTCGATT CCAGATCTCA TAGCCACCAT 36420

TATCACCATC AGTATCAAAT ACATGGTACT GAGCGTGCAT TGAAGCTGTT GCACAGGCGT 36480

GGTTCGGCAA AATATGTAGA CGACTACCTA CCGGGAACTG CGCTAAATCA ATAACGCCGC 36540

CATCAACTGC TTCAATAATG CCGTGCTCTT GATTAACAGT TATAACCTGT AGACCTGATA 36600

ACACGTGACC GCTGTCGTCA CACACTAAAC CATAACCACA ATCTTTTGGC TGCTCTGCAG 36660

TACCTCTATC ACCCGAAAGA GCCATCCAAC CCGCATCAAT GAAAATCCAG TTTTTATCAG 36720

FIG. 4A-36

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GATTATGACC AATAACACTG GTCACTACCG TTGCGGCAAT ATCAGTTAAC TGACACACGT 36780
TTAGCCCTGC CATGACTAAA TCGAAGAAGG TGTACACACC CGCTCTAACC TCGGTGATCC 36840
CATCAAGGTT TTGATAGCTT TGCGCTGTTG GTGTTGAACC AATACTAACG ATGTCACATT 36900
GCATACCCGC TGCGCGAATG CGTCAGCAGC TTGTACAGCC GCTGCAACTT CATTTTGCGC 36960
CGCATCAATT AATTGCTGTT TTTCAAAACA TTGATATGAC TCACCAGCGT GAGTNAGTAC 37020
GCCGTGAAAA CTCGCTGCGC CAGACGTTAG TATCTGAGCA ATTTCAATCA ACTTATCGGC 37080
TTCCGGTGGA ATACCACCAC GATGGCCATC ACAATCAATT TCAATTAATG CTGGTATTTG 37140
GCAGTCATAA GAACCACAGA AATGATTTAG CTGATGCGCT TGCTCAACAC TATCAAGTAA 37200
AACTCTTGCA TTAATACCTT GGTCCAACAT TTTAGCAATA CGCGGCAACT TACCATCGGC 37260
AATACCTACT GCATAAATAA TGTCTGTGTA ACCTTTAGAT GCTAAGGCCT CGGCCTCTTT 37320
TACCGTTGAT ACAGTGACTG GTGAGTTTTT AGTGGGTAAT AAAAACTCGG CTGCTTCAAG 37380
TGATCTTAAC GTTTTAAAAT GCGGTCTTAG GTTTGCACCT AATCCTTCAA TTTTTTGGCG 37440
TAGTTGACTG AGGTTATTAA TAAATACTGG CTTATTTACA TATAAAAACG GTGTATCAAT 37500
TGCTTGATAC TGACTTTGCT GAGTCGTGGA AAGTATTTGA GTAGATGGCA TCTTTAATAT 37560
CCTAGTTCAT CAATCAATCT AACAAGTTTG ATGCCTAGCC ACAGTGGCTT GTATTCATGA 37620
TGCTTTGGAA AATGCTTATA TTCAAAGTAT TTGAAAGACA TCAAACTTCT TGTTTAATGC 37680
TCAGTATCCA CCAGCACGCA TTTATTTTAT ATTAACTATT ATCAAGATAT AGATTAGGTT 37740
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FIG. 4A-37

CAAACCAAAT GATTAGTACT GAAGATCTAC GTTTTATCAG CGTAATCGCC AGTCATCGCA 37800

CCTTAGCTGA TGCCGCTAGA ACACTAAATA TCACGCCACC ATCAGTGACA TTAAGGTTGC 37860

AGCATATTGA AAAGAAACTA TCGATTAGCC TGATC 37895

FIG. 4A-38

6121

*

MKQTLMAISI MSLFSFNALA AQHEHDHITV DYEGKAATEH

TIAHNQAVAK TLNFADTRAF EQSSKNLVAK FDKATADILR

AEFAFISDEI PDSVNPSLYR QAQLNMVPNG YKVSDGIYQV

RGTDLSNLTL IRSDNGWIAY DVLLTKEAAK ASLQFALKNL

PKDGDPVVAM IYSHSHADHF GGARGVQEMF PDVKVYGSDN

ITKEIVDENV LAGNAMSRRA AYQYGATLGK HDHGIVDAAL

GKGLSKGEIT YVAPDYTLNS EGKWETLTID GLEMVFMDAS

GTEAESEMIT YIPSKKALWT AELTYQGMHN IYTLRGAKVR

DALKWSKDIN EMINAFGQDV EVLFASHSAP VWGNQAINDF

LRLQRDNYGL VHNQTLRLAN DGVGIQDIGD AIQDTIPESI

YKTWHTNGYH GTYSHNAKAV YNKYLGYFD MNPANLNPLP

TKQESAKFVE YMGGADAAIK RAKDDYAQGE YRFVATALNK

VVMAEPENDS ARQLLADTYE QLGYQAEGAG WRNIYLTGAQ

ELRVGIQAGA PKTASADVIS EMDMPTLFDF LAVKIDSQQA

AKHGLVKMNV ITPDTKDILY IELSNGNLSN AVVDKEQAAD

ANLMVNKADV NRILLGQVTL KALLASGDAK LTGDKTAFSK

IADSMVEFTP DFEIVPTPVK

*

8103

FIG. 4B

8186

*STKASARVVA KFNVEEAAIS IQQCQGISLA FRYSDDLHGL

LCHWNDAANM QQEKAEILGL GSKQPEANPK NSSSELLALG

IDQKLLVQRQ NLQHEVKHDA IADSIDVCHS LSKPANVGLF

TESLASFDFA FSKLSLALGL GKAKIYSEKL AWLDFFRDRQ

LAEPLALLAR KESESFYHSL ISHINTSNRC REIDVGFEIS

ASDTEEKSAQ SAGKNDATCI GVLLWDGSHS VNFHVGTQAF

QADSLRPKGK DGYEFRWENP RIESHQSLLA RLYGRVM

*9016

FIG. 4C

8186

*GCTAGTCTTA GCTGASRTHR YSAASRAGCT CGAACAACAG CTTTAAAATT
CACTTCTTCT GCTGCAATAC TTATTTGCTG ACACTGACCA ATACTCAGTG
CAAAACGATA ACTATCATCA AGATGGAAAR GVAVAAAYSH ASNVAGGAAA
ASRGNGNCYS GNGYSRAAHA RGTYRSRASA SHSCCCAGTA AACAATGCCA
ATTATCAGCA GCGTTCATTT GCTGTTCTTT AGCCTCAATC AAACCTAAAC
CAGACTTTTG TGGCTCAGCG TTAGGCTTAT TAGGYCYSHS TRASNASAAA
AASNMTGNGN GYSAAGGYGY SRYSGNRGAA ASNRYSASNS RAACTCGACT
CTAGTAAAGC AAGACCAATA TCTTGTTTTA ACAAAACCTG TCGCTGATTA
AGTTGATGCT CAACCTTGTG ATCCGCAATA GCATCGGAAA TSRSRGAAGY
ASGNYSVAGN ARGGNASNGN HSGVAYSHSA SAAAAASSRA TCAACACAAT
GGCTCAAGCT TTTAGGTGCA TTAACTCCAA GAAAAGTTTC GCTCAGTGCA
GAGAAGTCAA ACGCAAAAGA TTTTAGCGAT AATGCCAGCA SVACYSHSSR
SRYSRAAASN VAGYHTHRGS RAASRHASHA AHSRYSSRAA CCAAGTCCTT
TCGCTTTAAT GTAAGACTCC TTGAGCGCCC ACAAATCAAA AAAGCGGTCT
CGCTGCAAGG CCTCTGGTAA CGCTAACAAG GCTCGCTTTT GYGYYSAAYS
TYRSRGYSAA TRASHHARGA SARGGNAAGR AAAAARGYSG CTGATTCAGA
GAAATAATGA CTAAGAATAG AGTGGATATT GGTGCTGTTA CGGCAACGCT
CAATGTCGAC GCCAAACTCA ATACTAGCAG AGTCAGTTTC SRGSRHTYRH
SSRSRHSASN THRSRASNAR GCYSARGGAS VAGYHGSRAA SRASTHRGCT
CCTTGCTTGC CTGACTGGCG CCTTTATTAT CAGCAGTGCA AATGCCTACT
AATAGCCAAT CTCCACTATG ACTCACATTA AAGTGGACCC CGGTTTGAGY
SSRAAGNSRA AGYYSASNAS AATHRCYSGY VATRASGYSR HSSRVAASNH
HSVAGYTHRG NGCAAATTGC GCATCACTCA ATCTAGGCTT ACCTTTGTCG

FIG. 4D-1

CCATATTCAA AGCGCCATTC ATTGGGGCGT ATTTCACTAT GTTGTGACAA

TAAAGCGCGC AAAHGNAAAS SRARGRYSGY YSASGYTYRG HARGTRGASN

RARGGSRHSG NSRAAARGAA TAGCCTCTTA CCATTAAACC TTGAGTTTTA

GCTTCTTGTT TAATGTAGCG ATTAACCTTA ATTAACTCAT CTTCAGGCAG

CCATGACTTA ACCAACTCTY RGYARGVAMT GYGNTHRYSA AGGNYSTYRA

RGASNVAYSG ASGRTRSRYS VAGTGTAGTC TGGTTATCGC ACTCTTGTAT

TGTTAACGGA CAGAAGTATA AGGAAATCAA

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9157

FIG. 4D-2

9681

*MSMFLNSKLS RSVKLAISAG LTASLAMPVF AEETAAEEQI ERVAVTGSRI
AKAELTQPAP VVSLSAEELT KFGNQDLGSV LAELPAIGAT NTIIGNNNSN
SSAGVSSADL RRLGANRTLV LVNGKRYVAG QPGSAEVDLS TIPTSMISRV
EIVTGGASAI YGSDAVSGVI NVILKEDFEG FEFNARTSGS TESVGTQEHS
FDILGGANVA DGRGNVTFYA GYERTKEVMA TDIRQFDAWG TIKNEADGGE
DDGIPDRLRV PRVYSEMINA TGVINAFGGG IGRSTFDSNG NPIAQQERDG
TNSFAFGSFP NGCDTCFNTE AYENYIPGVE RINVGSSFNF DFTDNIQFYT
DFRYVKSDIQ QQFQPSFRFG NININVEDNA FLNDDLRQQM LDAGQTNASF
AKFFDELGNR SAENKRELFR YVGGFKGGFD ISETIFDYDL YYVYGETNNR
RKTLNDLIPD NFVAAVDSVI DPDTGLAACR SQVASAQGDD YTDPASVNGS
DCVAYNPFGM GQASAEARDW VSADVTREDK ITQQVIGGTL GTDSEELFEL
QGGAIAMVVG FEYREETSGS TTDEFTKAGF LTSAATPDSY GEYDVTEYFV
EVNIPVLKEL PFAHELSFDG AYRNADYSHA GKTEAWKAGM FYSPLEQLAL
RGTVGEAVRA PNIAEAFSPR SPGFGRVSDP CDADNINDDP DRVSNCAALG
IPPGFQANDN VSVDTLSGGN PDLKPETSTS FTGGLVWTPT FADNLSFTVD
YYDIQIEDAI LSVATQTVAD NCVDSTGGPD TDFCSQVDRN PTTYDIELVR
SGYLNAAALN TKGIEFQAAY SLDLESFNAP GELRFNLLGN QLLELERLEF
QNRPDEINDE KGEVGDPELQ FRLGIDYRLD DLSVSWNTRY IDSVVTYDVS
ENGGSPEDLY PGHIGSMTTH DLSATYYINE NFMINGGVRN LFDALPPGYT
NDALYDLVGR RAFLGIKVMM*

12590

FIG. 4E

13040

*MAKINSEHLD EATITSNKCT QTETEARHRN ATTTPEMRRF IQESDLSVSQ

LSKILNISEA TVRKWRKRDS VENCPNTPHH LNTTLTPLQE YVVVGLRYQL

KMPLDRLLKA TQEFINPNVS RSGLARCLKR YGVSRVSDIQ SPHVPMRYFN

QIPVTQGSDV QTYTLHYETL AKTLALPSTD GDNVVQVVSL TIPPKLTEEA

PSSILLGIDP HSDWIYLDIY QDGNTQATNR YMAYVLKHGP FHLRKLLVRN

YHTFLQRFPG ATQNRRPSKD MPETINKTPE TQAPSGDS*

13903

FIG. 4F

13906
*
MSQTSKPTNS ATEQAQDSQA DSRLNKRLKD MPIAIVGMAS IFANSRYLNK
FWDLISEKID AITELPSTHW QPEEYYDADK TAADKSYCKR GGFLPDVDFN
PMEFGLPPNI LELTDSSQLL SLIVAKEVLA DANLPENYDR DKIGITLGVG
GGQKISHSLT ARLQYPVLKK VFANSGISDT DSEMLIKKFQ DQYVHWEENS
FPGSLGNVIA GRIANRFDFG GMNCVVDAAC AGSLAAMRMA LTELTEGRSE
MMITGGVCTD NSPSMYMSFS KTPAFTTNET IQPFDIDSKG MMIGEGIGMV
ALKRLEDAER DGDRIYSVIK GVGASSDGKF KSIYAPRPSG QAKALNRAYD
DAGFAPHTLG LIEAHGTGTA AGDAAEFAGL CSVFAEGNDT KQHIALGSVK
SQIGHTKSTA GTAGLIKAAL ALHHKVLPPT INVSQPSPKL DIENSPFYLN
TETRPWLPRV DGTPRRAGIS SFGFGGTNFH FVLEEYNQEH SRTDSEKAKY
RQRQVAQSFL VSASDKASLI NELNVLAASA SQAEFILKDA AANYGVRELD
KNAPRIGLVA NTAEELAGLI KQALAKLAAS DDNAWQLPGG TSYRAAAVEG
KVAALFAGQG SQYLNMGRDL TCYYPEMRQQ FVTADKVFAA NDKTPLSQTL
YPKPVFNKDE LKAQEAILTN TANAQSAIGA ISMGQYDLFT AAGFNADMVA
GHSFGELSAL CAAGVISADD YYKLAFARGE AMATKAPAKD GVEADAGAMF
AIITKSAADL ETVEATIAKF DGVKVANYNA PTQSVIAGPT ATTADAAKAL
TELGYKAINL PVSGAFHTEL VGHAQAPFAK AIDAAKFTKT SRALYSNATG
GLYESTAAKI KASFKKHMLQ SVRFTSQLEA MYNDGARVFV EFGPKNILQK
LVQGTLVNTE NEVCTISINP NPKVDSDLQL KQAAMQLAVT GVVLSEIDPY
QADIAAPAKK SPMSISLNAA NHISKATRAK MAKSLETGIV TSQIEHVIEE
KIVEVEKLVE VEKIVEKVVE VEKVVEVEAP VNSVQANAIQ TRSVVAPVIE
NQVVSKNSKP AVQSISGDAL SNFFAAQQQT AQLHQQFLAI PQQYGETFTT
LMTEQAKLAS SGVAIPESLQ RSMEQFHQLQ AQTLQSHTQF LEMQAGSNIA
ALNLLNSSQA TYAPAIHNEA IQSQVVQSQT AVQPVISTQV NHVSEQPTQA
PAPKAQPAPV TTAVQTAPAQ VVRQAAPVQA AIEPINTSVA TTTPSAFSAE

FIG. 4G-1

TALSATKVQA TMLEVVAEKT GYPTEMLELE MDMEADLGID SIKRVEILGT

VQDELPGLPE LSPEDLAECR TLGEIVDYMG SKLPAEGSMN SQLSTGSAAA

TPAANGLSAE KVQATMMSVV AEKTGYPTEM LELEMDMEAD LGIDSIKRVE

ILGTVQDELP GLPELSPEDL AECRTLGEIV DYMNSKLADG SKLPAEGSMN

SQLSTSAAAA TPAANGLSAE KVQATMMSVV AEKTGYPTEM LELEMDMEAD

LGIDSIKRVE ILGTVQDELP GLPELNPEDL AECRTLGEIV TYMNSKLADG

SKLPAEGSMH YQLSTSTAAA TPVANGLSAE KVQATMMSVV ADKTGYPTEM

LELEMDMEAD LGIDSIKRVE ILGTVQDELP GLPELNPEDL AECRTLGEIV

DYMGSKLPAE GSANTSAAAS LNVSAVAAPQ AAATPVSNGL SAEKVQSTMM

SVVAEKTGYP TEMLELGMDM EADLGIDSIK RVEILGTVQD ELPGLPELNP

EDLAECRTLG EIVDYMNSKL ADGSKLPAEG SANTSATAAT PAVNGLSADK

VQATMMSVVA EKTGYPTEML ELGMDMEADL GIDSIKRVEI LGTVQDELPG

LPELNPEDLA ECRTLGEIVS YMNSQLADGS KLSTSAAEGS ADTSAANAAK

PAAISAEPSV ELPPHSEVAL KKLNAANKLE NCFAADASVV INDDGHNAGV

LAEKLIKQGL KVAVVRLPKG QPQSPLSSDV ASFELASSQE SELEASITAV

IAQIETQVGA IGGFIHLQPE ANTEEQTAVN LDAQSFTHVS NAFLWAKLLQ

PKLVAGADAR RCFVTVSRID GGFGYLNTDA LKDAELNQAA LAGLTKTLSH

EWPQVFCRAL DIATDVDATH LADAITSELF DSQAQLPEVG LSLIDGKVNR

VTLVAAEAAD KTAKAELNST DKILVTGGAK GVTFECALAL ASRSQSHFIL

AGRSELQALP SWAEGKQTSE LKSAAIAHII STGQKPTPKQ VEAAVWPVQS

SIEINAALAA FNKVGASAEY VSMDVTDSAA ITAALNGRSN EITGLIHGAG

VLADKHIQDK TLAELAKVYG TKVNGLKALL AALEPSKIKL LAMFSSAAGF

YGNIGQSDYA MSNDILNKAA LQFTARNPQA KVMSFNWGPW DGGMVNPALK

FIG. 4G-2

KMFTERGVYV IPLKAGAELF ATQLLAETGV QLLIGTSMQG GSDTKATETA

SVKKLNAGEV LSASHPRAGA QKTPLQAVTA TRLLTPSAMV FIEDHRIGGN

SVLPTVCAID WMREAASDML GAQVKVLDYK LLKGIVFETD EPQELTLELT

PDDSDEATLQ ALISCNGRPQ YKATLISDNA DIKQLNKQFD LSAKAITTAK

ELYSNGTLFH GPRLQGIQSV VQFDDQGLIA KVALPKVELS DCGEFLPQTH

MGGSQPFAED LLLQAMLVWA RLKTGSASLP SSIGEFTSYQ PMAFGETGTI

ELEVIKHNKR SLEANVALYR DNGELSAMFK SAKITISKSL NSAFLPAVLA

NDSEAN

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22173

FIG. 4G-3

22203

*
MPLRIALILL PTPQFEVNSV DQSVLASYQT LQPELNALLN SAPTPEMLSI

TISDDSDANS FESQLNAATN AINNGYIVKL ATATHALLML PALKAAQMRI

HPHAQLAAMQ QAKSTPMSQV SGELKLGANA LSLAQTNALS HALSQAKRNL

TDVSVNECFE NLKSEQQFTE VYSLIQQLAS RTHVRKEVNQ GVELGPKQAK

SHYWFSEFHQ NRVAAINFIN GQQATSYVLT QGSGLLAAKS MLNQQRLMFI

LPGNSQQQIT ASITQLMQQL ERLQVTEVNE LSLECQLELL SIMYDNLVNA

DKLTTRDSKP AYQAVIQASS VSAAKQELSA LNDALTALFA EQTNATSTNK

GLIQYKTPAG SYLTLTPLGS NNDNAQAGLA FVYPGVGTVY ADMLNELHQY

FPALYAKLER EGDLKAMLQA EDIYHLDPKH AAQMSLGDLA IAGVGSSYLL

TQLLTDEFNI KPNFALGYSM GEASMWASLG VWQNPHALIS KTQTDPLFTS

AISGKLTAVR QAWQLDDTAA EIQWNSFVVR SEAAPIEALL KDYPHAYLAI

IQGDTCVIAG CEIQCKALLA ALGKRGIAAN RVTAMHTQPA MQEHQNVMDF

YLQPLKAELP SEISFISAAD LTAKQTVSEQ ALSSQVVAQS IADTFCQTLD

FTALVHHAQH QGAKLFVEIG ADRQNCTLID KIVKQDGASS VQHQPCCTVP

MNAKGSQDIT SVIKALGQLI SHQVPLSVQP FIDGLKRELT LCQLTSQQLA

AHANVDSKFE SNQDHLLQGE V

*
24515

FIG. 4H

24518

*MSLPDNASNH LSANQKGASQ ASKTSKQSKI AIVGLATLYP DAKTPQEFWQ
NLLDKRDSRS TLTNEKLGAN SQDYQGVQGQ SDRFYCNKGG YIENFSFNAA
GYKLPEQSLN GLDDSFLWAL DTSRNALIDA GIDINGADLS RAGVVMGALS
FPTTRSNDLF LPIYHSAVEK ALQDKLGVKA FKLSPTNAHT ARAANESSLN
AANGAIAHNS SKVVADALGL GGAQLSLDAA CASSVYSLKL ACDYLSTGKA
DIMLAGAVSG ADPFFINMGF SIFHAYPDHG ISVPFDASSK GLFAGEGAGV
LVLKRLEDAE RDNDKIYAVV SGVGLSNDGK GQFVLSPNPK GQVKAFERAY
AASDIEPKDI EVIECHATGT PLGDKIELTS METFFEDKLQ GTDAPLIGSA
KSNLGHLLTA AHAGIMKMIF AMKEGYLPPS INISDAIASP KKLFGKPTLP
SMVQGWPDKP SNNHFGVRTR HAGVSVFGFG GCNAHLLLES YNGKGTVKAE
ATQVPRQAEP LKVVGLASHF GPLSSINALN NAVTQDGNGF IELPKKRWKG
LEKHSELLAE FGLASAPKGA YVDNFELDFL RFKLPPNEDD RLISQQLMLM
RVTDEAIRDA KLEPGQKVAV LVAMETELEL HQFRGRVNLH TQLAQSLAAM
GVSLSTDEYQ ALEAIAMDSV LDAAKLNQYT SFIGNIMASR VASLWDFNGP
AFTISAAEQS VSRCIDVAQN LIMEDNLDAV VIAAVDLSGS FEQVILKNAI
APVAIEPNLE ASLNPTSASW NVGEGAGAVV LVKNEATSGC SYGQIDALGF
AKTAETALAT DKLLSQTATD FNKVKVIETM AAPASQIQLA PIVSSQVTHT
AAEQRVGHCF AAAGMASLLH GLLNLNTVAQ TNKANCALIN NISENQLSQL
LISQTASEQQ ALTARLSNEL KSDAKHQLVK QVTLGGRDIY QHIVDTPLAS
LESITQKLAQ ATASTVVNQV KPIKAAGSVE MANSFETESS AEPQITIAAQ
QTANIGVTAQ ATKRELGTPP MTTNTIANTA NNLDKTLETV AGNTVASKVG
SGDIVNFQQN QQLAQQAHLA FLESRSAGMK VADALLKQQL AQVTGQTIDN
QALDTQAVDT QTSENVAIAA ESPVQVTTPV QVTTPVQISV VELKPDHANV
PPYTPPVPAL KPCIWNYADL VEYAEGDIAK VFGSDYAIID SYSRRVRLPT
TDYLLVSRVT KLDATINQFK PCSMTTEYDI PVDAPYLVDG QIPWAVAVES
GQCDLMLISY LGIDFENKGE RVYRLLDCTL TFLGDLPRGG DTLRYDIKIN
NYARNGDTLL FFFSYECFVG DKMILKMDGG CAGFFTDEEL ADGKGVIRTE

FIG. 4I-1

EEIKARSLVQ KQRFNPLLDC PKTQFSYGDI HKLLTADIEG CFGPSHSGVH
QPSLCFASEK FLMIEQVSKV DRTGGTWGLG LIEGHKQLEA DHWYFPCHFK
GDQVMAGSLM AEGCGQLLQF YMLHLGMHTQ TKNGRFQPLE NASQQVRCRG
QVLPQSGVLT YRMEVTEIGF SPRPYAKANI DILLNGKAVV DFQNLGVMIK
EEDECTRYPL LTESTTASTA QVNAQTSAKK VYKPASVNAP LMAQIPDLTK
EPNKGVIPIS HVEAPITPDY PNRVPDTVPF TPYHMFEFAT GNIENCFGPE
FSIYRGMIPP RTPCGDLQVT TRVIEVNGKR GDFKKPSSCI AEYEVPADAW
YFDKNSHGAV MPYSILMEIS LQPNGFISGY MGTTLGFPGL ELFFRNLDGS
GELLREVDLR GKTIRNDSRL LSTVMAGTNI IQSFSFELST DGEPFYRGTA
VFGYFKGDAL KDQLGLDNGK VTQPWHVANG VAASTKVNLL DKSCRHFNAP
ANQPHYRLAG GQLNFIDSVE IVDNGGTEGL GYLYAERTID PSDWFFQFHF
HQDPVMPGSL GVEAIIETMQ AYAISKDLGA DFKNPKFGQI LSNIKWKYRG
QINPLNKQMS MDVSITSIKD EDGKKVITGN ASLSKDGLRI YEVFDIAISI
EESV
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30529

FIG. 4I-2

30730

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MNPTATNEML SPWPWAVTES NISFDVQVME QQLKDFSRAC
YVVNHADHGF GIAQTADIVT EQAANSTDLP VSAFTPALGT
ESLGDNNFRR VHGVKYAYYA GAMANGISSE ELVIALGQAG
ILCGSFGAAG LIPSRVEAAI NRIQAALPNG PYMFNLIHSP
SEPALERGSV ELFLKHKVRT VEASAFLGLT PQIVYYRAAG
LSRDAQGKVV VGNKVIAKVS RTEVAEKFMM PAPAKMLQKL
VDDGSITAEQ MELAQLVPMA DDITAEADSG GHTDNRPLVT
LLPTILALKE EIQAKYQYDT PIRVGCGGGV GTPDAALATF
NMGAAYIVTG SINQACVEAG ASDHTRKLLA TTEMADVTMA
PAADMFEMGV KLQVVKRGTL FPMRANKLYE IYTRYDSIEA
IPLDEREKLE KQVFRSSLDE IWAGTVAHFN ERDPKQIERA
EGNPKRKMAL IFRWYLGLSS RWSNSGEVGR EMDYQIWAGP
ALGAFNQWAK GSYLDNYQDR NAVDLAKHLM YGAAYLNRIN
SLTAQGVKVP AQLLRWKPNQ RMA

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32358

FIG. 4J

32834
*
MRKPLQTINY DYAVWDRTYS YMKSNSASAK RYYEKHEYPD
DTFKSLKVDG VFIFNRTNQP VFSKGFNHRN DIPLVFELTD
FKQHPQNIAL SPQTKQAHPP ASKPLDSPDD VPSTHGVIAT
RYGPAIYYSS TSILKSDRSG SQLGYLVFIR LIDEWFIAEL
SQYTAAGVEI AMADAADAQL ARLGANTKLN KVTATSERLI
TNVDGKPLLK LVLYHTNNQP PPMLDYSIII LLVEMSFLLI
LAYFLYSYFL VRPVRKLASD IKKMDKSREI KKLRYHYPIT
ELVKVATHFN ALMGTIQEQT KQLNEQVFID KLTNIPNRRA
FEQRLETYCQ LLARQQIGFT LIIADVDHFK EYNDTLGHLA
GDEALIKVAQ TLSQQFYRAE DICARFGGEE FIMLFRDIPD
EPLQRKLDAM LHSFAELNLP HPNSSTANYV TVSLGVCTVV
AVDDFEFKSE SHIIGSQAAL IADKALYHAK ACGRNQALSK
TTITVDEIEQ LEANKIGHQ
*
34327

FIG. 4K

1

ÄATAGATCGACTCGCAAAAGTTGCTTAAGATAGTGTCAATATAGCTTCTTATTTGTA

AATATTGTTTTTTATGTGTAAACATGTTTAGTGTGTGTAAATGCTGTTAATTATCCT

TTTGGGATTGTAATAGCTGATGTTGCTGGCTAATGAGTACTTTTAGTTCGGCAATAT

CTTGCTTTAAATCGCTAACTTCAGTTTTTAATTCACCCACACTTGTTGTATTTTTAA

GGCTCTCTTCCCCACCATCGACAAACCAGGATGATATGAAACCGGTAAACGTACCAA

AGAGACCGACACCTGCAGTCATGAGTAATGCCGCAATGATACGTCCGCCAGTGGTGA

CGGGGTAGTAGTCACCGTAACCAACAGTCGTTATTGTCACAAATGACCACCAAAGTG

CGTCGATGCCGTTATTGATGTTACTGCCTACTTGATCCTGTTCTAACAATAAAATAC

CGATAGCACCAAAGGTGACAAGGATGAAGGATATCGCAGATACCAGCGAAAAGGTGG

CTTTAAACCGATGTTCAAAAATCATTTTTAAGATAATTTTTGATGAGCGTATATTCT

GAATAGATCTTAATACTCTAGCGATACGAATTATGCGAATAAACTGCAGTTGCTCGA

CCATCGGAATACTCGACAGTAGGTCAATCCAACCCCATTTCATAAACTGAAATTTAT

TCTCAGCTTGGTGAAAGCGAATTACAAAGTCAGTGAAAAAGAATAAGCAAATCGTAT

TATCTACGCTCGTTAATATTTCAGTGACGTTACTTGAAAAGGTAAAAATAAGTTGCA

GTAGTGATGATACGACCACATGAAGTGATAAAATAAGCATGAAAATCTGAAATGGAT

TTACATCACTGTTGTTTTTGGTGCCACTTTTAAGGTTCGTTTTCACAATCTGCTGCC

TCGGTTCATTGATTTTGTTAATATAAACCTTAGTCAGTAGCAAGACAAAATATATTT

ACATCAATGTCATCGTATTATTCAACCGCGCGTCGTGTATTCAGACCAAGATCGTTG

TATATGTTAGTCATGTAGCGATGAGATTATCATGCGACAGGAGAGAATTATGTTTGT

TATTATTTTTTACGTACCTAAAGTTAATGTTGAAGAAGTAAAACAGGCGTTATTTAA

CGTCGGAGCTGGCACCATCGGTGATTATGATAGTTGTGCTTGGCAATGTTTGGGGAC

TGGGCAGTTCCAACCTTTACTTGGTAGCCAGCCACATATTGGTAAGCTAAATGAGGT

TGAATTCGTTGATGAGTTTAGAGTAGAAATGGTTTGTCGAGCAGAAAATGTAAGGGC

AGCAATAAATGCACTTATTGCTGCGCACCCTTATGAAGAACCTGCTTATCATATTCT

GCAAACATTGAATCTTGATGAGTTACCTTAAGTTAGATGCACTGCACTTAATTGGTT

CGCTGTGCTAGGTTAGCAATTAGCAATTTTGACCATGTTAGCGATAGTTTTGGCACA

FIG. 5-1

AGTGATCGATATTAAACTATCCGATTCAGATCCCATTTTTACTGCTGAATTAGGTTT
CATTACACTTGTTCTAGTGGTTTTTCCCGACAGGTGTAACTCTGTTACTTGCGTAAG
GTTGATAATCTCTACCGCATTGGCAGGAGTTACACCTGCACCAGGCATAATACTAAT
TCTACCATCTGCTTGGTTAACTAACGTTTGGATTAAGGCGCAGCCTTCTAGCGCTTG
AGCTTGTTGACCAGAGGTTAAAATACGCTCACAACCAGCAGTGATCAAGGTCTCCAA
GGCTTGTTGTGGATCATTACACAAGTCGAAAGCGCGGTGGAAGGTTACGCCGAGATC
ACGTGATGCCACCATTAAGCGTTTTAAAGCTGGCTCGTCAATATTACCATCTGCTGT
TAACGCGCCAATAACGACCCCTTGGACACCGAGTAACTTCATGAATTTGATGTCGGA
AACCATAATATCAACTTCTTGTTCGCTATATACAAAATCACCGGCGCGAGGGCGAAT
AATGGCATAAATGGGGATCGTTGCTAGATCAATAGACTTTTGTACAAAACCTGCGTT
GGCGGTCAAGCCACCTAATGCTAATGCCGAGCACAACTCAATACGATCGGCGCCAGA
TGCTTGAGCCGTCAGCAGTGATTCTATATTATCGACACATACTTCTATTGTCATTGT
CATATACTTCTCTTTAAAAAGTTTATTAAAAATAATAAAGCCAGCATAAGTCGTTTT
ATACAATATGAAAGGGGAAAAGGCGACTTAGCTCGCCTAGATCAATTATTATGGCAG
AATACTGCCGTATTGTGATTAGAAAGACAGTTTTTTAAGCTCAATAGCCGTTATCGC
GTTGTTATCTACCATCGTGTAACTTTTCTGGCCTGGGTGCTTTATTAACACTGTTTC
AGTGGCTGGATTAGGGTGAAATGATTCTTTTTTCAAATCTGTTTTTTTTGTATTTGAA
CGTACCTGTAATGTCTTGCTGCTCACGAAGACGTACAAATATTGGTTGCGCATAGCT
TGGTAGTGCCGCATTGACATGTTGATAGAATTCAGACGCTGAAAATTCATGAATAGG
GCAATTCAAAGTCAGCGCGACCATGCCTGCTCGGCCATCGTGATGTGGGAGCTTGAC
ACCATAAGCCACACTTTGCTCAATTTGCACAAAATCGTTAACTTGAGCTTCTACTTG
CGTCGTGGCGACATTTTCACCTTTCCAGCGGAATGTATCACCTAATCTATCCACAAA
GGAAATATGGCGATAACCTTGGTAATGAACGAGATCGCCGGTATTAAAATAACAGTC
ACCGTCTTTTAATACTGACTTAAATAGCTTTTTATTACTTTCGTTGTCATCGGTATA
ACCATCAAATGGTGAACGTTTAGTTATCTTTGTTAGCAGTAGCCCTGTTTCTCCCGT

FIG. 5-2

TTTTACTTTGGTCATTTTCCCTTTCGCATTATACACAGGTTTGTCATTGTCAATATC

ATATTGTATGACGGTAAAAGCAAGTGGAGTAACCCCCGCTGTATGCGGTAAGTTCAG

CGCATTGGAGAACACAAGATTACACTCACTGGCGCCATAGAATTCATTAATATGCTC

GATCCCAAAACGTTGTTGGAAATGATCCCAAATTTCGGGGCGTAATCCATTACCTAT

GATTTTCTTTATATTATGCTGTTTGTCTTTATTGCTAGGCGGTACATTTAATAAATA

ACGGCAGAGCTCGCCGATGTAAGTAAACGCAGTGGCATTATGAGCACGAACTTCATC

CCAAAAGCGACTTGAACTGAATTTTTCAGAAAGTGCGAGGGTTGCTGCGCTACCAAA

CACGGCGCTTAATGACACTGTCAGTGCATTGTTATGGTATAGGGGGAGTGATAAATA

CAATACATCATCAGCTGTTAAGCGTAATGATGCCATCCCCATGCCTGCCATGGATTT

AAACCAACGGTGATGGCTCATTCTTGCTGCTTTTGGCAGTCCAGTTTTTCCCGAGGT

AAAGATATAAAACGCGCAATGCTTAAGCTGTATTTGTGCTGTTGATTCAGGGTTCAA

TACTGAATATCCTGCGACTAGTGTAGATATGTTTTTATAACCATCACTCATGTCTGG

CGTTTCTAAAGCGGGTACGTAAAAGACATTCTGTTGTAATGTCGATGACAAATTGGT

TTCAATATTATTAATGGCGGATGTGTATAGTTCATCTGCGATGAGTAATTTGGTATC

GACCACGCTAAGACTATGTTCGAGGATTGAATCCCGTTGTGTCGTATTTATCATACA

AGCAATCGCGCCAAGCTTGACAACTGCGAGGGCAATAATGATGGTTTCAGGCCTGTT

ATCGAGCATGATGGCGACTTTATCATTTTTACCAATGCCGTATTCATGAAGGAAATG

GGCATATTGATTTGCTTGCTTATTCAATGAATCGTAACTATAACGCTGGTCTTTAAA

TTGTATTGCGATCAAGTCAGAGTTATTGACAGCTTGCTGCTCTAGTAATAAACCAAT

AGACATAAAACGTTCGGGCTTTGCTTGTTGTAAGTGCCATAAGCCTTTGATGATTGG

CTTTGGGGTTTTTAATAGATTGATGGTACTTTTCAGGAATTGTTTGCCGGTTATAAC

AGTCATAAGCTAATTCTTTTTATCAAGAAGAGGGGTTATGACACCAAATAAATGGGT

CACGCGTTGGTTTAATTTGGTTAGACTAAATGTGTTGTTTTGCTGTGATAATGCGAC

GTTCAAACAAACTTGAGAAGGTAAAAAAATAGCATTTTTAAATTGAACATCAATACT

AATGTGTTGAATATCAATCAAGTTTTCTAACTGTGCGAGCACGCGTGCTTTAGCAAA

FIG. 5-3

CATGCCATGTGCTATTGCTGTTTTAAACCCCATTAGTTTCGCTGGGATAAAATGTAA

ATGGATTGGATTTGTGTCTTTGGAGATATAAGCATATTTATATACGTCAAAAGGACT

AAATTTAAACAATGAAATCGGCTCGTAAGCATAATTCGCTGGCGTATTTACTATTTT

CTCACCGCTGGAACGTTGAGATCGTTGGCACGTTTTTCGCTGTTTCGTTTTCTGTAA

GAATGTCGATGTACACTCCCACGCAAATTGTCCATCTACAAACACATCAATATGAGT

ATCAATGAAACGTCCTGTATCCGTTATGTACTCCTTAATTACACGACATGTGCTCGT

CAATATCGCGTTTAATGCTATCGGTTGATGTTGTGTTATGCGATTTCGATAATGGAC

TAGTCCTAATATAGATATCGGAAATTGTGTTGATGTCATGAGTTTCATCAATAATGG

AAAGATCATCACAAATGGATAAGTAACCGGTACATAGTTTGTGTTATTAAACCCACA

GCATTTAATATATTGCTTTAAATTTCGCTGATCTATTTTTTGTCCACTGATACTAAA

TTGCTCAGTACACACTTGTGTCGACCAAGTGTTCATCAGTGTTTTAACAATTGTATT

GACCACTGCTTTCACATATAAAAGCGAGATAATCGGTTGCTTTGTTAACAGTGTGAT

CTGGTTAGCGTGCATTGAAATAATTCATATAAGAGTATGTAGCATTTATGTTAATAT

TTTGTTTTGGAAGTTGAATTGGCGAATCCGTAATCGGTTTATGGCAGTTCGGTCAAA

TACTTCAGGTAAACTCGTTACTCATACCATTGATAGTGTTAAAGTGATTGACTGAAT

AAAGAATAGAGCTAAAAGTGGAAAAATTATGCAAGATGCGGGTATGTTATTACGCAT

TGCTTATGAGGCAATGAAAGAGTTAGAGGTTGATGTCATTGAAGTACTTTCTCGTTG

TAACATAAGTGAAGAAGTACTGAATGATAAGGATCTTCGCACACCTAATCATGCACA

AACACATTTTTGGCAAGTATTAGAAGACATATCACAAGATCCTAACATCGGCATTTC

ACTTGGTGAGAGAATGCCAGTGTTCACGGGGCAGGTATTACAGTATCTTTTTCTCAG

TAGTCCTACATTTGGTACTGGCTGGGAACGCGCAACAAAATACTTTCGATTAATCAG

TGATGCGGCGAGTGTTTCTATCAAGATGGAAGGCTGTGAAGCGCGATTATCTGTGAA

CTTAGATGGTTTAGCGGAAGATGCGAATCGTCATTTGAATGATTGCCTAGTGATCGG

TGCATTTAAATTTTGTTTATATGTGACAGAAGGCGAATTTAAAGTAAGCAAAATAGC

CTTTGCTCATGCTCGCCCGAAAGATATTACTGCCTATACCAATGTATTTACATGTCC

FIG. 5-4

GATTGAGTTTGCTGCCGAAGATAATTATATTTATTTCGATGCTGATTTACTCGAACG

TCCTTCTTCGCATGCGGAGCCTGAGCTATTCGCCTTACACGATCAGCTTGCAAGCCG

TAAAATAGCCAAGTTAGAACTGCAAGATTTAGTGGATAAAGTACGTAAGGTTATTGC

ACAACAACTTGAGTCTGGTGTGGTGACTTTAGAAAGTATCGCCACTGAACTTGACAT

GAAACCACGTATGCTAAGAGCGAAGTTAGCTGACATTGATTATAACTTTAATCAAAT

ACTCGCTGATTTTCGTTGCGAGTTATCAAAAAAACTGTTGGCGAATACGGACGAGTC

TATTGATCAGATTGTCTATCTCACTGGTTTTTCTGAACCAAGTACTTTTTATCGTGC

CTTTAAGCGCTGGGTTAAAATGACGCCAATTGAATATCGCCGTAGCAAACTCGCGGT

TAGGCATGCTAATCAACACGAGTCCTAAAAATTCGCTGCTTAGTGCATAGTGCATAG

TGCATAGTGCTAGTAAGCCAAGTACAAAGCGTTAAAGTTAAGTACTTGAGCGAACCA

TCAGACACCACTTACTAGATTAAGCACCTATTAATGATTGACCACAAATTCTGATCG

TATTGCCTGTGATCCCTGCAGCTTGAGGTTGCGCAAAAAAAGCTATCGCTTCAGCAA

CATCAACTGGCTTACCACCTTGTTTTAATGAATTCATACGACGACCAGCTTCACGAA

CTGTAAATGGAATCGCTGCTGTCATTTTTGTTTCAATAAAGCCTGGTGCAACAGCAT

TAATGGTGATGTATTTGTCTGCAAGCGGAGTTTGCATTGCATCAACATAACCAATGA

CTGCGGCCTTAGACGTTGCATAATTAGTCTGACCAAAGTTACCCGCAATCCCACTCA

TCGAAGACACACAAACAATGCGGCCATAGTCGTTGAGCAGATCATCATTTAGCAGTC

GCTCATTGATTCTTTCCATTGCCGACAAGTTAATATCCATCAGTACATCCCAATGGT

TATCCGGCATACGTGCTAGCGTTTTGTCTTTTGTTACCCCGGCATTATGGACGATGA

TATCAAGCGACTGTTCTCGCACAAAGTCAGCAATGATATTTGGGGCGTCAGCAGCGG

TAATATCAGCAACAATGCTGCTACCTTTCAAGCAATGAGCTACTTTTTCAAGGTCCT

GTTTTAATGCCGGAATGTCTAAGCAAATAACATGTGCGCCATCACGGGCGAGTGTTT

CAGCAATAGCAGCCCCGATGCCACGTGATGCACCAGTGACAAGTGCTGTCTTTCCTT

GTAATGGTTTTGCCGTGTTACTTGTTTCGTTAATAACTTCGTTAATAACTTCGTTAA

FIG. 5-5

TAACTTCGTTAATAGCCCCATTAATCGAACCGGGTTTTACGTTAATAACCTGTGCTG

AGATATAGGCTGATTTTGCTGAGGTTAAGAAACGTAGCGGGGCCTCTAATAATTGCT

CACTACCAGGTTGTACATAGATAAGTTGACAGGTACTACCATTCTTGCCTATTTCTT

TGGCGACACTGCGACAAAACCCTTCTAAAGATCTTTGTACAGTCGCGTAGCTTACAT

CGTCAAGATGTTCACTCGGATGACCTAACACGATCACTCTGCTGCATGGCGAGAGCT

GCTTAATTACAGGTTGAAAAAAACGATGTAATGCACTTAATTGCTTGCTGTTCTTAA

TGCCTGAGGCGTCGAAGATAATACCGTTGAAGCGATCTGTTTTAGCGATAGCATTAA

GGCTAATAGGTGTCGCGACTAAAGACGTTTGATTAAATTCAATATTAAGATCGGCTA

ACGCTGACGTGTTATTAGGATAAGAAATCGTGACTTCAGCATCTTTAAATGTGTTAA

GAATGGGTTTAATTAATTTGCTGTTGCTGGCTGCGCCGATGAGTAAGTTGCCAGAGA

TGAGATCGGTTCCCTGATCGTAGCGTGTTAACGTAACCGGTCGTGGCAGATTAAGCG

CTTTAAATAAACCTGATGTCCACTTGCCATTAGCGAGTTTTGCGTATGTATCCGTCA

TTTTCTAATCCTTGTTATAGTGAACAGTTTGAATCTCGAAGATGTACATGTGTTAAA

AATTATCTGATAGCTATGACTTATCTGCCACTACGTAATAATAAATAGACCAGTTCA

TTACATCGTTAATCGATATAGTATAACTAAATACTAAGTAAATTATAATGATAAGAC

TGTTATCGTACTCGGATCAAACTCTGATCAGCAAATAATCAAATTAGAGTTTTTATT

TTAAACTTGTATCAACAATGTTACATTAATGTATCTTACGTCTAATGTGCTACGGGC

ATATTTAAGTCACTAAATTAAAGGAATAAACCATGACAGGTCAAACAATAAGAAGAG

TAGCAATTATCGGCGGTAACCGTATCCCGTTTGCACGTTCAAATACAGCGTATTCAA

AACTAAGTAACCAAGATATGCTGACGGAAACTATCCGTGGCTTGGTGGTTAAATATA

ACCTACGTGGTGAACAACTGGGGGAAGTTGTTGCTGGTGCGGTAATTAAGCATTCTC

GTGATTTTAACTTAACACGTGAAGCCGTGCTAAGTGCAGGTCTTGCACCTGAAACGC

CTTGTTATGACATTCAACAAGCTTGTGGTACTGGTCTAGCTGCAGCTATCCAAGTAG

CAAACAAAATTGCGCTTGGTCAAATAGAAGCGGGTATTGCTGGTGGTTCTGATACGA

FIG. 5-6

CATCAGATGCACCGATTGCAGTCAGTGAAGGCATGCGTAGTGTATTACTTGAGCTTA

ATCGAGCTAAAACGGGTAAGCAACGTTTGAAAGCACTATCTCGTCTACGTCTAAAAC

ACTTTGCGCCACTAACGCCTGCAAATAAAGAGCCGCGTACCAAAATGGCGATGGGCG

ATCATTGTCAAGTAACAGCGAAAGAGTGGAATATCTCACGTGAAGCACAAGATGCAT

TGGCCTGCGCAAGTCATCAAAAATTAGCTGCAGCATATGAAGAAGGTTTCTTTGATA

CGTTAGTTTCACCTATGGCCGGCTTAACGAAAGATAACGTATTACGCGCAGATACAA

CAGTTGAGAAACTGGCTAAATTGAAACCTTGTTTTGATAAAGTAAACGGCACTATGA

CGGCGGGTAACAGTACTAACCTTACCGATGGAGCATCAGCTGTATTACTTGCAAGTG

AAGAATGGGCAGCGGCACATAACTTACCAGTACAAGCTTATCTAACATTTGGTGAAA

CGGCCGCTATCGACTTCGTTGATAAGAAAGAAGGTCTGTTAATGGCGCCTGCATACG

CAGTGCCAAAAATGTTGAAGCGTGCTGGCCTTACATTACAAGACTTCGATTACTATG

AAATACATGAAGCATTTGCTGCGCAGTTATTAGCAACGCTAGCAGCTTGGGAAGACG

AAAAATTCTGTAAAGAAAAACTGGGTCTAGATGCTGCGCTTGGTTCAATTGATATGA

CCAAGTTAAACGTGAAAGGGAGTAGCTTAGCCACGGGTCACCCATTTGCCGCAACTG

GTGGTCGTGTTGTCGCTACGCTAGCGCAATTACTTGATCAGAAAGGTTCAGGTCGTG

GTTTGATCTCGATTTGTGCTGCTGGTGGTCAAGGTATCACGGCAATTTTAGAGAAAT

AAACGCACTGTTTATTATCTATTGATTAAGCTGTCCTGAGATACTGGATATTTTTAA

ATAAAACGCCAATACTGCAGAGTATTGGCGTTTTTTTTGTAATACCAATTCCTATATA

ACGGTGCATTTTAAACACTTAATTTCCGGCATTGGTATCATAAAAAAGCAGCACCGA

AGTGCTGCTTGATTGTAGATTAACCTATTAAAATAGAGAGGCTAGAATTAGTCTTCG

TATGCTTCATTATGTACGCCAGCTGCACGACCCGATGGATCAGCATTGTTTTGGAAA

CTTTCATCCCAAGCTAATGCTTCTACAGTTGAACAAGCAACGGATTTACCAAACGGT

ACGCATTTCGCTGCTGAATCACCTGGGAAGTGATCTTCAAAGATGGCACGATAGTAG

TAACCTTCTTTCGTATCTGGTGTGTTAATTGGGAACTTAAATGCTGCACTTGCTAAC

ATTTGATCAGTTACCGCTTCTTCAACGTGTACTTTAAGTTGGTCAATCCAAGAATAA

FIG. 5-7

CCAACACCATCAGAGAATTGTTCTTTTTGACGCCATACAATTTCTTCAGGTAGTAAA

TCTTCAAATGCTTCTCGAATGATGTTTTTCTCAATGCGGTCGCCCGTGATCATTTTT

AGTTCAGGGTTTAGACGCATTGACGCATCAACAAATTCTTTATCTAAGAAAGGAACA

CGTGCTTCGATGCCCCAAGCTGCCATAGATTTGTTTGCACGTAAGCAATCAAACATA

TGTAATTTATTTACTTTACGTACCGTCTCTTCATGGAATTCTTTCGCATTTGGCGCT

TTGTGGAAGTACAAGTAACCACCGAACAGTTCATCAGCACCTTCACCAGAAAGCACC

ATCTTAATCCCCATGGCTTTAATTTTACGTGCCATTAGGTACATAGGGGTTGATGCA

CGAATTGTTGTTACATCGTAGGTTTCAATGTGGTAAATCACGTCGCGTAAAGCGTCG

ATACCTTCTTGCACAGTAAATTCAATTGAATGATGGATAGTACCTAAGTGATCTGCC

ACTTTTTGTGCAGCGGCTAAATCTGGAGAACCATTTAGGCCTACAGAGAAAGAGTGT

AGTTGTGGCCACCATGCTTCGGTTTTACCACCGTCTTCAATACGACGTTTTGCATAC

TGTTGGGTGATTGCTGAAATAACAGATGAATCTAACCCGCCTGATAATAATACGCCG

TAAGGTACATCACACATTAATTGACGTTTAACTGCATCTTCCAAACCTTGCTTAACA

ACGCTTTTATCACCACCATTTTGTGCAACGTTATCAAAATCTTTCCAATCACGTTGA

TAATAAGGCGTGACTACACCATCCTTACTCCACAGGTAATGACCTGCTGGGAATTCT

TCAATTTGAGTACAAATTGGCACTAGTGCTTTCATTTCAGAGGCAACATAAAAGTTA

CCGTGTTCATCATAGCCCGTATAAAGAGGGATGATACCGATATGGTCACGGCCAATC

AGGTAAGCGTCCTCTGTTTCGTCATATAAAGCGAAAGCAAAAATACCATTTAGATCA

TCTAAAAATTGTGTGCCTTTTTCTTTATATAGCGCAAGTATCACTTCGCAATCTGAT

TCTGTTTGGAATTCAAAGTCTACGTTCAGCGTTTTCTTTAAATCTTTGTGGTTATAA

ATTTCACCATTAACAGCAAGTACGTGTGTCTTTTCTTCATTATATAGCGGCTGTGCA

CCATTATTTACATCGACAATAGCAAGACGTTCATGAACTAAAATAGCATTGTCACTT

GTATAGATACCTGACCAATCTGGGCCGCGGTGACGTAGTAACTTTGATAGTTCTAGT

GCTTGTTCGCGAAGAGGTTTAATGTCTGATTTGATGTCTAGAATTCCGAATATTGAG

FIG. 5-8

CACATAACTAATTCCTTCTGGGGCTGCGTCTGCAGCTAACTTTCTAAATAGTGTGTC

TAATTTGCCACATTGTAGATTTAATGCAAACATTAATGATAAAACATTTATAAAAAA

TGTAATTCAATGTGGAATCGATAATTTAATGGCTTAAAAGTGAAGATCCATTAATTG

TGATGGCGAGGTGATAGACCAATGTAGACCTTAATGAATAAAGCAGGCACGATTGAA

TCCATTCAACGCAAAGTGGTACTAACTATTGTTTTAAACGTTATAAATAGTGTTTTA

AAGGTTATAAGTAAATAATTTAAAAACAATAATAATCCACATGCATTAAATTTATCA

TGATAAACCGCTATATCTCAATGGCAATTTGGGATAAGTGTAAAATATATGTAAAAT

GAATGAGTTGACTTGCTTTTTTTACACTAAGTGATGAAATTAAAGCTAGATGTCGTT

GTTAGCATTGATTAATAACGTACTAAAATACGACATCTAGTATAGAAATTTAAAAAA

CAGTTGGTTTTGATAGCATAACTGCATAAACTAATCAGCTTATTGTCTGTAATATTT

TTGTAATTTAAATAGGTTTAATAAAATTATATGTCTGATAAATATAAACCGTACGAC

CTTTCCTTTAAAAAGACGTTTTTGCTGCCTAAGTTTTGGCCTGTGTGGTTCGGGGTG

TTTGCAATATACTTATTAGCTTTTATGCCAGTAAAGCCGCGTGATAAATTTGCTCGA

TTCATAGCGAAGAAATTGTTTAGTCTAAAAATGATGGCAAAGCGTAAAAAGGTAGCA

AAGATCAATTTATCTATGTGCTTCCCTGAAATGGATGATACGGAACAAGACCGTATA

ATCATGGTCAATCTAGTTACTTTTTGTCAAACTATCTTAAGTTATGCAGAGCCAAGT

GCGCGTAGTCGTGCTTATAACCGTGACCGTATGATAGTGCATGGTGGCGAGAATTTA

TTTCCGCTACTTGAACAAGGTAAGGCTTGTATCTTATTAGTGCCGCATAGCTTCGCT

ATTGATTTTGCAGGTTTACACATTGCTTCTTATGGCGCGCCATTTTGTACTATGTTT

AACAATTCTGAGAATGAGTTGTTCGATTGGCTGATGACACGTCAACGCGCTATGTTT

GGAGGCACTGTTTATCACCGCAAGGCAGGGCTAGGGGCTCTAGTTAAATCACTTAAG

AGCGGTGAAAGCTGTTATTACTTACCTGATGAAGACCATGGACCTAAGCGTAGTGTA

TTTGCGCCTTTATTTGCGACTCAAAAAGCAACTTTACCTGTAATGGGCAAGCTAGCA

GAAAAAACAAATGCACTCGTTGTTCCTGTTTATGCGGCATATAATGAATCACTAGGT

AAATTTGAAACCTTTATTCGACCAGCAATGCAAAACTTTCCATCAGAAAGCCCAGAA

CAAGATGCAGTGATGATGAATAAAGAGATTGAAGCCTTGATTGAATGTGGTGTTGAT

FIG. 5-9

CAATATATGTGGACACTTAGATTATTGAGAACACGTCCGGACGGTAAAAAAATCTAC

TAATAAAGTTTAATAAACACCATAATCTTCGTTGAATATGGTGTTTACCCCCCTGAA

TACCCTCTAAATTAATAACAAAAAAAGCCATTTACGTAACATCTAATGATGATTTAG

CCTGCACTTGCTTTGTTTTTAGTCTTAAGAGCCTAATAAACTTGATCTAGGTATAGA

TTCTGTCTTTCTTTACGTAACGCGATCTATTTTTTTTAACCGATAGTTGTTATAATT

AGTTTCATATGAAAGAGATATCGTTTCAGTAAAAGCTATTTCGTTTCAATAGATAAT

TTATTTATAGTCATATTTTCTGTAATGACAATCATTTTCTCATCTAGACTATAGATA

AGAATACGAATTAAGTAAGAACATTAATTTTACAAGAATATAAAATATCCCATCGGA

GCTATAAGAATGAAAAAGACTAAAATTGTTTGTACAATTGGTCCAAAAACTGAATCA

GTAGAGAAACTAACAGAGCTTGTTAATGCAGGCATGAACGTTATGCGTTTAAATTTC

TCTCATGGTAACTTTGCTGAACATTCAGTGCGTATTCAAAATATCCGTCAAGTAAGT

GAAAACCTGAATAAGAAAATTGCTGTTTTACTGGATACTAAAGGTCCAGAAATCCGT

ACGATTAAACTAGAAAACGGTGACGATGTAATGTTGACCGCTGGTCAGTCATTCACG

TTTACAACAGACATTAACGTGGTAGGTAATAAAGACTGTGTTGCTGTAACATATGCT

GGTTTTGCTAAAGACCTTAATCCTGGTGCAATCATCCTTGTTGATGATGGTTTAATT

GAAATGGAAGTTGTTGCAACAACTGACACTGAAGTTAAATGTACAGTATTAAATACT

GGTGCACTTGGTGAAAATAAAGGCGTTAACTTACCTAACATCAGTGTAGGTCTACCT

GCATTGTCAGAAAAAGATAAAGCTGATTTAGCGTTTGGTTGTGAGCAAGAAGTTGAT

TTTGTTGCTGCATCATTTATTCGTAAGGCTGATGATGTAAGAGAAATTCGTGAAATC

CTATTTAATAATGGTGGCGAAAACATTCAGATTATCTCGAAAATTGAAAACCAAGAA

GGTGTAGACAATTTCGATGAAATCTTAGCTGAATCAGACGGTATCATGGTTGCTCGT

GGCGATCTCGGTGTTGAGATCCCAGTTGAAGAAGTGATCATGGCACAGAAGATGATG

ATCAAAAAAATGTAATAAAGCAGGTAAAGTTGTAATTACTGCAACACAAATGCTTGAT

TCAATGATCAGTAACCCACGTCCAACACGTGCAGAAGCGGGCGATGTTGCCAATGCT

GTGCTTGACGGTACCGACGCGGTAATGCTTTCTGGTGAAACTGCGAAAGGTAAATAC

FIG. 5-10

CCAGTTGAAGCTGTGTCTATCATGGCAAACATCTGTGAACGTACTGATAACTCAATG

TCTTCGGATTTAGGTGCGAACATTGTTGCTAAAAGCATGCGCATTACAGAAGCTGTG

TGTAAAGGTGCGGTAGAAACAACAGAAAAATTGTGTGCTCCACTTATTGTTGTTGCA

ACTCGTGGCGGTAAATCAGCAAAATCTGTTCGTAAATACTTCCCGAAAGCAAATATT

CTTGCTATCACAACAAATGAAAAAGCAGCGCAACAGTTATGCCTAACTAAAGGCGTA

AGCAGCTGCATCGTTGAGCAGATTGATAGCACTGATGAGTTCTACCGTAAAGGTAAA

GAGCTTGCATTAGCAACTGGTTTAGCTAAAGAAGGCGATATCGTTGTTATGGTATCA

GGTGCGTTAGTACCATCAGGTACAACGAATACGGCATCTGTTCACCAACTTTAAGTT

GCCATATTGATATTATAAAAAAGAGAGCGTATGCTCTCTTTTTTTATATCTGTAGTT

TATATGTCTGTACAAAAAAATGATAAAGAGTACATAAACTATTAATATAGCGTAATA

TATAATGATTAACGGTGATGAAAGGGTTAAATAAATGGATAGTGCTAAACATAAAAT

TGGCTTAGTCCTTTCTGGCGGTGGTGCGAAAGGTATTGCTCATCTTGGTGTATTAAA

ATACCTGTTAGAGCAAGATATAAGACCGAATGTAATTGCGGGTACAAGTGCTGGCTC

TATGGTTGGTGCACTTTATTGCTCAGGACTTGAGATTGATGACATTTTACAATTCTT

CATCGATGTAAAACCTTTTTCTTGGAAGTTTACCCGTGCCCGTGCTGGCTTTATAGA

CCCGGCAAAATTATATCCTGAAGTGCTAAAATATATCCCCGAGGATAGCTTTGAGTA

CCTTCAACCTGAATTGCGCATTGTTGCCACCAACATGTTACTCGGTAAAGAGCATAT

ATTTAAAGATGGCTCCGTGATTAATGCCTTATTAGCATCAGCCAGCTACCCTTTAGT

TTTTTCTCCGATGATCATTGACGATCAAGTGTATTCAGATGGCGGTATTGTTAATCA

TTTCCCCCGTGAGTGTCATTGAAGATGATTGCGATAAAATAATCGGCGTATACGTGTC

GCCCATTCGTCAGGTCGAAGCTGACGAACTCTCGAGTATAAAAGACGTGGTATTACG

TGCGTTCACGCTGCAGGGTAGTGGTGCTGAATTAGATAAACTATCGCAATGTGATGT

GCAAATTTATCCAGAAGCGCTATTGAATTACAATACGTTTGCAACCGATGAAAAATC

ATTACGGGAGATCTACCAGATTGGTTATGATGCTGCAAAAGATCAACATGACAACCT

TATGGCATTGAAAGAAAGTATCACCACCAGCGAGGTTAAAAAGAACGTCTTTAGCAA

FIG. 5-11

ATGGTTTGGTGATAAACTTGCTAGCAACAGCGGCAAATAGCGGCCCACACGGATTTA

TACACTAGGATAATGGGCGTTAATAGCCTCACTGTCGTTGTGTGGTCTCTAATTTTA

GCTAAATCTTGTGTTATACTGACTTCCTATTAATCATAAACGATTTATCACGGTAAA

CATGACTCAAATAAATAACCCGCTTCACGGCATGACACTCGAAAAAGTAATTAACAG

TCTCGTTGAACAATATGGCTGGGATGGTCTTGGATACTACATCAACATTCGTTGCTT

TACTGAAAATCCAAGTGTTAAGTCTAGTCTTAAATTTTTACGTAAAACCCCTTGGGC

ACGTGATAAAGTAGAAGCGCTATATATCAAAATGGTGACTGAAGGCTAACTGTCTCC

ACGCTAGCGAACCGCTGTTTATAGTTAATATAAGTACTATAAGCAGGGCTCGTTAAT

TCAGTATGTAATTAATCCTGAATACCTCCGCTTATTTCAACATTGTACTCTCTAGAT

AACACTCTCAACATTACACCTTCAACATCACAGCCTCCACATAACATCCGATGACAT

AGCCCTGTTATTTTTCACATTTATCTATATGCTATATATTTTAGCCATTTGATCAAT

TGAGTTAATTTCTGCAATGACAAAGATATACCATCATCCAGTACAAATTTATTATGA

AGATACCGACCATTCTGGTGTTGTTTACCACCCTAACTTTTTTAAAATACTTTGAACG

TGCACGTGAGCATGTGATAAATAGTGACTTACTAGCAACATTGTGGAATGAACGCGG

TTTAGGTTTTGCGGTGTATAAAGCCAATATGACTTTTCAGGATGGGGTCGAATTTGC

TGAAGTGTGTGATATTCGCACTTCTTTTGTCCTAGACGGTAAGTACAAAACGATCTG

GCGCCAAGAAGTATGGCGTCCGAATGCGACTAGGGCTGCCGTTATCGGTGATATTGA

AATGGTGTGCTTAGACAAACAAAAACGTTTACAGCCCATCCCTGATGATGTGTTAGC

TGCAATGGTTAGTGAATAAATGGTTCATGCATAAATAGTTAATACATGATTCTGGCC

CGTCACGTTTACAGATAAGAGGCATCCGATGCCTCCTTCCTATTACCAATACTACTG

CTTATCCCTTTCTAACTATCTTTAGCGTCCATAACACACTGAGCATTTATTCTATTA

ATCAGTGATTGTGATTTAATTATCTTCTATATATGTAATTTAATGTAATTTTCAATT

TATTTTTAGCTACATTAAGGCTTACGAATGTACGCTAAAATGAGATGTCAGACTAAT

TTTAGCTTATTAATCTGTTAGCCGTTTATATTTTATAAAGATGGGATTTAACTTAAA

FIG. 5-12

TGCAATTAATTATGGCGTAAATAGAGTGAAAACATGGCTAATATTCACTAAGTCCTG

AATTTTATATAAAGTTTAATCTGTTATTTTAGCGTTTACCTGGTCTTATCAGTGAGG

TTTATAGCCATTATTAGTGGGATTGAAGTGATTTTTAAAGCTATGTATATTATTGCA

AATATAAATTGTAACAATTAAGACTTTGGACACTTGAGTTCAATTTCGAATTGATTG

GCATAAAATTTAAAACAGCTAAATCTACCTCAATCATTTTAGCAAATGTATGCAGGT

AGATTTTTTTTCGCCATTTAAGAGTACACTTGTACGCTAGGTTTTTGTTTAGTGTGCA

AATGAACGTTTTGATGAGCATTGTTTTTAGAGCACAAAATAGATCCTTACAGGAGCA

ATAACGCAATGGCTAAAAAGAACACCACATCGATTAAGCACGCCAAGGATGTGTTAA

GTAGTGATGATCAACAGTTAAATTCTCGCTTGCAAGAATGTCCGATTGCCATCATTG

GTATGGCATCGGTTTTTGCAGATGCTAAAAACTTGGATCAATTCTGGGATAACATCG

TTGACTCTGTGGACGCTATTATTGATGTGCCTAGCGATCGCTGGAACATTGACGACC

ATTACTCGGCTGATAAAAAAGCAGCTGACAAGACATACTGCAAACGCGGTGGTTTCA

TTCCAGAGCTTGATTTTGATCCGATGGAGTTTGGTTTACCGCCAAATATCCTCGAGT

TAACTGACATCGCTCAATTGTTGTCATTAATTGTTGCTCGTGATGTATTAAGTGATG

CTGGCATTGGTAGTGATTATGACCATGATAAAATTGGTATCACGCTGGGTGTCGGTG

GTGGTCAGAAACAAATTTCGCCATTAACGTCGCGCCTACAAGGCCCGGTATTAGAAA

AAGTATTAAAAGCCTCAGGCATTGATGAAGATGATCGCGCTATGATCATCGACAAAT

TTAAAAAAGCCTACATCGGCTGGGAAGAGAACTCATTCCCAGGCATGCTAGGTAACG

TTATTGCTGGTCGTATCGCCAATCGTTTTGATTTTGGTGGTACTAACTGTGTGGTTG

ATGCGGCATGCGCTGGCTCCCTTGCAGCTGTTAAAATGGCGATCTCAGACTTACTTG

AATATCGTTCAGAAGTCATGATATCGGGTGGTGTATGTTGTGATAACTCGCCATTCA

TGTATATGTCATTCTCGAAAACACCAGCATTTACCACCAATGATGATATCCGTCCGT

TTGATGACGATTCAAAAGGCATGCTGGTTGGTGAAGGTATTGGCATGATGGCGTTTA

AACGTCTTGAAGATGCTGAACGTGACGGCGACAAAATTTATTCTGTACTGAAAGGTA

TCGGTACATCTTCAGATGGTCGTTTCAAATCTATTTACGCTCCACGCCCAGATGGCC

AAGCAAAAGCGCTAAAACGTGCTTATGAAGATGCCGGTTTTGCCCCTGAAACATGTG

FIG. 5-13

GTCTAATTGAAGGCCATGGTACGGGTACCAAAGCGGGTGATGCCGCAGAATTTGCTG

GCTTGACCAAACACTTTGGCGCCGCCAGTGATGAAAAGCAATATATCGCCTTAGGCT

CAGTTAAATCGCAAATTGGTCATACTAAATCTGCGGCTGGCTCTGCGGGTATGATTA

AGGCGGCATTAGCGCTGCATCATAAAATCTTACCTGCAACGATCCATATCGATAAAC

CAAGTGAAGCCTTGGATATCAAAAACAGCCCGTTATACCTAAACAGCGAAACGCGTC

CTTGGATGCCACGTGAAGATGGTATTCCACGTCGTGCAGGTATCAGCTCATTTGGTT

TTGGCGGCACCAACTTCCATATTATTTTAGAAGAGTATCGCCCAGGTCACGATAGCG

CATATCGCTTAAACTCAGTGAGCCAAACTGTGTTGATCTCGGCAAACGACCAACAAG

GTATTGTTGCTGAGTTAAATAACTGGCGTACTAAACTGGCTGTCGATGCTGATCATC

AAGGGTTTGTATTTAATGAGTTAGTGACAACGTGGCCATTAAAAACCCCATCCGTTA

ACCAAGCTCGTTTAGGTTTTGTTGCGCGTAATGCAAATGAAGCGATCGCGATGATTG

ATACGGCATTGAAACAATTCAATGCGAACGCAGATAAAATGACATGGTCAGTACCTA

CCGGGGTTTACTATCGTCAAGCCGGTATTGATGCAACAGGTAAAGTGGTTGCGCTAT

TCTCAGGGCAAGGTTCGCAATACGTGAACATGGGTCGTGAATTAACCTGTAACTTCC

CAAGCATGATGCACAGTGCTGCGGCGATGGATAAAGAGTTCAGTGCCGCTGGTTTAG

GCCAGTTATCTGCAGTTACTTTCCCTATCCCTGTTTATACGGATGCCGAGCGTAAGC

TACAAGAAGAGCAATTACGTTTAACGCAACATGCGCAACCAGCGATTGGTAGTTTGA

GTGTTGGTCTGTTCAAAACGTTTAAGCAAGCAGGTTTTAAAGCTGATTTTGCTGCCG

GTCATAGTTTCGGTGAGTTAACCGCATTATGGGCTGCCGATGTATTGAGCGAAAGCG

ATTACATGATGTTAGCGCGTAGTCGTGGTCAAGCAATGGCTGCGCCAGAGCAACAAG

ATTTTGATGCAGGTAAGATGGCCGCTGTTGTTGGTGATCCAAAGCAAGTCGCTGTGA

TCATTGATACCCTTGATGATGTCTCTATTGCTAACTTCAACTCGAATAACCAAGTTG

TTATTGCTGGTACTACGGAGCAGGTTGCTGTAGCGGTTACAACCTTAGGTAATGCTG

GTTTCAAAGTTGTGCCACTGCCGGTATCTGCTGCGTTCCATACACCTTTAGTTCGTC

ACGCGCAAAAACCATTTGCTAAAGCGGTTGATAGCGCTAAATTTAAAGCGCCAAGCA

TTCCAGTGTTTGCTAATGGCACAGGCTTGGTGCATTCAAGCAAACCGAATGACATTA

FIG. 5-14

AGAAAAACCTGAAAAACCACATGCTGGAATCTGTTCATTTCAATCAAGAAATTGACA

ACATCTATGCTGATGGTGGCCGCGTATTTATCGAATTTGGTCCAAAGAATGTATTAA

CTAAATTGGTTGAAAACATTCTCACTGAAAAATCTGATGTGACTGCTATCGCGGTTA

ATGCTAATCCTAAACAACCTGCGGACGTACAAATGCGCCAAGCTGCGCTGCAAATGG

CAGTGCTTGGTGTCGCATTAGACAATATTGACCCGTACGACGCCGTTAAGCGTCCAC

TTGTTGCGCCGAAAGCATCACCAATGTTGATGAAGTTATCTGCAGCGTCTTATGTTA

GTCCGAAAACGAAGAAAGCGTTTGCTGATGCATTGACTGATGGCTGGACTGTTAAGC

AAGCGAAAGCTGTACCTGCTGTTGTGTCACAACCACAAGTGATTGAAAAGATCGTTG

AAGTTGAAAAGATAGTTGAACGCATTGTCGAAGTAGAGCGTATTGTCGAAGTAGAAA

AAATCGTCTACGTTAATGCTGACGGTTCGCTTATATCGCAAAATAATCAAGACGTTA

ACAGCGCTGTTGTTAGCAACGTGACTAATAGCTCAGTGACTCATAGCAGTGATGCTG

ACCTTGTTGCCTCTATTGAACGCAGTGTTGGTCAATTTGTTGCACACCAACAGCAAT

TATTAAATGTACATGAACAGTTTATGCAAGGTCCACAAGACTACGCGAAAACAGTGC

AGAACGTACTTGCTGCGCAGACGAGCAATGAATTACCGGAAAGTTTAGACCGTACAT

TGTCTATGTATAACGAGTTCCAATCAGAAACGCTACGTGTACATGAAACGTACCTGA

ACAATCAGACGAGCAACATGAACACCATGCTTACTGGTGCTGAAGCTGATGTGCTAG

CAACCCCAATAACTCAGGTAGTGAATACAGCCGTTGCCACTAGTCACAAGGTAGTTG

CTCCAGTTATTGCTAATACAGTGACGAATGTTGTATCTAGTGTCAGTAATAACGCGG

CGGTTGCAGTGCAAACTGTGGCATTAGCGCCTACGCAAGAAATCGCTCCAACAGTCG

CTACTACGCCAGCACCCGCATTGGTTGCTATCGTGGCTGAACCTGTGATTGTTGCGC

ATGTTGCTACAGAAGTTGCACCAATTACACCATCAGTTACACCAGTTGTCGCAACTC

AAGCGGCTATCGATGTAGCAACTATTAACAAAGTAATGTTAGAAGTTGTTGCTGATA

AAACCGGTTATCCAACGGATATGCTGGAACTGAGCATGGACATGGAAGCTGACTTAG

GTATCGACTCAATCAAACGTGTTGAGATATTAGGCGCAGTACAGGAATTGATCCCTG

ACTTACCTGAACTTAATCCTGAAGATCTTGCTGAGCTACGCACGCTTGGTGAGATTG

TCGATTACATGAATTCAAAAGCCCAGGCTGTAGCTCCTACAACAGTACCTGTAACAA

FIG. 5-15

GTGCACCTGTTTCGCCTGCATCTGCTGGTATTGATTTAGCCCACATCCAAAACGTAA

TGTTAGAAGTGGTTGCAGACAAAACCGGTTACCCAACAGACATGCTAGAACTGAGCA

TGGATATGGAAGCTGACTTAGGTATTGATTCAATCAAGCGTGTGGAAATCTTAGGTG

CAGTACAGGAGATCATAACTGATTTACCTGAGCTAAACCCTGAAGATCTTGCTGAAT

TACGCACCCTAGGTGAAATCGTTAGTTACATGCAAAGCAAAGCGCCAGTCGCTGAAA

GTGCGCCAGTGGCGACGGCTCCTGTAGCAACAAGCTCAGCACCGTCTATCGATTTGA

ACCACATTCAAACAGTGATGATGGATGTAGTTGCAGATAAGACTGGTTATCCAACTG

ACATGCTAGAACTTGGCATGGACATGGAAGCTGATTTAGGTATCGATTCAATCAAAC

GTGTGGAAATATTAGGCGCAGTGCAGGAGATCATCACTGATTTACCTGAGCTAAACC

CAGAAGACCTCGCTGAATTACGCACGCTAGGTGAAATCGTTAGTTACATGCAAAGCA

AAGCGCCAGTCGCTGAGAGTGCGCCAGTAGCGACGGCTTCTGTAGCAACAAGCTCTG

CACCGTCTATCGATTTAAACCATATCCAAACAGTGATGATGGAAGTGGTTGCAGACA

AAACCGGTTATCCAGTAGACATGTTAGAACTTGCTATGGACATGGAAGCTGACCTAG

GTATCGATTCAATCAAGCGTGTAGAAATTTTAGGTGCGGTACAGGAAATCATTACTG

ACTTACCTGAGCTTAACCCTGAAGATCTTGCTGAACTACGTACATTAGGTGAAATCG

TTAGTTACATGCAAAGCAAAGCGCCCGTAGCTGAAGCGCCTGCAGTACCTGTTGCAG

TAGAAAGTGCACCTACTAGTGTAACAAGCTCAGCACCGTCTATCGATTTAGACCACA

TCCAAAATGTAATGATGGATGTTGTTGCTGATAAGACTGGTTATCCTGCCAATATGC

TTGAATTAGCAATGGACATGGAAGCCGACCTTGGTATTGATTCAATCAAGCGTGTTG

AAATTCTAGGCGCGGTACAGGAGATCATTACTGATTTACCTGAACTAAACCCAGAAG

ACTTAGCTGAACTACGTACGTTAGAAGAAATTGTAACCTACATGCAAAGCAAGGCGA

GTGGTGTTACTGTAAATGTAGTGGCTAGCCCTGAAAATAATGCTGTATCAGATGCAT

TTATGCAAAGCAATGTGGCGACTATCACAGCGGCCGCAGAACATAAGGCGGAATTTA

AACCGGCGCCGAGCGCAACCGTTGCTATCTCTCGTCTAAGCTCTATCAGTAAAATAA

GCCAAGATTGTAAAGGTGCTAACGCCTTAATCGTAGCTGATGGCACTGATAATGCTG

FIG. 5-16

TGTTACTTGCAGACCACCTATTGCAAACTGGCTGGAATGTAACTGCATTGCAACCAA

CTTGGGTAGCTGTAACAACGACGAAAGCATTTAATAAGTCAGTGAACCTGGTGACTT

TAAATGGCGTTGATGAAACTGAAATCAACAACATTATTACTGCTAACGCACAATTGG

ATGCAGTTATCTATCTGCACGCAAGTAGCGAAATTAATGCTATCGAATACCCACAAG

CATCTAAGCAAGGCCTGATGTTAGCCTTCTTATTAGCGAAATTGAGTAAAGTAACTC

AAGCCGCTAAAGTGCGTGGCGCCTTTATGATTGTTACTCAGCAGGGTGGTTCATTAG

GTTTTGATGATATCGATTCTGCTACAAGTCATGATGTGAAAACAGACCTAGTACAAA

GCGGCTTAAACGGTTTAGTTAAGACACTGTCTCACGAGTGGGATAACGTATTCTGTC

GTGCGGTTGATATTGCTTCGTCATTAACGGCTGAACAAGTTGCAAGCCTTGTTAGTG

ATGAACTACTTGATGCTAACACTGTATTAACAGAAGTGGGTTATCAACAAGCTGGTA

AAGGCCTTGAACGTATCACGTTAACTGGTGTGGCTACTGACAGCTATGCATTAACAG

CTGGCAATAACATCGATGCTAACTCGGTATTTTTAGTGAGTGGTGGCGCAAAAGGTG

TAACTGCACATTGTGTTGCTCGTATAGCTAAAGAATATCAGTCTAAGTTCATCTTAT

TGGGACGTTCAACGTTCTCAAGTGACGAACCGAGCTGGGCAAGTGGTATTACTGATG

AAGCGGCGTTAAAGAAAGCAGCGATGCAGTCTTTGATTACAGCAGGTGATAAACCAA

CACCCGTTAAGATCGTACAGCTAATCAAACCAATCCAAGCTAATCGTGAAATTGCGC

AAACCTTGTCTGCAATTACCGCTGCTGGTGGCCAAGCTGAATATGTTTCTGCAGATG

TAACTAATGCAGCAAGCGTACAAATGGCAGTCGCTCCAGCTATCGCTAAGTTCGGTG

CAATCACTGGCATCATTCATGGCGCGGGTGTGTTAGCTGACCAATTCATTGAGCAAA

AAACACTGAGTGATTTTGAGTCTGTTTACAGCACTAAAATTGACGGTTTGTTATCGC

TACTATCAGTCACTGAAGCAAGCAACATCAAGCAATTGGTATTGTTCTCGTCAGCGG

CTGGTTTCTACGGTAACCCCGGCCAGTCTGATTACTCGATTGCCAATGAGATCTTAA

ATAAAACCGCATACCGCTTTAAATCATTGCACCCACAAGCTCAAGTATTGAGCTTTA

ACTGGGGTCCTTGGGACGGTGGCATGGTAACGCCTGAGCTTAAACGTATGTTTGACC

AACGTGGTGTTTACATTATTCCACTTGATGCAGGTGCACAGTTATTGCTGAATGAAC

FIG. 5-17

TAGCCGCTAATGATAACCGTTGTCCACAAATCCTCGTGGGTAATGACTTATCTAAAG

ATGCTAGCTCTGATCAAAAGTCTGATGAAAAGAGTACTGCTGTAAAAAAGCCACAAG

TTAGTCGTTTATCAGATGCTTTAGTAACTAAAAGTATCAAAGCGACTAACAGTAGCT

CTTTATCAAACAAGACTAGTGCTTTATCAGACAGTAGTGCTTTTCAGGTTAACGAAA

ACCACTTTTTAGCTGACCACATGATCAAAGGCAATCAGGTATTACCAACGGTATGCG

CGATTGCTTGGATGAGTGATGCAGCAAAAGCGACTTATAGTAACCGAGACTGTGCAT

TGAAGTATGTCGGTTTCGAAGACTATAAATTGTTTAAAGGTGTGGTTTTTGATGGCA

ATGAGGCGGCGGATTACCAAATCCAATTGTCGCCTGTGACAAGGGCGTCAGAACAGG

ATTCTGAAGTCCGTATTGCCGCAAAGATCTTTAGCCTGAAAAGTGACGGTAAACCTG

TGTTTCATTATGCAGCGACAATATTGTTAGCAACTCAGCCACTTAATGCTGTGAAGG

TAGAACTTCCGACATTGACAGAAAGTGTTGATAGCAACAATAAAGTAACTGATGAAG

CACAAGCGTTATACAGCAATGGCACCTTGTTCCACGGTGAAAGTCTGCAGGGCATTA

AGCAGATATTAAGTTGTGACGACAAGGGCCTGCTATTGGCTTGTCAGATAACCGATG

TTGCAACAGCTAAGCAGGGATCCTTCCCGTTAGCTGACAACAATATCTTTGCCAATG

ATTTGGTTTATCAGGCTATGTTGGTCTGGGTGCGCAAACAATTTGGTTTAGGTAGCT

TACCTTCGGTGACAACGGCTTGGACTGTGTATCGTGAAGTGGTTGTAGATGAAGTAT

TTTATCTGCAACTTAATGTTGTTGAGCATGATCTATTGGGTTCACGCGGCAGTAAAG

CCCGTTGTGATATTCAATTGATTGCTGCTGATATGCAATTACTTGCCGAAGTGAAAT

CAGCGCAAGTCAGTGTCAGTGACATTTTGAACGATATGTCATGATCGAGTAAATAAT

AACGATAGGCGTCATGGTGAGCATGGCGTCTGCTTTCTTCATTTTTTAACATTAACA

ATATTAATAGCTAAACGCGGTTGCTTTAAACCAAGTAAACAAGTGCTTTTAGCTATT

ACTATTCCAAACAGGATATTAAAGAGAATATGACGGAATTAGCTGTTATTGGTATGG

ATGCTAAATTTAGCGGACAAGACAATATTGACCGTGTGGAACGCGCTTTCTATGAAG

GTGCTTATGTAGGTAATGTTAGCCGCGTTAGTACCGAATCTAATGTTATTAGCAATG

GCGAAGAACAAGTTATTACTGCCATGACAGTTCTTAACTCTGTCAGTCTACTAGCGC

FIG. 5-18

AAACGAATCAGTTAAATATAGCTGATATCGCGGTGTTGCTGATTGCTGATGTAAAAA

GTGCTGATGATCAGCTTGTAGTCCAAATTGCATCAGCAATTGAAAAACAGTGTGCGA

GTTGTGTTGTTATTGCTGATTTAGGCCAAGCATTAAATCAAGTAGCTGATTTAGTTA

ATAACCAAGACTGTCCTGTGGCTGTAATTGGCATGAATAACTCGGTTAATTTATCTC

GTCATGATCTTGAATCTGTAACTGCAACAATCAGCTTTGATGAAACCTTCAATGGTT

ATAACAATGTAGCTGGGTTCGCGAGTTTACTTATCGCTTCAACTGCGTTTGCCAATG

CTAAGCAATGTTATATATACGCCAACATTAAGGGCTTCGCTCAATCGGGCGTAAATG

CTCAATTTAACGTTGGAAACATTAGCGATACTGCAAAGACCGCATTGCAGCAAGCTA

GCATAACTGCAGAGCAGGTTGGTTTGTTAGAAGTGTCAGCAGTCGCTGATTCGGCAA

TCGCATTGTCTGAAAGCCAAGGTTTAATGTCTGCTTATCATCATACGCAAACTTTGC

ATACTGCATTAAGCAGTGCCCGTAGTGTGACTGGTGAAGGCGGGTGTTTTTCACAGG

TCGCAGGTTTATTGAAATGTGTAATTGGTTTACATCAACGTTATATTCCGGCGATTA

AAGATTGGCAACAACCGAGTGACAATCAAATGTCACGGTGGCGGAATTCACCATTCT

ATATGCCTGTAGATGCTCGACCTTGGTTCCCACATGCTGATGGCTCTGCACACATTG

CCGCTTATAGTTGTGTGACTGCTGACAGCTATTGTCATATTCTTTTACAAGAAAACG

TCTTACAAGAACTTGTTTTGAAAGAAACAGTCTTGCAAGATAATGACTTAACTGAAA

GCAAGCTTCAGACTCTTGAACAAAACAATCCAGTAGCTGATCTGCGCACTAATGGTT

ACTTTGCATCGAGCGAGTTAGCATTAATCATAGTACAAGGTAATGACGAAGCACAAT

TACGCTGTGAATTAGAAACTATTACAGGGCAGTTAAGTACTACTGGCATAAGTACTA

TCAGTATTAAACAGATCGCAGCAGACTGTTATGCCCGTAATGATACTAACAAAGCCT

ATAGCGCAGTGCTTATTGCCGAGACTGCTGAAGAGTTAAGCAAAGAAATAACCTTGG

CGTTTGCTGGTATCGCTAGCGTGTTTAATGAAGATGCTAAAGAATGGAAAACCCCGA

AGGGCAGTTATTTTACCGCGCAGCCTGCAAATAAACAGGCTGCTAACAGCACACAGA

ATGGTGTCACCTTCATGTACCCAGGTATTGGTGCTACATATGTTGGTTTAGGGCGTG

ATCTATTTCATCTATTCCCACAGATTTATCAGCCTGTAGCGGCTTTAGCCGATGACA

FIG. 5-19

TTGGCGAAAGTCTAAAAGATACTTTACTTAATCCACGCAGTATTAGTCGTCATAGCT

TTAAAGAACTCAAGCAGTTGGATCTGGACCTGCGCGGTAACTTAGCCAATATCGCTG

AAGCCGGTGTGGGTTTTGCTTGTGTGTTTACCAAGGTATTTGAAGAAGTCTTTGCCG

TTAAAGCTGACTTTGCTACAGGTTATAGCATGGGTGAAGTAAGCATGTATGCAGCAC

TAGGCTGCTGGCAGCAACCGGGATTGATGAGTGCTCGCCTTGCACAATCGAATACCT

TTAATCATCAACTTTGCGGCGAGTTAAGAACACTACGTCAGCATTGGGGCATGGATG

ATGTAGCTAACGGTACGTTCGAGCAGATCTGGGAAACCTATACCATTAAGGCAACGA

TTGAACAGGTCGAAATTGCCTCTGCAGATGAAGATCGTGTGTATTGCACCATTATCA

ATACACCTGATAGCTTGTTGTTAGCCGGTTATCCAGAAGCCTGTCAGCGAGTCATTA

AGAATTTAGGTGTGCGTGCAATGGCATTGAATATGGCGAACGCAATTCACAGCGCGC

CAGCTTATGCCGAATACGATCATATGGTTGAGCTATACCATATGGATGTTACTCCAC

GTATTAATACCAAGATGTATTCAAGCTCATGTTATTTACCGATTCCACAACGCAGCA

AAGCGATTTCCCACAGTATTGCTAAATGTTTGTGTGATGTGGTGGATTTCCCACGTT

TGGTTAATACCTTACATGACAAAGGTGCGCGGGTATTCATTGAAATGGGTCCAGGTC

GTTCGTTATGTAGCTGGGTAGATAAGATCTTAGTTAATGGCGATGGCGATAATAAAA

AGCAAAGCCAACATGTATCTGTTCCTGTGAATGCCAAAGGCACCAGTGATGAACTTA

CTTATATTCGTGCGATTGCTAAGTTAATTAGTCATGGCGTGAATTTGAATTTAGATA

GCTTGTTTAACGGGTCAATCCTGGTTAAAGCAGGCCATATAGCAAACACGAACAAAT

AGTCAACATCGATATCTAGCGCTGGTGAGTTATACCTCATTAGTTGAAATATGGATT

TAAAGAGAGTAATTATGGAAAATATTGCAGTAGTAGGTATTGCTAATTTGTTCCCGG

GCTCACAAGCACCGGATCAATTTTGGCAGCAATTGCTTGAACAACAAGATTGCCGCA

GTAAGGCGACCGCTGTTCAAATGGGCGTTGATCCTGCTAAATATACCGCCAACAAAG

GTGACACAGATAAATTTTACTGTGTGCACGGCGGTTACATCAGTGATTTCAATTTTG

ATGCTTCAGGTTATCAACTCGATAATGATTATTTAGCCGGTTTAGATGACCTTAATC

AATGGGGGCTTTATGTTACGAAACAAGCCCTTACCGATGCGGGTTATTGGGGCAGTA

FIG. 5-20

CTGCACTAGAAAACTGTGGTGTGATTTTAGGTAATTTGTCATTCCCAACTAAATCAT

CTAATCAGCTGTTTATGCCTTTGTATCATCAAGTTGTTGATAATGCCTTAAAGGCGG

TATTACATCCTGATTTTCAATTAACGCATTACACAGCACCGAAAAAAACACATGCTG

ACAATGCATTAGTAGCAGGTTATCCAGCTGCATTGATCGCGCAAGCGGCGGGTCTTG

GTGGTTCACATTTTGCACTGGATGCGGCTTGTGCTTCATCTTGTTATAGCGTTAAGT

TAGCGTGTGATTACCTGCATACGGGTAAAGCCAACATGATGCTTGCTGGTGCGGTAT

CTGCAGCAGATCCTATGTTCGTAAATATGGGTTTCTCGATATTCCAAGCTTACCCAG

CTAACAATGTACATGCCCCGTTTGACCAAAATTCACAAGGTCTATTTGCCGGTGAAG

GCGCGGGCATGATGGTATTGAAACGTCAAAGTGATGCAGTACGTGATGGTGATCATA

TTTACGCCATTATTAAAGGCGGCGCATTATCGAATGACGGTAAAGGCGAGTTTGTAT

TAAGCCCGAACACCAAGGGCCAAGTATTAGTATATGAACGTGCTTATGCCGATGCAG

ATGTTGACCCGAGTACAGTTGACTATATTGAATGTCATGCAACGGGCACACCTAAGG

GTGACAATGTTGAATTGCGTTCGATGGAAACCTTTTTCAGTCGCGTAAATAACAAAC

CATTACTGGGCTCGGTTAAATCTAACCTTGGTCATTTGTTAACTGCCGCTGGTATGC

CTGGCATGACCAAAGCTATGTTAGCGCTAGGTAAAGGTCTTATTCCTGCAACGATTA

ACTTAAAGCAACCACTGCAATCTAAAAACGGTTACTTTACTGGCGAGCAAATGCCAA

CGACGACTGTGTCTTGGCCAACAACTCCGGGTGCCAAGGCAGATAAACCGCGTACCG

CAGGTGTGAGCGTATTTGGTTTTGGTGGCAGCAACGCCCATTTGGTATTACAACAGC

CAACGCAAACACTCGAGACTAATTTTAGTGTTGCTAAACCACGTGAGCCTTTGGCTA

TTATTGGTATGGACAGCCATTTTGGTAGTGCCAGTAATTTAGCGCAGTTCAAAACCT

TATTAAATAATAATCAAAATACCTTCCGTGAATTACCAGAACAACGCTGGAAAGGCA

TGGAAAGTAACGCTAACGTCATGCAGTCGTTACAATTACGCAAAGCGCCTAAAGGCA

GTTACGTTGAACAGCTAGATATTGATTTCTTGCGTTTTAAAGTACCGCCTAATGAAA

AAGATTGCTTGATCCCGCAACAGTTAATGATGATGCAAGTGGCAGACAATGCTGCGA

AAGACGGAGGTCTAGTTGAAGGTCGTAATGTTGCGGTATTAGTAGCGATGGGCATGG

FIG. 5-21

AACTGGAATTACATCAGTATCGTGGTCGCGTTAATCTAACCACCCAAATTGAAGACA

GCTTATTACAGCAAGGTATTAACCTGACTGTTGAGCAACGTGAAGAACTGACCAATA

TTGCTAAAGACGGTGTTGCCTCGGCTGCACAGCTAAATCAGTATACGAGTTTCATTG

GTAATATTATGGCGTCACGTATTTCGGCGTTATGGGATTTTTCTGGTCCTGCTATTA

CCGTATCGGCTGAAGAAAACTCTGTTTATCGTTGTGTTGAATTAGCTGAAAATCTAT

TTCAAACCAGTGATGTTGAAGCCGTTATTATTGCTGCTGTTGATTTGTCTGGTTCAA

TTGAAAACATTACTTTACGTCAGCACTACGGTCCAGTTAATGAAAAGGGATCTGTAA

GTGAATGTGGTCCGGTTAATGAAAGCAGTTCAGTAACCAACAATATTCTTGATCAGC

AACAATGGCTGGTGGGTGAAGGCGCAGCGGCTATTGTCGTTAAACCGTCATCGCAAG

TCACTGCTGAGCAAGTTTATGCGCGTATTGATGCGGTGAGTTTTGCCCCTGGTAGCA

ATGCGAAAGCAATTACGATTGCAGCGGATAAAGCATTAACACTTGCTGGTATCAGTG

CTGCTGATGTAGCTAGTGTTGAAGCACATGCAAGTGGTTTTAGTGCCGAAAATAATG

CTGAAAAAACCGCGTTACCGACTTTATACCCAAGCGCAAGTATCAGTTCGGTGAAAG

CCAATATTGGTCATACGTTTAATGCCTCGGGTATGGCGAGTATTATTAAAACGGCGC

TGCTGTTAGATCAGAATACGAGTCAAGATCAGAAAAGCAAACATATTGCTATTAACG

GTCTAGGTCGTGATAACAGCTGCGCGCATCTTATCTTATCGAGTTCAGCGCAAGCGC

ATCAAGTTGCACCAGCGCCTGTATCTGGTATGGCCAAGCAACGCCCACAGTTAGTTA

AAACCATCAAACTCGGTGGTCAGTTAATTAGCAACGCGATTGTTAACAGTGCGAGTT

CATCTTTACACGCTATTAAAGCGCAGTTTGCCGGTAAGCACTTAAACAAAGTTAACC

AGCCAGTGATGATGGATAACCTGAAGCCCCAAGGTATTAGCGCTCATGCAACCAATG

AGTATGTGGTGACTGGAGCTGCTAACACTCAAGCTTCTAACATTCAAGCATCTCATG

TTCAAGCGTCAAGTCATGCACAAGAGATAGCACCAAACCAAGTTCAAAATATGCAAG

CTACAGCAGCCGCTGTAAGTTCACCCCTTTCTCAACATCAACACACAGCGCAGCCCG

TAGCGGCACCGAGCGTTGTTGGAGTGACTGTGAAACATAAAGCAAGTAACCAAATTC

ATCAGCAAGCGTCTACGCATAAAGCATTTTTAGAAAGTCGTTTAGCTGCACAGAAAA

FIG. 5-22

ACCTATCGCAACTTGTTGAATTGCAAACCAAGCTGTCAATCCAAACTGGTAGTGACA

ATACATCTAACAATACTGCGTCAACAAGCAATACAGTGCTAACAAATCCTGTATCAG

CAACGCCATTAACACTTGTGTCTAATGCGCCTGTAGTAGCGACAAACCTAACCAGTA

CAGAAGCAAAAGCGCAAGCAGCTGCTACACAAGCTGGTTTTCAGATAAAAGGACCTG

TTGGTTACAACTATCCACCGCTGCAGTTAATTGAACGTTATAATAAACCAGAAAACG

TGATTTACGATCAAGCTGATTTGGTTGAATTCGCTGAAGGTGATATTGGTAAGGTAT

TTGGTGCTGAATACAATATTATTGATGGCTATTCGCGTCGTGTACGTCTGCCAACCT

CAGATTACTTGTTAGTAACACGTGTTACTGAACTTGATGCCAAGGTGCATGAATACA

AGAAATCATACATGTGTACTGAATATGATGTGCCTGTTGATGCACCGTTCTTAATTG

ATGGTCAGATCCCTTGGTCTGTTGCCGTCGAATCAGGCCAGTGTGATTTGATGTTGA

TTTCATATATCGGTATTGATTTCCAAGCGAAAGGCGAACGTGTTTACCGTTTACTTG

ATTGTGAATTAACTTTCCTTGAAGAGATGGCTTTTGGTGGCGATACTTTACGTTACG

AGATCCACATTGATTCGTATGCACGTAACGGCGAGCAATTATTATTCTTCTTCCATT

ACGATTGTTACGTAGGGGATAAGAAGGTACTTATCATGCGTAATGGTTGTGCTGGTT

TCTTTACTGACGAAGAACTTTCTGATGGTAAAGGCGTTATTCATAACGACAAAGACA

AAGCTGAGTTTAGCAATGCTGTTAAATCATCATTCACGCCGTTATTACAACATAACC

GTGGTCAATACGATTATAACGACATGATGAAGTTGGTTAATGGTGATGTTGCCAGTT

GTTTTGGTCCGCAATATGATCAAGGTGGCCGTAATCCATCATTGAAATTCTCGTCTG

AGAAGTTCTTGATGATTGAACGTATTACCAAGATAGACCCAACCGGTGGTCATTGGG

GACTAGGCCTGTTAGAAGGTCAGAAAGATTTAGACCCTGAGCATTGGTATTTCCCTT

GTCACTTTAAAGGTGATCAAGTAATGGCTGGTTCGTTGATGTCGGAAGGTTGTGGCC

AAATGGCGATGTTCTTCATGCTGTCTCTTGGTATGCATACCAATGTGAACAACGCTC

GTTTCCAACCACTACCAGGTGAATCACAAACGGTACGTTGTCGTGGGCAAGTACTGC

CACAGCGCAATACCTTAACTTACCGTATGGAAGTTACTGCGATGGGTATGCATCCAC

AGCCATTCATGAAAGCTAATATTGATATTTTGCTTGACGGTAAAGTGGTTGTTGATT

FIG. 5-23

TCAAAAACTTGAGCGTGATGATCAGCGAACAAGATGAGCATTCAGATTACCCTGTAA

CACTGCCGAGTAATGTGGCGCTTAAAGCGATTACTGCACCTGTTGCGTCAGTAGCAC

CAGCATCTTCACCCGCTAACAGCGCGGATCTAGACGAACGTGGTGTTGAACCGTTTA

AGTTTCCTGAACGTCCGTTAATGCGTGTTGAGTCAGACTTGTCTGCACCGAAAAGCA

AAGGTGTGACACCGATTAAGCATTTTGAAGCGCCTGCTGTTGCTGGTCATCATAGAG

TGCCTAACCAAGCACCGTTTACACCTTGGCATATGTTTGAGTTTGCGACGGGTAATA

TTTCTAACTGTTTCGGTCCTGATTTTGATGTTTATGAAGGTCGTATTCCACCTCGTA

CACCTTGTGGCGATTTACAAGTTGTTACTCAGGTTGTAGAAGTGCAGGGCGAACGTC

TTGATCTTAAAAATCCATCAAGCTGTGTAGCTGAATACTATGTACCGGAAGACGCTT

GGTACTTTACTAAAAACAGCCATGAAAACTGGATGCCTTATTCATTAATCATGGAAA

TTGCATTGCAACCAAATGGCTTTATTTCTGGTTACATGGGCACGACGCTTAAATACC

CTGAAAAAGATCTGTTCTTCCGTAACCTTGATGGTAGCGGCACGTTATTAAAGCAGA

TTGATTTACGCGGCAAGACCATTGTGAATAAATCAGTCTTGGTTAGTACGGCTATTG

CTGGTGGCGCGATTATTCAAAGTTTCACGTTTGATATGTCTGTAGATGGCGAGCTAT

TTTATACTGGTAAAGCTGTATTTGGTTACTTTAGTGGTGAATCACTGACTAACCAAC

TGGGCATTGATAACGGTAAAACGACTAATGCGTGGTTTGTTGATAACAATACCCCCG

CAGCGAATATTGATGTGTTTGATTTAACTAATCAGTCATTGGCTCTGTATAAAGCGC

CTGTGGATAAACCGCATTATAAATTGGCTGGTGGTCAGATGAACTTTATCGATACAG

TGTCAGTGGTTGAAGGCGGTGGTAAAGCGGGCGTGGCTTATGTTTATGGCGAACGTA

CGATTGATGCTGATGATTGGTTCTTCCGTTATCACTTCCACCAAGATCCGGTGATGC

CAGGTTCATTAGGTGTTGAAGCTATTATTGAGTTGATGCAGACCTATGCGCTTAAAA

ATGATTTGGGTGGCAAGTTTGCTAACCCACGTTTCATTGCGCCGATGACGCAAGTTG

ATTGGAAATACCGTGGGCAAATTACGCCGCTGAATAAACAGATGTCACTGGACGTGC

ATATCACTGAGATCGTGAATGACGCTGGTGAAGTGCGAATCGTTGGTGATGCGAATC

TGTCTAAAGATGGTCTGCGTATTTATGAAGTTAAAAACATCGTTTTAAGTATTGTTG

FIG. 5-24

AAGCGTAAAGGGTCAAGTGTAACGTGCTTAAGCGCCGCATTGGTTAAAGACGCTTTG

CACGCCGTGAATCCGTCCATGGAGGCTTGGGGTTGGCATCCATGCCAACAACAGCAA

GCTTACTTTAATCAATACGGCTTGGTGTCCATTTAGACGCCTCGAACTTAGTAGTTA

ATAGACAAAATAATTTAGCTGTGGAATGAATATAGTAAGTAATCATTCGGCAGCTAC

AAAAAAGGAATTAAGAATGTCGAGTTTAGGTTTTAACAATAACAACGCAATTAACTG

GGCTTGGAAAGTAGATCCAGCGTCAGTTCATACACAAGATGCAGAAATTAAAGCAGC

TTTAATGGATCTAACTAAACCTCTCTATGTGGCGAATAATTCAGGCGTAACTGGTAT

AGCTAATCATACGTCAGTAGCAGGTGCGATCAGCAATAACATCGATGTTGATGTATT

GGCGTTTGCGCAAAAGTTAAACCCAGAAGATCTGGGTGATGATGCTTACAAGAAACA

GCACGGCGTTAAATATGCTTATCATGGCGGTGCGATGGCAAATGGTATTGCCTCGGT

TGAATTGGTTGTTGCGTTAGGTAAAGCAGGGCTGTTATGTTCATTTGGTGCTGCAGG

TCTAGTGCCTGATGCGGTTGAAGATGCAATTCGTCGTATTCAAGCTGAATTACCAAA

TGGCCCTTATGCGGTTAACTTGATCCATGCACCAGCAGAAGAAGCATTAGAGCGTGG

CGCGGTTGAACGTTTCCTAAAACTTGGCGTCAAGACGGTAGAGGCTTCAGCTTACCT

TGGTTTAACTGAACACATTGTTTGGTATCGTGCTGCTGGTCTAACTAAAAACGCAGA

TGGCAGTGTTAATATCGGTAACAAGGTTATCGCTAAAGTATCGCGTACCGAAGTTGG

TCGCCGCTTTATGGAACCTGCACCGCAAAAATTACTGGATAAGTTATTAGAACAAAA

TAAGATCACCCCTGAACAAGCTGCTTTAGCGTTGCTTGTACCTATGGCTGATGATAT

TACTGGGGAAGCGGATTCTGGTGGTCATACAGATAACCGTCCGTTTTTAACATTATT

ACCGACGATTATTGGTCTGCGTGATGAAGTGCAAGCGAAGTATAACTTCTCTCCTGC

ATTACGTGTTGGTGCTGGTGGTGGTATCGGAACGCCTGAAGCAGCACTCGCTGCATT

TAACATGGGCGCGGCTTATATCGTTCTGGGTTCTGTGAATCAGGCGTGTGTTGAAGC

GGGTGCATCTGAATATACTCGTAAACTGTTATCGACAGTTGAAATGGCTGATGTGAC

TATGGCACCTGCTGCAGATATGTTTGAAATGGGTGTGAAGCTGCAAGTATTAAAACG

CGGTTCTATGTTCGCGATGCGTGCGAAGAAACTGTATGACTTGTATGTGGCTTATGA

FIG. 5-25

CTCGATTGAAGATATCCCAGCTGCTGAACGTGAGAAGATTGAAAAACAAATCTTCCG

TGCAAACCTAGACGAGATTTGGGATGGCACTATCGCTTTCTTTACTGAACGCGATCC

AGAAATGCTAGCCCGTGCAACGAGTAGTCCTAAACGTAAAATGGCACTTATCTTCCG

TTGGTATCTTGGCCTTTCTTCACGCTGGTCAAACACAGGCGAGAAGGGACGTGAAAT

GGATTATCAGATTTGGGCAGGCCCAAGTTTAGGTGCATTCAACAGCTGGGTGAAAGG

TTCTTACCTTGAAGACTATACCCGCCGTGGCGCTGTAGATGTTGCTTTGCATATGCT

TAAAGGTGCTGCGTATTTACAACGTGTAAACCAGTTGAAATTGCAAGGTGTTAGCTT

AAGTACAGAATTGGCAAGTTATCGTACGAGTGATTAATGTTACTTGATGATATGTGA

ATTAATTAAAGCGCCTGAGGGCGCTTTTTTTGGTTTTTAACTCAGGTGTTGTAACTC

GAAATTGCCCCTTTCAAGTTAGATCGATTACTCACTCACAATATGTTGATATCGCAC

TTGCCATATACTTGCTCATCCAAAGCCCTATATTGATAATGGTGTTAATAGTCTTTA

ATATCCGAGTCTTTCTTCAGCATAATACTAATATAGAGACTCGACCAATGTTAAACA

CAACAAAGAATATATTCTTGTGTACTGCCTTATTATTAACGAGTGCGAGTACGACAG

CTACTACGCTAAACAATTCGATATCAGCAATTGAACAACGTATTTCTGGTCGTATCG

GTGTGGCTGTTTTAGATACGCAAAATAAACAAACGTGGGCTTACAATGGTGATGCAC

ATTTTCCGATGATGAGTACATTCAAAACCCTCGCTTGCGCGAAAATGCTAAGTGAAT

CGACAAATGGTAATCTGGATCCCAGTACTAGCTCATTGATAAAGGCTGAAGAATTAA

TCCCTTGGTCACCAGTCACTAAAACGTTTGTGAATAACACTATTACAGTGGCGAAAG

CGTGTGAAGCAACAATGCTGACCAGTGATAATACCGCGGCTAATATTGTTTTACAGT

ATATCGGAGGCCCTCAAGGCGTTACTGCATTCTTGCGAGAAATTGGTGATGAAGAGA

GTCAGTTAGATCGTATAGAACCTGAATTGAATGAAGCTAAGGTCGGAGACTTGCGTG

ATACCACGACACCGAAAGCCATAGTTACCACGCTCAACAAACTACTACTTGGTGATG

TTCTACTTGATTTGGATAAAAACCAACTTAAAACATGGATGCAAAATAATAAAGTGT

CAGATCCTTTACTGCGTTCTATATTACCGCAAGGCTGGTTTATTGCCGACCGCTCAG

GTGCGGGTGGTAATGGTTCTCGAGGTATAACTGCTATGCTTTGGCACTCCGAGCGTC

FIG. 5-26

AACCGCTAATCATCAGTATTTATTTAACCGAAACTGAGTTAGCAATGGCAATGCGCA

ATGAGATTATTGTTGAGATCGGTAAGCTGATATTCAAAGAATACGCGGTGAAATAAT

AAGTTATTTTTTGATAATACTTTAACGAGCGTAGCTATCGAAGTGAGGGCGTCAATT

AGACACCTTTGCTTCCCCTACAAAATCTAATGTGTATTACCTCGGCTAGTACAATTG

CCCTAAGTTATTTCTGTCCAGCTTTGGCTTAGTGCAATTGCGTTAGCCAATGTGAAC

ACCAAGGGACTTTGTCGTACCATAACTACCAAGCGACTTTGTCGTTTTTATCTTTTC

TTAGACAAACAGAGGTTAAATGAGTGACGCCTTCCAAATCACAGGAATGAATCCGCA

TTTCAATAAAATCTAACCCGTACCAACTCCGTACAAGTTGATCTTTAGTTGTTTAAA

ATCTATAATAAATTCAATTACGGAATTAATCCGTACAACTGGAGGTTTTATGGCTAC

TGCAAGACTTGATATCCGTTTGGATGAAGAAATCAAAGCTAAGGCTGAGAAAGCATC

AGCTTTACTCGGCTTAAAAAGTTTAACCGAATACGTTGTTCGCTTAATGGACGAAGA

TTCAACTAAAGTAGTTTCTGAGCATGAGAGTATTACCGTTGAAGCGAATGTATTCGA

CCAATTTATGGCTGCTTGTGATGAAGCGAAAGCCCCAAATAAAGCATTACTTGAAGC

CGCTGTATTTACTCAGAATGGTGAGTTTAAGTGAGTTATTCCAAACGTTTCAAAGAA

CTGGATAAATCAAAACATGACAGAGCATCATTTGACTGTGGCGAAAAAGAGCTAAAT

GATTTTATCCAAACTCAAGCAGCCAAACATATGCAAGCAGGTATTAGCCGCACTCTG

GTTTTACCTGCTTCTGCGCCGTTACCAAACAAAAAATATCCAATTTGCTCATTTTAT

AGTATCGCGCCAAGCTCAATTAGCCGCGATACGTTACCACAAGCAATGGCTAAAAAG

TTACCACGTTATCCTATCCCTGTTTTTCTTTTGGCTCAACTTGCCGTCCATAAAGAG

TTTCATGGGAGTGGGTTAGGCAAAGTTAGCTTAATTAAAGCGTTAGAGTACCTTTGG

GAAATTAACTCTCACATGAGAGCTTACGCCATCGTTGTTGATTGTTTAACTGAACAA

GCTGAGTCATTCTACGCTAAATATGGTTTCGACGTTCTCTGCGAAATAAATGGTCGA

GTAAGAATGTTCATATCAATGAAAACAGTCAATCAGTTATTCACTTAACAGTAAGAG

TTAGTATAACAGTTGTATGAATTAAATTTATTATATTCGGTAATCTCATTGCGATCA

CGCTAGAAGTGCGAGCGGGTCAGACCGAGGCCACAATAGCAGCCGTTACGTTTAGGG

FIG. 5-27

GATGACTTAAAAAGATAACTACTACGTCAGTGGCGATCCTAGAGGATTAAAGGTTTA
TGATTCACAACATTTATTTATTGTGCTTAATTTTTTCTATCCAATATGCGCAAGCTG
TAAATATCACTGAAGTAGACTTTTATGTCAGTGATGATATCCCTAAAGATGTTGCCA
AATTAAAGATAGGTGAATCCATAACGAACTCCAGCCTTATTCTAAGTAACTCATCTA
TTCCACTCTCGCGGGAGACGGGTAACATATATTACTCTTCATCAATTGCTAACTTGA
ACTATGACTCGATAGAATTTGTTATGGCTCAATTGATGGCCGAAGATTCCAGCCTTT
ACAAGATGCTGGTAAATAGCGATAGGTTGTCCGTGCTAGTAATGACATCTTCCCAGT
CCACAGATCTCTATGGCTCGACTTACTCGGCTTATTTTCCTAATGTTGCGGTCATCG
ATTTGAATTGTGACTCGCTAACTTTAGAACATGAGCTCGGCCATCTATACGGAGCTG
AACATGAAGAAATATATGACGACTATGTCTTCTATGCTGCGATATGTGGAGACTATA
CGACTATCATGAACTCTATGCAGCCTGAAATGAAAGAAAAACAAATGATAAAGGCAT
ATTCATTCCCTGAATTAAAAGTGGATGGCTTGCAGTGCGGAAATGAAAATACGAATA
ACAAAAAGGTTATTTTAGACAATATTGGTCGGTTTAGATAGGATTGGGATATTATTC
TCATTCGGCTCTACTTAGTGCTGTTATTATGAGTGCCAGTGCTTCTATCTACGATAT
TGGTCTTAACAAGTATTTATCTATAGACGCTAAGGTGTTATGTATTTAAGGGATGTT
CAAGATGAAACTAGGTGTAAACGATGTATAGTTGTATAACATTTTTTCAACGGTTGG
AACGTTCGATTCTATCGGGTAACAAGACCGCGACGATCCGCGATAAGTCCGATAGTC
ATTACTTAGTTGGTCAGATGTTAGATGCTTGTACTCACGAAGATAATCGGAAAATGT
GTCAAATAGAAATACTGAGCATTGAATATGTGACGTTTAGTGAATTAAACCGTGCGC
ACGCCAATGCTGAAGGTTTACCGTTTTTGTTTATGCTTAAGTGGATAGTTCGAAAGA
TTTATCCGACTTCAAATGATTTATTTTTCATAAGTTTCAGAGTTGTAACTATCGATA
TCTTATAAGTCTTAGTGCACAAAACAGAACTATTTATAGCGCTCAAGAAGGCGATAA
TTTGATAATGAATTATCGCCTTGTTACTATTAAGAGACTTTAAATGACTGAGATATA
AGATATGACACGGAAGAACATATTGATCACAGGCGCAAGTTCAGGGTTGGGCCGAGG
TATGGCCATCGAATTTGCAAAATCAGGTCATAACTTAGCACTTTGTGCACGTAGACT

FIG. 5-28

TGATAATTTAGTTGCACTGAAAGCAGAACTCTTAGCCCTCAATCCTCACATCCAAAT

CGAAATAAAACCTCTTGATGTCAATGAACATGAACAAGTCTTCACTGTTTTCCATGA

ATTCAAAGCTGAATTTGGTACGCTTGATCGTATTATTGTTAATGCTGGATTAGGCAA

GGGTGGATCC

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FIG. 5-29

1

*AAATGCAATTAATTATGGCGTAAATAGAGTGAAAACATGGCTAATATTCACTAAGTC

CTGAATTTTATATAAAGTTTAATCTGTTATTTTAGCGTTTACCTGGTCTTATCAGTG

AGGTTTATAGCCATTATTAGTGGGATTGAAGTGATTTTTAAAGCTATGTATATTATT

GCAAATATAAATTGTAACAATTAAGACTTTGGACACTTGAGTTCAATTTCGAATTGA

TTGGCATAAAATTTAAAACAGCTAAATCTACCTCAATCATTTTAGCAAATGTATGCA

GGTAGATTTTTTTCGCCATTTAAGAGTACACTTGTACGCTAGGTTTTTGTTTAGTGT

GCAAATGAACGTTTTGATGAGCATTGTTTTTAGAGCACAAAATAGATCCTTACAGGA

GCAATAACGCAATGGCTAAAAAGAACACCACATCGATTAAGCACGCCAAGGATGTGT

TAAGTAGTGATGATCAACAGTTAAATTCTCGCTTGCAAGAATGTCCGATTGCCATCA

TTGGTATGGCATCGGTTTTTGCAGATGCTAAAAACTTGGATCAATTCTGGGATAACA

TCGTTGACTCTGTGGACGCTATTATTGATGTGCCTAGCGATCGCTGGAACATTGACG

ACCATTACTCGGCTGATAAAAAAGCAGCTGACAAGACATACTGCAAACGCGGTGGTT

TCATTCCAGAGCTTGATTTTGATCCGATGGAGTTTGGTTTACCGCCAAATATCCTCG

AGTTAACTGACATCGCTCAATTGTTGTCATTAATTGTTGCTCGTGATGTATTAAGTG

ATGCTGGCATTGGTAGTGATTATGACCATGATAAAATTGGTATCACGCTGGGTGTCG

GTGGTGGTCAGAAACAAATTTCGCCATTAACGTCGCGCCTACAAGGCCCGGTATTAG

AAAAAGTATTAAAAGCCTCAGGCATTGATGAAGATGATCGCGCTATGATCATCGACA

AATTTAAAAAAGCCTACATCGGCTGGGAAGAGAACTCATTCCCAGGCATGCTAGGTA

ACGTTATTGCTGGTCGTATCGCCAATCGTTTTGATTTTGGTGGTACTAACTGTGTGG

TTGATGCGGCATGCGCTGGCTCCCTTGCAGCTGTTAAAATGGCGATCTCAGACTTAC

TTGAATATCGTTCAGAAGTCATGATATCGGGTGGTGTATGTTGTGATAACTCGCCAT

TCATGTATATGTCATTCTCGAAAACACCAGCATTTACCACCAATGATGATATCCGTC

CGTTTGATGACGATTCAAAAGGCATGCTGGTTGGTGAAGGTATTGGCATGATGGCGT

TTAAACGTCTTGAAGATGCTGAACGTGACGGCGACAAAATTTATTCTGTACTGAAAG

GTATCGGTACATCTTCAGATGGTCGTTTCAAATCTATTTACGCTCCACGCCCAGATG

GCCAAGCAAAAGCGCTAAAACGTGCTTATGAAGATGCCGGTTTTGCCCCTGAAACAT

GTGGTCTAATTGAAGGCCATGGTACGGGTACCAAAGCGGGTGATGCCGCAGAATTTG

FIG. 6-1

CTGGCTTGACCAAACACTTTGGCGCCGCCAGTGATGAAAAGCAATATATCGCCTTAG

GCTCAGTTAAATCGCAAATTGGTCATACTAAATCTGCGGCTGGCTCTGCGGGTATGA

TTAAGGCGGCATTAGCGCTGCATCATAAAATCTTACCTGCAACGATCCATATCGATA

AACCAAGTGAAGCCTTGGATATCAAAAACAGCCCGTTATACCTAAACAGCGAAACGC

GTCCTTGGATGCCACGTGAAGATGGTATTCCACGTCGTGCAGGTATCAGCTCATTTG

GTTTTGGCGGCACCAACTTCCATATTATTTTAGAAGAGTATCGCCCAGGTCACGATA

GCGCATATCGCTTAAACTCAGTGAGCCAAACTGTGTTGATCTCGGCAAACGACCAAC

AAGGTATTGTTGCTGAGTTAAATAACTGGCGTACTAAACTGGCTGTCGATGCTGATC

ATCAAGGGTTTGTATTTAATGAGTTAGTGACAACGTGGCCATTAAAAACCCCATCCG

TTAACCAAGCTCGTTTAGGTTTTGTTGCGCGTAATGCAAATGAAGCGATCGCGATGA

TTGATACGGCATTGAAACAATTCAATGCGAACGCAGATAAAATGACATGGTCAGTAC

CTACCGGGGTTTACTATCGTCAAGCCGGTATTGATGCAACAGGTAAAGTGGTTGCGC

TATTCTCAGGGCAAGGTTCGCAATACGTGAACATGGGTCGTGAATTAACCTGTAACT

TCCCAAGCATGATGCACAGTGCTGCGGCGATGGATAAAGAGTTCAGTGCCGCTGGTT

TAGGCCAGTTATCTGCAGTTACTTTCCCTATCCCTGTTTATACGGATGCCGAGCGTA

AGCTACAAGAAGAGCAATTACGTTTAACGCAACATGCGCAACCAGCGATTGGTAGTT

TGAGTGTTGGTCTGTTCAAAACGTTTAAGCAAGCAGGTTTTAAAGCTGATTTTGCTG

CCGGTCATAGTTTCGGTGAGTTAACCGCATTATGGGCTGCCGATGTATTGAGCGAAA

GCGATTACATGATGTTAGCGCGTAGTCGTGGTCAAGCAATGGCTGCGCCAGAGCAAC

AAGATTTTGATGCAGGTAAGATGGCCGCTGTTGTTGGTGATCCAAAGCAAGTCGCTG

TGATCATTGATACCCTTGATGATGTCTCTATTGCTAACTTCAACTCGAATAACCAAG

TTGTTATTGCTGGTACTACGGAGCAGGTTGCTGTAGCGGTTACAACCTTAGGTAATG

CTGGTTTCAAAGTTGTGCCACTGCCGGTATCTGCTGCGTTCCATACACCTTTAGTTC

GTCACGCGCAAAAACCATTTGCTAAAGCGGTTGATAGCGCTAAATTTAAAGCGCCAA

GCATTCCAGTGTTTGCTAATGGCACAGGCTTGGTGCATTCAAGCAAACCGAATGACA

TTAAGAAAAACCTGAAAAACCACATGCTGGAATCTGTTCATTTCAATCAAGAAATTG

FIG. 6-2

ACAACATCTATGCTGATGGTGGCCGCGTATTTATCGAATTTGGTCCAAAGAATGTAT

TAACTAAATTGGTTGAAAACATTCTCACTGAAAAATCTGATGTGACTGCTATCGCGG

TTAATGCTAATCCTAAACAACCTGCGGACGTACAAATGCGCCAAGCTGCGCTGCAAA

TGGCAGTGCTTGGTGTCGCATTAGACAATATTGACCCGTACGACGCCGTTAAGCGTC

CACTTGTTGCGCCGAAAGCATCACCAATGTTGATGAAGTTATCTGCAGCGTCTTATG

TTAGTCCGAAAACGAAGAAAGCGTTTGCTGATGCATTGACTGATGGCTGGACTGTTA

AGCAAGCGAAAGCTGTACCTGCTGTTGTGTCACAACCACAAGTGATTGAAAAGATCG

TTGAAGTTGAAAAGATAGTTGAACGCATTGTCGAAGTAGAGCGTATTGTCGAAGTAG

AAAAAATCGTCTACGTTAATGCTGACGGTTCGCTTATATCGCAAAATAATCAAGACG

TTAACAGCGCTGTTGTTAGCAACGTGACTAATAGCTCAGTGACTCATAGCAGTGATG

CTGACCTTGTTGCCTCTATTGAACGCAGTGTTGGTCAATTTGTTGCACACCAACAGC

AATTATTAAATGTACATGAACAGTTTATGCAAGGTCCACAAGACTACGCGAAAACAG

TGCAGAACGTACTTGCTGCGCAGACGAGCAATGAATTACCGGAAAGTTTAGACCGTA

CATTGTCTATGTATAACGAGTTCCAATCAGAAACGCTACGTGTACATGAAACGTACC

TGAACAATCAGACGAGCAACATGAACACCATGCTTACTGGTGCTGAAGCTGATGTGC

TAGCAACCCCAATAACTCAGGTAGTGAATACAGCCGTTGCCACTAGTCACAAGGTAG

TTGCTCCAGTTATTGCTAATACAGTGACGAATGTTGTATCTAGTGTCAGTAATAACG

CGGCGGTTGCAGTGCAAACTGTGGCATTAGCGCCTACGCAAGAAATCGCTCCAACAG

TCGCTACTACGCCAGCACCCGCATTGGTTGCTATCGTGGCTGAACCTGTGATTGTTG

CGCATGTTGCTACAGAAGTTGCACCAATTACACCATCAGTTACACCAGTTGTCGCAA

CTCAAGCGGCTATCGATGTAGCAACTATTAACAAAGTAATGTTAGAAGTTGTTGCTG

ATAAAACCGGTTATCCAACGGATATGCTGGAACTGAGCATGGACATGGAAGCTGACT

TAGGTATCGACTCAATCAAACGTGTTGAGATATTAGGCGCAGTACAGGAATTGATCC

CTGACTTACCTGAACTTAATCCTGAAGATCTTGCTGAGCTACGCACGCTTGGTGAGA

TTGTCGATTACATGAATTCAAAAGCCCAGGCTGTAGCTCCTACAACAGTACCTGTAA

FIG. 6-3

CAAGTGCACCTGTTTCGCCTGCATCTGCTGGTATTGATTTAGCCCACATCCAAAACG

TAATGTTAGAAGTGGTTGCAGACAAAACCGGTTACCCAACAGACATGCTAGAACTGA

GCATGGATATGGAAGCTGACTTAGGTATTGATTCAATCAAGCGTGTGGAAATCTTAG

GTGCAGTACAGGAGATCATAACTGATTTACCTGAGCTAAACCCTGAAGATCTTGCTG

AATTACGCACCCTAGGTGAAATCGTTAGTTACATGCAAAGCAAAGCGCCAGTCGCTG

AAAGTGCGCCAGTGGCGACGGCTCCTGTAGCAACAAGCTCAGCACCGTCTATCGATT

TGAACCACATTCAAACAGTGATGATGGATGTAGTTGCAGATAAGACTGGTTATCCAA

CTGACATGCTAGAACTTGGCATGGACATGGAAGCTGATTTAGGTATCGATTCAATCA

AACGTGTGGAAATATTAGGCGCAGTGCAGGAGATCATCACTGATTTACCTGAGCTAA

ACCCAGAAGACCTCGCTGAATTACGCACGCTAGGTGAAATCGTTAGTTACATGCAAA

GCAAAGCGCCAGTCGCTGAGAGTGCGCCAGTAGCGACGGCTTCTGTAGCAACAAGCT

CTGCACCGTCTATCGATTTAAACCATATCCAAACAGTGATGATGGAAGTGGTTGCAG

ACAAAACCGGTTATCCAGTAGACATGTTAGAACTTGCTATGGACATGGAAGCTGACC

TAGGTATCGATTCAATCAAGCGTGTAGAAATTTTAGGTGCGGTACAGGAAATCATTA

CTGACTTACCTGAGCTTAACCCTGAAGATCTTGCTGAACTACGTACATTAGGTGAAA

TCGTTAGTTACATGCAAAGCAAAGCGCCCGTAGCTGAAGCGCCTGCAGTACCTGTTG

CAGTAGAAAGTGCACCTACTAGTGTAACAAGCTCAGCACCGTCTATCGATTTAGACC

ACATCCAAAATGTAATGATGGATGTTGTTGCTGATAAGACTGGTTATCCTGCCAATA

TGCTTGAATTAGCAATGGACATGGAAGCCGACCTTGGTATTGATTCAATCAAGCGTG

TTGAAATTCTAGGCGCGGTACAGGAGATCATTACTGATTTACCTGAACTAAACCCAG

AAGACTTAGCTGAACTACGTACGTTAGAAGAAATTGTAACCTACATGCAAAGCAAGG

CGAGTGGTGTTACTGTAAATGTAGTGGCTAGCCCTGAAAATAATGCTGTATCAGATG

CATTTATGCAAAGCAATGTGGCGACTATCACAGCGGCCGCAGAACATAAGGCGGAAT

TTAAACCGGCGCCGAGCGCAACCGTTGCTATCTCTCGTCTAAGCTCTATCAGTAAAA

TAAGCCAAGATTGTAAAGGTGCTAACGCCTTAATCGTAGCTGATGGCACTGATAATG

CTGTGTTACTTGCAGACCACCTATTGCAAACTGGCTGGAATGTAACTGCATTGCAAC

CAACTTGGGTAGCTGTAACAACGACGAAAGCATTTAATAAGTCAGTGAACCTGGTGA

FIG. 6-4

CTTTAAATGGCGTTGATGAAACTGAAATCAACAACATTATTACTGCTAACGCACAAT

TGGATGCAGTTATCTATCTGCACGCAAGTAGCGAAATTAATGCTATCGAATACCCAC

AAGCATCTAAGCAAGGCCTGATGTTAGCCTTCTTATTAGCGAAATTGAGTAAAGTAA

CTCAAGCCGCTAAAGTGCGTGGCGCCTTTATGATTGTTACTCAGCAGGGTGGTTCAT

TAGGTTTTGATGATATCGATTCTGCTACAAGTCATGATGTGAAAACAGACCTAGTAC

AAAGCGGCTTAAACGGTTTAGTTAAGACACTGTCTCACGAGTGGGATAACGTATTCT

GTCGTGCGGTTGATATTGCTTCGTCATTAACGGCTGAACAAGTTGCAAGCCTTGTTA

GTGATGAACTACTTGATGCTAACACTGTATTAACAGAAGTGGGTTATCAACAAGCTG

GTAAAGGCCTTGAACGTATCACGTTAACTGGTGTGGCTACTGACAGCTATGCATTAA

CAGCTGGCAATAACATCGATGCTAACTCGGTATTTTTAGTGAGTGGTGGCGCAAAAG

GTGTAACTGCACATTGTGTTGCTCGTATAGCTAAAGAATATCAGTCTAAGTTCATCT

TATTGGGACGTTCAACGTTCTCAAGTGACGAACCGAGCTGGGCAAGTGGTATTACTG

ATGAAGCGGCGTTAAAGAAAGCAGCGATGCAGTCTTTGATTACAGCAGGTGATAAAC

CAACACCCGTTAAGATCGTACAGCTAATCAAACCAATCCAAGCTAATCGTGAAATTG

CGCAAACCTTGTCTGCAATTACCGCTGCTGGTGGCCAAGCTGAATATGTTTCTGCAG

ATGTAACTAATGCAGCAAGCGTACAAATGGCAGTCGCTCCAGCTATCGCTAAGTTCG

GTGCAATCACTGGCATCATTCATGGCGCGGGTGTGTTAGCTGACCAATTCATTGAGC

AAAAAACACTGAGTGATTTTGAGTCTGTTTACAGCACTAAAATTGACGGTTTGTTAT

CGCTACTATCAGTCACTGAAGCAAGCAACATCAAGCAATTGGTATTGTTCTCGTCAG

CGGCTGGTTTCTACGGTAACCCCGGCCAGTCTGATTACTCGATTGCCAATGAGATCT

TAAATAAAACCGCATACCGCTTTAAATCATTGCACCCACAAGCTCAAGTATTGAGCT

TTAACTGGGGTCCTTGGGACGGTGGCATGGTAACGCCTGAGCTTAAACGTATGTTTG

ACCAACGTGGTGTTTACATTATTCCACTTGATGCAGGTGCACAGTTATTGCTGAATG

AACTAGCCGCTAATGATAACCGTTGTCCACAAATCCTCGTGGGTAATGACTTATCTA

AAGATGCTAGCTCTGATCAAAAGTCTGATGAAAAGAGTACTGCTGTAAAAAAGCCAC

AAGTTAGTCGTTTATCAGATGCTTTAGTAACTAAAAGTATCAAAGCGACTAACAGTA

FIG. 6-5

GCTCTTTATCAAACAAGACTAGTGCTTTATCAGACAGTAGTGCTTTTCAGGTTAACG

AAAACCACTTTTTAGCTGACCACATGATCAAAGGCAATCAGGTATTACCAACGGTAT

GCGCGATTGCTTGGATGAGTGATGCAGCAAAAGCGACTTATAGTAACCGAGACTGTG

CATTGAAGTATGTCGGTTTCGAAGACTATAAATTGTTTAAAGGTGTGGTTTTTGATG

GCAATGAGGCGGCGGATTACCAAATCCAATTGTCGCCTGTGACAAGGGCGTCAGAAC

AGGATTCTGAAGTCCGTATTGCCGCAAAGATCTTTAGCCTGAAAAGTGACGGTAAAC

CTGTGTTTCATTATGCAGCGACAATATTGTTAGCAACTCAGCCACTTAATGCTGTGA

AGGTAGAACTTCCGACATTGACAGAAAGTGTTGATAGCAACAATAAAGTAACTGATG

AAGCACAAGCGTTATACAGCAATGGCACCTTGTTCCACGGTGAAAGTCTGCAGGGCA

TTAAGCAGATATTAAGTTGTGACGACAAGGGCCTGCTATTGGCTTGTCAGATAACCG

ATGTTGCAACAGCTAAGCAGGGATCCTTCCCGTTAGCTGACAACAATATCTTTGCCA

ATGATTTGGTTTATCAGGCTATGTTGGTCTGGGTGCGCAAACAATTTGGTTTAGGTA

GCTTACCTTCGGTGACAACGGCTTGGACTGTGTATCGTGAAGTGGTTGTAGATGAAG

TATTTTATCTGCAACTTAATGTTGTTGAGCATGATCTATTGGGTTCACGCGGCAGTA

AAGCCCGTTGTGATATTCAATTGATTGCTGCTGATATGCAATTACTTGCCGAAGTGA

AATCAGCGCAAGTCAGTGTCAGTGACATTTTGAACGATATGTCATGATCGAGTAAAT

AATAACGATAGGCGTCATGGTGAGCATGGCGTCTGCTTTCTTCATTTTTTAACATTA

ACAATATTAATAGCTAAACGCGGTTGCTTTAAACCAAGTAAACAAGTGCTTTTAGCT

ATTACTATTCCAAACAGGATATTAAAGAGAATATGACGGAATTAGCTGTTATTGGTA

TGGATGCTAAATTTAGCGGACAAGACAATATTGACCGTGTGGAACGCGCTTTCTATG

AAGGTGCTTATGTAGGTAATGTTAGCCGCGTTAGTACCGAATCTAATGTTATTAGCA

ATGGCGAAGAACAAGTTATTACTGCCATGACAGTTCTTAACTCTGTCAGTCTACTAG

CGCAAACGAATCAGTTAAATATAGCTGATATCGCGGTGTTGCTGATTGCTGATGTAA

AAAGTGCTGATGATCAGCTTGTAGTCCAAATTGCATCAGCAATTGAAAAACAGTGTG

CGAGTTGTGTTGTTATTGCTGATTTAGGCCAAGCATTAAATCAAGTAGCTGATTTAG

FIG. 6-6

TTAATAACCAAGACTGTCCTGTGGCTGTAATTGGCATGAATAACTCGGTTAATTTAT

CTCGTCATGATCTTGAATCTGTAACTGCAACAATCAGCTTTGATGAAACCTTCAATG

GTTATAACAATGTAGCTGGGTTCGCGAGTTTACTTATCGCTTCAACTGCGTTTGCCA

ATGCTAAGCAATGTTATATATACGCCAACATTAAGGGCTTCGCTCAATCGGGCGTAA

ATGCTCAATTTAACGTTGGAAACATTAGCGATACTGCAAAGACCGCATTGCAGCAAG

CTAGCATAACTGCAGAGCAGGTTGGTTTGTTAGAAGTGTCAGCAGTCGCTGATTCGG

CAATCGCATTGTCTGAAAGCCAAGGTTTAATGTCTGCTTATCATCATACGCAAACTT

TGCATACTGCATTAAGCAGTGCCCGTAGTGTGACTGGTGAAGGCGGGTGTTTTTCAC

AGGTCGCAGGTTTATTGAAATGTGTAATTGGTTTACATCAACGTTATATTCCGGCGA

TTAAAGATTGGCAACAACCGAGTGACAATCAAATGTCACGGTGGCGGAATTCACCAT

TCTATATGCCTGTAGATGCTCGACCTTGGTTCCCACATGCTGATGGCTCTGCACACA

TTGCCGCTTATAGTTGTGTGACTGCTGACAGCTATTGTCATATTCTTTTACAAGAAA

ACGTCTTACAAGAACTTGTTTTGAAAGAAACAGTCTTGCAAGATAATGACTTAACTG

AAAGCAAGCTTCAGACTCTTGAACAAAACAATCCAGTAGCTGATCTGCGCACTAATG

GTTACTTTGCATCGAGCGAGTTAGCATTAATCATAGTACAAGGTAATGACGAAGCAC

AATTACGCTGTGAATTAGAAACTATTACAGGGCAGTTAAGTACTACTGGCATAAGTA

CTATCAGTATTAAACAGATCGCAGCAGACTGTTATGCCCGTAATGATACTAACAAAG

CCTATAGCGCAGTGCTTATTGCCGAGACTGCTGAAGAGTTAAGCAAAGAAATAACCT

TGGCGTTTGCTGGTATCGCTAGCGTGTTTAATGAAGATGCTAAAGAATGGAAAACCC

CGAAGGGCAGTTATTTTACCGCGCAGCCTGCAAATAAACAGGCTGCTAACAGCACAC

AGAATGGTGTCACCTTCATGTACCCAGGTATTGGTGCTACATATGTTGGTTTAGGGC

GTGATCTATTTCATCTATTCCCACAGATTTATCAGCCTGTAGCGGCTTTAGCCGATG

ACATTGGCGAAAGTCTAAAAGATACTTTACTTAATCCACGCAGTATTAGTCGTCATA

GCTTTAAAGAACTCAAGCAGTTGGATCTGGACCTGCGCGGTAACTTAGCCAATATCG

CTGAAGCCGGTGTGGGTTTTGCTTGTGTGTTTACCAAGGTATTTGAAGAAGTCTTTG

CCGTTAAAGCTGACTTTGCTACAGGTTATAGCATGGGTGAAGTAAGCATGTATGCAG

CACTAGGCTGCTGGCAGCAACCGGGATTGATGAGTGCTCGCCTTGCACAATCGAATA

FIG. 6-7

CCTTTAATCATCAACTTTGCGGCGAGTTAAGAACACTACGTCAGCATTGGGGCATGG
ATGATGTAGCTAACGGTACGTTCGAGCAGATCTGGGAAACCTATACCATTAAGGCAA
CGATTGAACAGGTCGAAATTGCCTCTGCAGATGAAGATCGTGTGTATTGCACCATTA
TCAATACACCTGATAGCTTGTTGTTAGCCGGTTATCCAGAAGCCTGTCAGCGAGTCA
TTAAGAATTTAGGTGTGCGTGCAATGGCATTGAATATGGCGAACGCAATTCACAGCG
CGCCAGCTTATGCCGAATACGATCATATGGTTGAGCTATACCATATGGATGTTACTC
CACGTATTAATACCAAGATGTATTCAAGCTCATGTTATTTACCGATTCCACAACGCA
GCAAAGCGATTTCCCACAGTATTGCTAAATGTTTGTGTGATGTGGTGGATTTCCCAC
GTTTGGTTAATACCTTACATGACAAAGGTGCGCGGGTATTCATTGAAATGGGTCCAG
GTCGTTCGTTATGTAGCTGGGTAGATAAGATCTTAGTTAATGGCGATGGCGATAATA
AAAAGCAAAGCCAACATGTATCTGTTCCTGTGAATGCCAAAGGCACCAGTGATGAAC
TTACTTATATTCGTGCGATTGCTAAGTTAATTAGTCATGGCGTGAATTTGAATTTAG
ATAGCTTGTTTAACGGGTCAATCCTGGTTAAAGCAGGCCATATAGCAAACACGAACA
AATAGTCAACATCGATATCTAGCGCTGGTGAGTTATACCTCATTAGTTGAAATATGG
ATTTAAAGAGAGTAATTATGGAAAATATTGCAGTAGTAGGTATTGCTAATTTGTTCC
CGGGCTCACAAGCACCGGATCAATTTTGGCAGCAATTGCTTGAACAACAAGATTGCC
GCAGTAAGGCGACCGCTGTTCAAATGGGCGTTGATCCTGCTAAATATACCGCCAACA
AAGGTGACACAGATAAATTTTACTGTGTGCACGGCGGTTACATCAGTGATTTCAATT
TTGATGCTTCAGGTTATCAACTCGATAATGATTATTTAGCCGGTTTAGATGACCTTA
ATCAATGGGGGCTTTATGTTACGAAACAAGCCCTTACCGATGCGGGTTATTGGGGCA
GTACTGCACTAGAAAACTGTGGTGTGATTTTAGGTAATTTGTCATTCCCAACTAAAT
CATCTAATCAGCTGTTTATGCCTTTGTATCATCAAGTTGTTGATAATGCCTTAAAGG
CGGTATTACATCCTGATTTTCAATTAACGCATTACACAGCACCGAAAAAAACACATG
CTGACAATGCATTAGTAGCAGGTTATCCAGCTGCATTGATCGCGCAAGCGGCGGGTC
TTGGTGGTTCACATTTTGCACTGGATGCGGCTTGTGCTTCATCTTGTTATAGCGTTA
AGTTAGCGTGTGATTACCTGCATACGGGTAAAGCCAACATGATGCTTGCTGGTGCGG

FIG. 6-8

TATCTGCAGCAGATCCTATGTTCGTAAATATGGGTTTCTCGATATTCCAAGCTTACC

CAGCTAACAATGTACATGCCCCGTTTGACCAAAATTCACAAGGTCTATTTGCCGGTG

AAGGCGCGGGCATGATGGTATTGAAACGTCAAAGTGATGCAGTACGTGATGGTGATC

ATATTTACGCCATTATTAAAGGCGGCGCATTATCGAATGACGGTAAAGGCGAGTTTG

TATTAAGCCCGAACACCAAGGGCCAAGTATTAGTATATGAACGTGCTTATGCCGATG

CAGATGTTGACCCGAGTACAGTTGACTATATTGAATGTCATGCAACGGGCACACCTA

AGGGTGACAATGTTGAATTGCGTTCGATGGAAACCTTTTTCAGTCGCGTAAATAACA

AACCATTACTGGGCTCGGTTAAATCTAACCTTGGTCATTTGTTAACTGCCGCTGGTA

TGCCTGGCATGACCAAAGCTATGTTAGCGCTAGGTAAAGGTCTTATTCCTGCAACGA

TTAACTTAAAGCAACCACTGCAATCTAAAAACGGTTACTTTACTGGCGAGCAAATGC

CAACGACGACTGTGTCTTGGCCAACAACTCCGGGTGCCAAGGCAGATAAACCGCGTA

CCGCAGGTGTGAGCGTATTTGGTTTTGGTGGCAGCAACGCCCATTTGGTATTACAAC

AGCCAACGCAAACACTCGAGACTAATTTTAGTGTTGCTAAACCACGTGAGCCTTTGG

CTATTATTGGTATGGACAGCCATTTTGGTAGTGCCAGTAATTTAGCGCAGTTCAAAA

CCTTATTAAATAATAATCAAAATACCTTCCGTGAATTACCAGAACAACGCTGGAAAG

GCATGGAAAGTAACGCTAACGTCATGCAGTCGTTACAATTACGCAAAGCGCCTAAAG

GCAGTTACGTTGAACAGCTAGATATTGATTTCTTGCGTTTTAAAGTACCGCCTAATG

AAAAAGATTGCTTGATCCCGCAACAGTTAATGATGATGCAAGTGGCAGACAATGCTG

CGAAAGACGGAGGTCTAGTTGAAGGTCGTAATGTTGCGGTATTAGTAGCGATGGGCA

TGGAACTGGAATTACATCAGTATCGTGGTCGCGTTAATCTAACCACCCAAATTGAAG

ACAGCTTATTACAGCAAGGTATTAACCTGACTGTTGAGCAACGTGAAGAACTGACCA

ATATTGCTAAAGACGGTGTTGCCTCGGCTGCACAGCTAAATCAGTATACGAGTTTCA

TTGGTAATATTATGGCGTCACGTATTTCGGCGTTATGGGATTTTTCTGGTCCTGCTA

TTACCGTATCGGCTGAAGAAAACTCTGTTTATCGTTGTGTTGAATTAGCTGAAAATC

TATTTCAAACCAGTGATGTTGAAGCCGTTATTATTGCTGCTGTTGATTTGTCTGGTT

CAATTGAAAACATTACTTTACGTCAGCACTACGGTCCAGTTAATGAAAAGGGATCTG

FIG. 6-9

TAAGTGAATGTGGTCCGGTTAATGAAAGCAGTTCAGTAACCAACAATATTCTTGATC

AGCAACAATGGCTGGTGGGTGAAGGCGCAGCGGCTATTGTCGTTAAACCGTCATCGC

AAGTCACTGCTGAGCAAGTTTATGCGCGTATTGATGCGGTGAGTTTTGCCCCTGGTA

GCAATGCGAAAGCAATTACGATTGCAGCGGATAAAGCATTAACACTTGCTGGTATCA

GTGCTGCTGATGTAGCTAGTGTTGAAGCACATGCAAGTGGTTTTAGTGCCGAAAATA

ATGCTGAAAAAACCGCGTTACCGACTTTATACCCAAGCGCAAGTATCAGTTCGGTGA

AAGCCAATATTGGTCATACGTTTAATGCCTCGGGTATGGCGAGTATTATTAAAACGG

CGCTGCTGTTAGATCAGAATACGAGTCAAGATCAGAAAAGCAAACATATTGCTATTA

ACGGTCTAGGTCGTGATAACAGCTGCGCGCATCTTATCTTATCGAGTTCAGCGCAAG

CGCATCAAGTTGCACCAGCGCCTGTATCTGGTATGGCCAAGCAACGCCCACAGTTAG

TTAAAACCATCAAACTCGGTGGTCAGTTAATTAGCAACGCGATTGTTAACAGTGCGA

GTTCATCTTTACACGCTATTAAAGCGCAGTTTGCCGGTAAGCACTTAAACAAAGTTA

ACCAGCCAGTGATGATGGATAACCTGAAGCCCCAAGGTATTAGCGCTCATGCAACCA

ATGAGTATGTGGTGACTGGAGCTGCTAACACTCAAGCTTCTAACATTCAAGCATCTC

ATGTTCAAGCGTCAAGTCATGCACAAGAGATAGCACCAAACCAAGTTCAAAATATGC

AAGCTACAGCAGCCGCTGTAAGTTCACCCCTTTCTCAACATCAACACACAGCGCAGC

CCGTAGCGGCACCGAGCGTTGTTGGAGTGACTGTGAAACATAAAGCAAGTAACCAAA

TTCATCAGCAAGCGTCTACGCATAAAGCATTTTTAGAAAGTCGTTTAGCTGCACAGA

AAAACCTATCGCAACTTGTTGAATTGCAAACCAAGCTGTCAATCCAAACTGGTAGTG

ACAATACATCTAACAATACTGCGTCAACAAGCAATACAGTGCTAACAAATCCTGTAT

CAGCAACGCCATTAACACTTGTGTCTAATGCGCCTGTAGTAGCGACAAACCTAACCA

GTACAGAAGCAAAAGCGCAAGCAGCTGCTACACAAGCTGGTTTTCAGATAAAAGGAC

CTGTTGGTTACAACTATCCACCGCTGCAGTTAATTGAACGTTATAATAAACCAGAAA

ACGTGATTTACGATCAAGCTGATTTGGTTGAATTCGCTGAAGGTGATATTGGTAAGG

TATTTGGTGCTGAATACAATATTATTGATGGCTATTCGCGTCGTGTACGTCTGCCAA

CCTCAGATTACTTGTTAGTAACACGTGTTACTGAACTTGATGCCAAGGTGCATGAAT

FIG. 6-10

ACAAGAAATCATACATGTGTACTGAATATGATGTGCCTGTTGATGCACCGTTCTTAA

TTGATGGTCAGATCCCTTGGTCTGTTGCCGTCGAATCAGGCCAGTGTGATTTGATGT

TGATTTCATATATCGGTATTGATTTCCAAGCGAAAGGCGAACGTGTTTACCGTTTAC

TTGATTGTGAATTAACTTTCCTTGAAGAGATGGCTTTTGGTGGCGATACTTTACGTT

ACGAGATCCACATTGATTCGTATGCACGTAACGGCGAGCAATTATTATTCTTCTTCC

ATTACGATTGTTACGTAGGGGATAAGAAGGTACTTATCATGCGTAATGGTTGTGCTG

GTTTCTTTACTGACGAAGAACTTTCTGATGGTAAAGGCGTTATTCATAACGACAAAG

ACAAAGCTGAGTTTAGCAATGCTGTTAAATCATCATTCACGCCGTTATTACAACATA

ACCGTGGTCAATACGATTATAACGACATGATGAAGTTGGTTAATGGTGATGTTGCCA

GTTGTTTTGGTCCGCAATATGATCAAGGTGGCCGTAATCCATCATTGAAATTCTCGT

CTGAGAAGTTCTTGATGATTGAACGTATTACCAAGATAGACCCAACCGGTGGTCATT

GGGGACTAGGCCTGTTAGAAGGTCAGAAAGATTTAGACCCTGAGCATTGGTATTTCC

CTTGTCACTTTAAAGGTGATCAAGTAATGGCTGGTTCGTTGATGTCGGAAGGTTGTG

GCCAAATGGCGATGTTCTTCATGCTGTCTCTTGGTATGCATACCAATGTGAACAACG

CTCGTTTCCAACCACTACCAGGTGAATCACAAACGGTACGTTGTCGTGGGCAAGTAC

TGCCACAGCGCAATACCTTAACTTACCGTATGGAAGTTACTGCGATGGGTATGCATC

CACAGCCATTCATGAAAGCTAATATTGATATTTTGCTTGACGGTAAAGTGGTTGTTG

ATTTCAAAAACTTGAGCGTGATGATCAGCGAACAAGATGAGCATTCAGATTACCCTG

TAACACTGCCGAGTAATGTGGCGCTTAAAGCGATTACTGCACCTGTTGCGTCAGTAG

CACCAGCATCTTCACCCGCTAACAGCGCGGATCTAGACGAACGTGGTGTTGAACCGT

TTAAGTTTCCTGAACGTCCGTTAATGCGTGTTGAGTCAGACTTGTCTGCACCGAAAA

GCAAAGGTGTGACACCGATTAAGCATTTTGAAGCGCCTGCTGTTGCTGGTCATCATA

GAGTGCCTAACCAAGCACCGTTTACACCTTGGCATATGTTTGAGTTTGCGACGGGTA

ATATTTCTAACTGTTTCGGTCCTGATTTTGATGTTTATGAAGGTCGTATTCCACCTC

GTACACCTTGTGGCGATTTACAAGTTGTTACTCAGGTTGTAGAAGTGCAGGGCGAAC

GTCTTGATCTTAAAAATCCATCAAGCTGTGTAGCTGAATACTATGTACCGGAAGACG

FIG. 6-11

CTTGGTACTTTACTAAAAACAGCCATGAAAACTGGATGCCTTATTCATTAATCATGG

AAATTGCATTGCAACCAAATGGCTTTATTTCTGGTTACATGGGCACGACGCTTAAAT

ACCCTGAAAAAGATCTGTTCTTCCGTAACCTTGATGGTAGCGGCACGTTATTAAAGC

AGATTGATTTACGCGGCAAGACCATTGTGAATAAATCAGTCTTGGTTAGTACGGCTA

TTGCTGGTGGCGCGATTATTCAAAGTTTCACGTTTGATATGTCTGTAGATGGCGAGC

TATTTTATACTGGTAAAGCTGTATTTGGTTACTTTAGTGGTGAATCACTGACTAACC

AACTGGGCATTGATAACGGTAAAACGACTAATGCGTGGTTTGTTGATAACAATACCC

CCGCAGCGAATATTGATGTGTTTGATTTAACTAATCAGTCATTGGCTCTGTATAAAG

CGCCTGTGGATAAACCGCATTATAAATTGGCTGGTGGTCAGATGAACTTTATCGATA

CAGTGTCAGTGGTTGAAGGCGGTGGTAAAGCGGGCGTGGCTTATGTTTATGGCGAAC

GTACGATTGATGCTGATGATTGGTTCTTCCGTTATCACTTCCACCAAGATCCGGTGA

TGCCAGGTTCATTAGGTGTTGAAGCTATTATTGAGTTGATGCAGACCTATGCGCTTA

AAAATGATTTGGGTGGCAAGTTTGCTAACCCACGTTTCATTGCGCCGATGACGCAAG

TTGATTGGAAATACCGTGGGCAAATTACGCCGCTGAATAAACAGATGTCACTGGACG

TGCATATCACTGAGATCGTGAATGACGCTGGTGAAGTGCGAATCGTTGGTGATGCGA

ATCTGTCTAAAGATGGTCTGCGTATTTATGAAGTTAAAAACATCGTTTTAAGTATTG

TTGAAGCGTAAAGGGTCAAGTGTAACGTGCTTAAGCGCCGCATTGGTTAAAGACGCT

TTGCACGCCGTGAATCCGTCCATGGAGGCTTGGGGTTGGCATCCATGCCAACAACAG

CAAGCTTACTTTAATCAATACGGCTTGGTGTCCATTTAGACGCCTCGAACTTAGTAG

TTAATAGACAAAATAATTTAGCTGTGGAATGAATATAGTAAGTAATCATTCGGCAGC

TACAAAAAAGGAATTAAGAATGTCGAGTTTAGGTTTTAACAATAACAACGCAATTAA

CTGGGCTTGGAAAGTAGATCCAGCGTCAGTTCATACACAAGATGCAGAAATTAAAGC

AGCTTTAATGGATCTAACTAAACCTCTCTATGTGGCGAATAATTCAGGCGTAACTGG

TATAGCTAATCATACGTCAGTAGCAGGTGCGATCAGCAATAACATCGATGTTGATGT

ATTGGCGTTTGCGCAAAAGTTAAACCCAGAAGATCTGGGTGATGATGCTTACAAGAA

ACAGCACGGCGTTAAATATGCTTATCATGGCGGTGCGATGGCAAATGGTATTGCCTC

FIG. 6-12

GGTTGAATTGGTTGTTGCGTTAGGTAAAGCAGGGCTGTTATGTTCATTTGGTGCTGC

AGGTCTAGTGCCTGATGCGGTTGAAGATGCAATTCGTCGTATTCAAGCTGAATTACC

AAATGGCCCTTATGCGGTTAACTTGATCCATGCACCAGCAGAAGAAGCATTAGAGCG

TGGCGCGGTTGAACGTTTCCTAAAACTTGGCGTCAAGACGGTAGAGGCTTCAGCTTA

CCTTGGTTTAACTGAACACATTGTTTGGTATCGTGCTGCTGGTCTAACTAAAAACGC

AGATGGCAGTGTTAATATCGGTAACAAGGTTATCGCTAAAGTATCGCGTACCGAAGT

TGGTCGCCGCTTTATGGAACCTGCACCGCAAAAATTACTGGATAAGTTATTAGAACA

AAATAAGATCACCCCTGAACAAGCTGCTTTAGCGTTGCTTGTACCTATGGCTGATGA

TATTACTGGGGAAGCGGATTCTGGTGGTCATACAGATAACCGTCCGTTTTTAACATT

ATTACCGACGATTATTGGTCTGCGTGATGAAGTGCAAGCGAAGTATAACTTCTCTCC

TGCATTACGTGTTGGTGCTGGTGGTGGTATCGGAACGCCTGAAGCAGCACTCGCTGC

ATTTAACATGGGCGCGGCTTATATCGTTCTGGGTTCTGTGAATCAGGCGTGTGTTGA

AGCGGGTGCATCTGAATATACTCGTAAACTGTTATCGACAGTTGAAATGGCTGATGT

GACTATGGCACCTGCTGCAGATATGTTTGAAATGGGTGTGAAGCTGCAAGTATTAAA

ACGCGGTTCTATGTTCGCGATGCGTGCGAAGAAACTGTATGACTTGTATGTGGCTTA

TGACTCGATTGAAGATATCCCAGCTGCTGAACGTGAGAAGATTGAAAAACAAATCTT

CCGTGCAAACCTAGACGAGATTTGGGATGGCACTATCGCTTTCTTTACTGAACGCGA

TCCAGAAATGCTAGCCCGTGCAACGAGTAGTCCTAAACGTAAAATGGCACTTATCTT

CCGTTGGTATCTTGGCCTTTCTTCACGCTGGTCAAACACAGGCGAGAAGGGACGTGA

AATGGATTATCAGATTTGGGCAGGCCCAAGTTTAGGTGCATTCAACAGCTGGGTGAA

AGGTTCTTACCTTGAAGACTATACCCGCCGTGGCGCTGTAGATGTTGCTTTGCATAT

GCTTAAAGGTGCTGCGTATTTACAACGTGTAAACCAGTTGAAATTGCAAGGTGTTAG

CTTAAGTACAGAATTGGCAAGTTATCGTACGAGTGATTAATGTTACTTGATGATATG

TGAATTAATTAAAGCGCCTGAGGGCGCTTTTTTTTGGTTTTTAACTCAGGTGTTGTAA

CTCGAAATTGCCCCTTTC

*

19227

FIG. 6-13

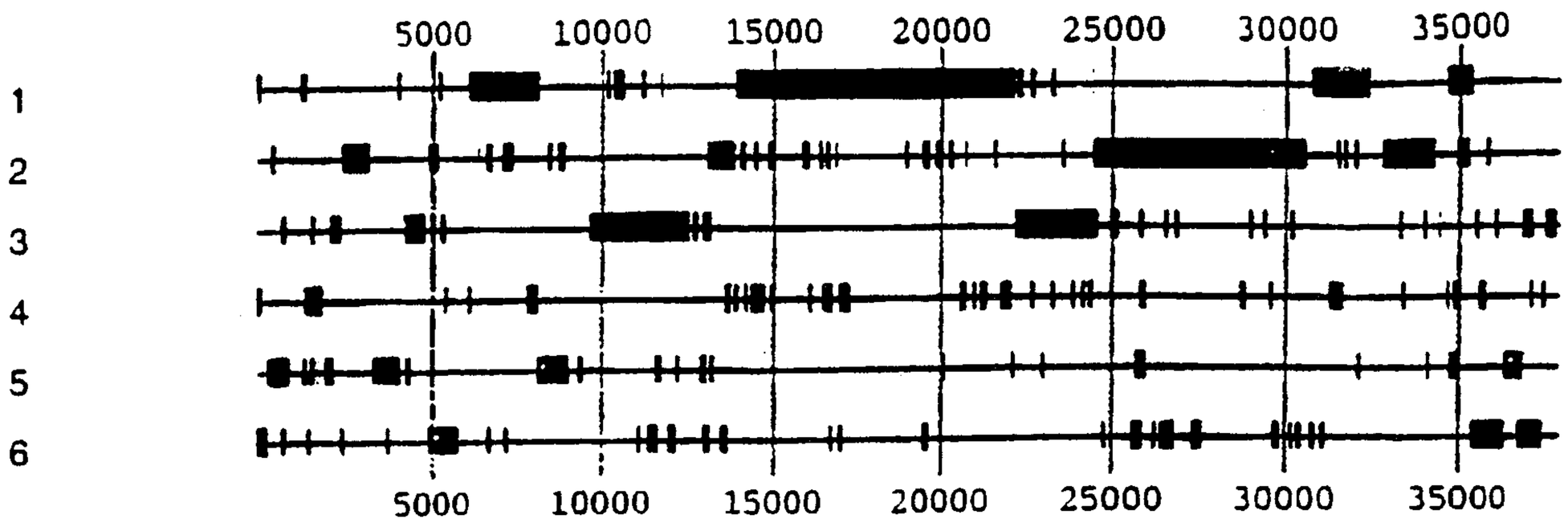

5000
10000
15000
20000
25000
30000
35000
1
2
3
4
5
6
5000
10000
15000
20000
25000
30000
35000

FIG. 7A

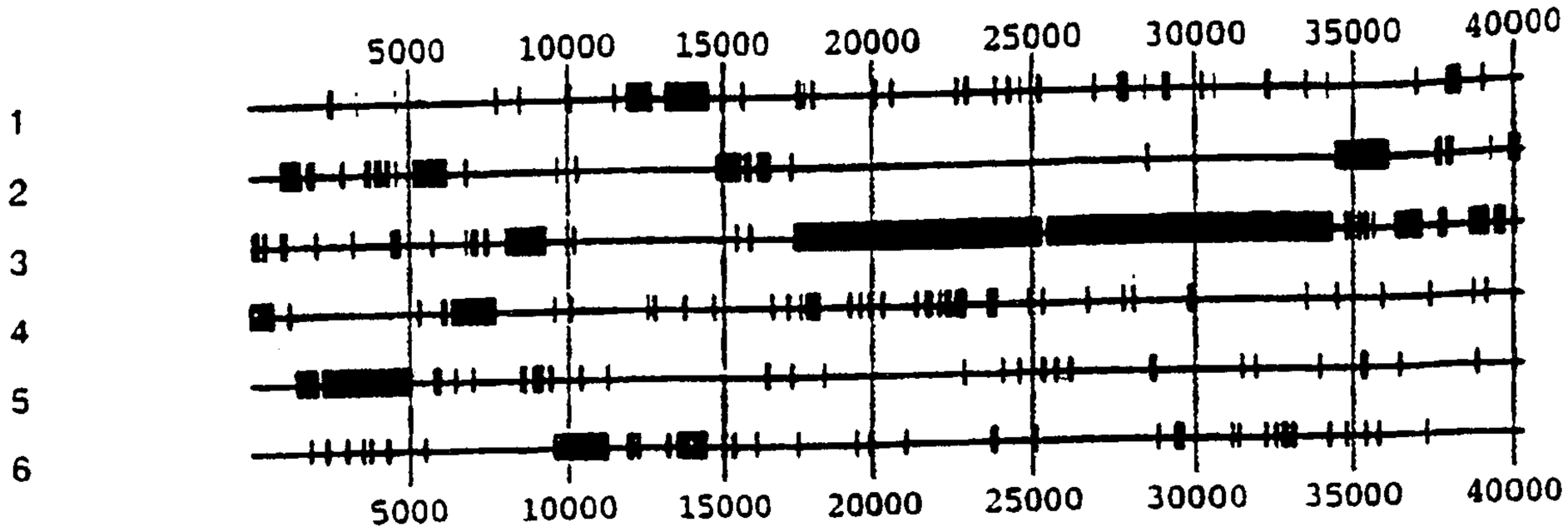


FIG. 7B

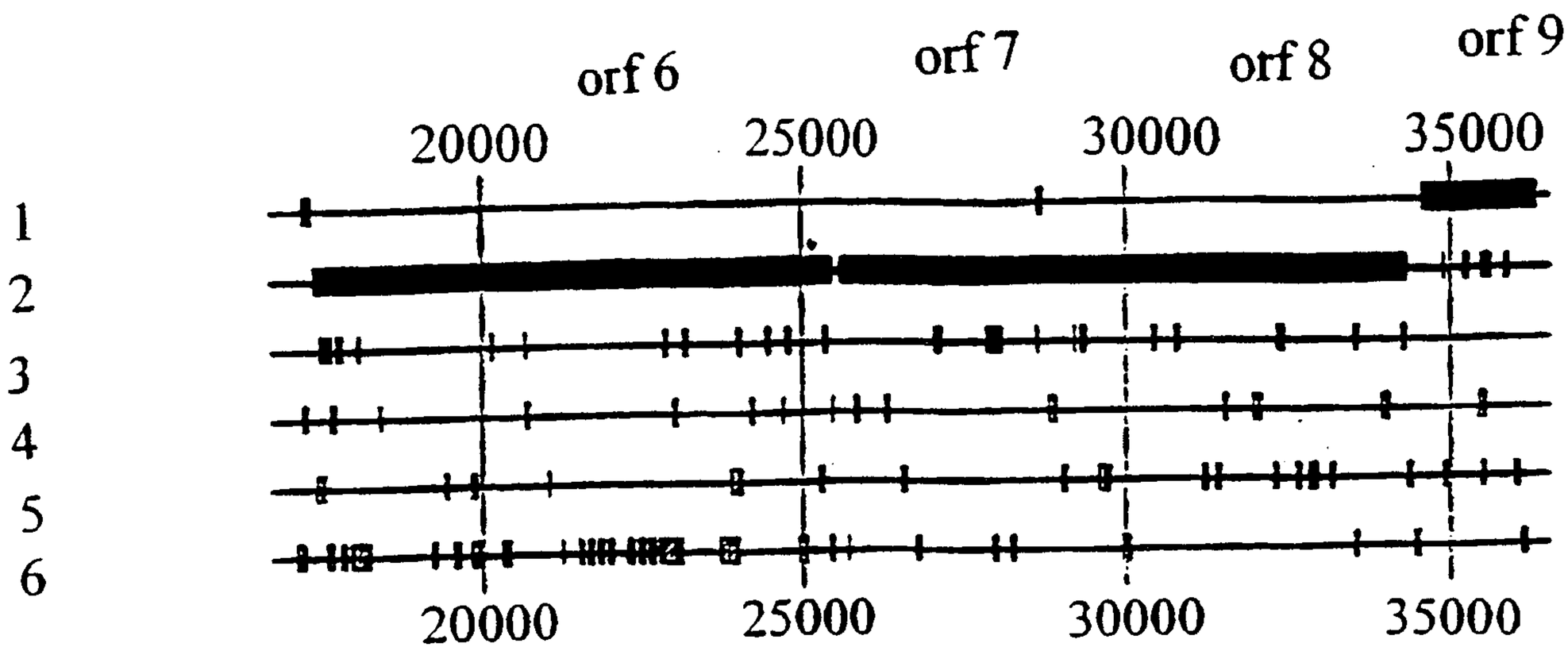

orf 6
orf 7
orf 8
orf 9
20000
25000
30000
35000
1
2
3
4
5
6
20000
25000
30000
35000

FIG. 8

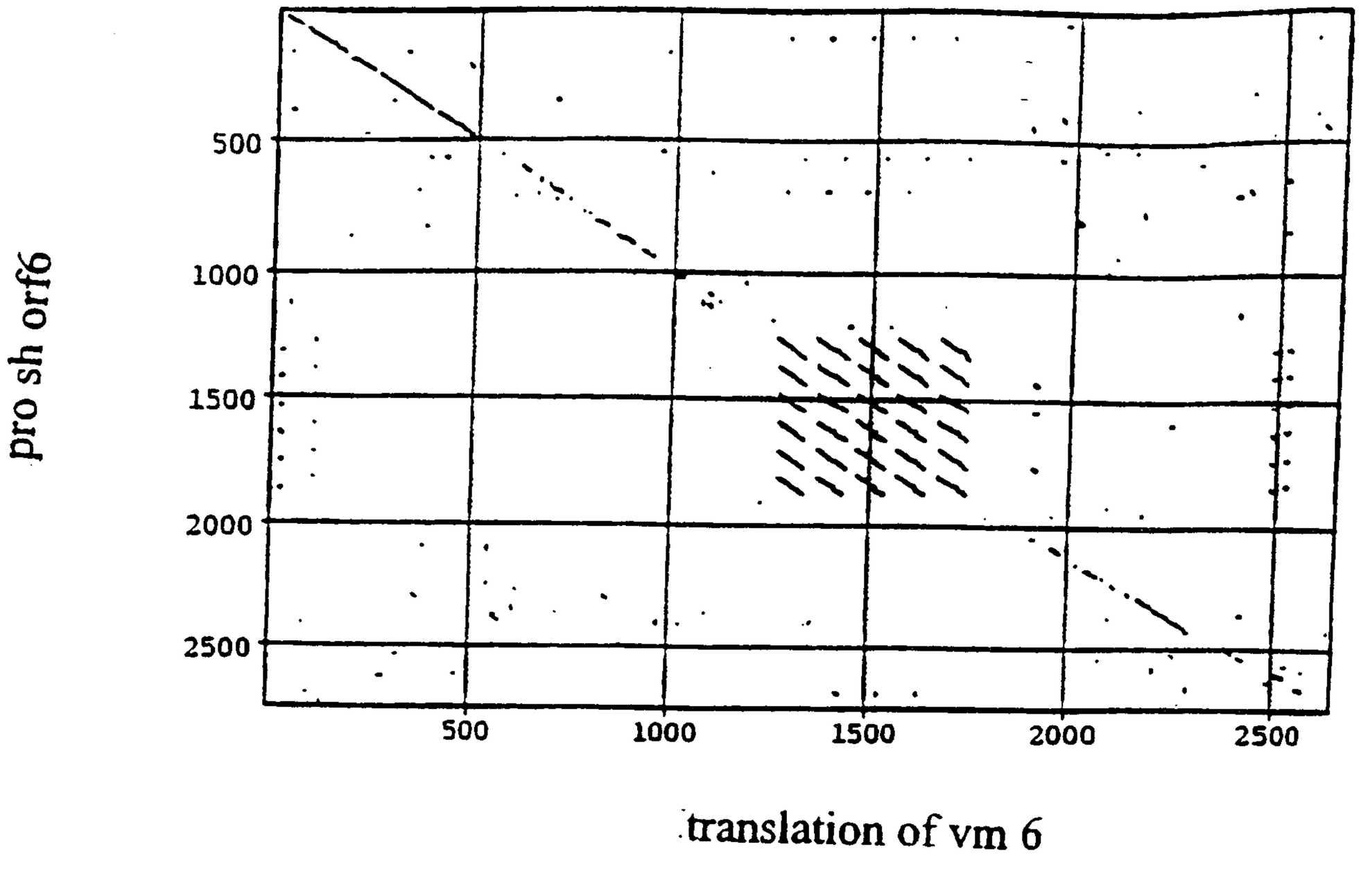

500
1000
1500
2000
2500
pro sh orf6
500
1000
1500
2000
2500
translation of vm 6

FIG. 9

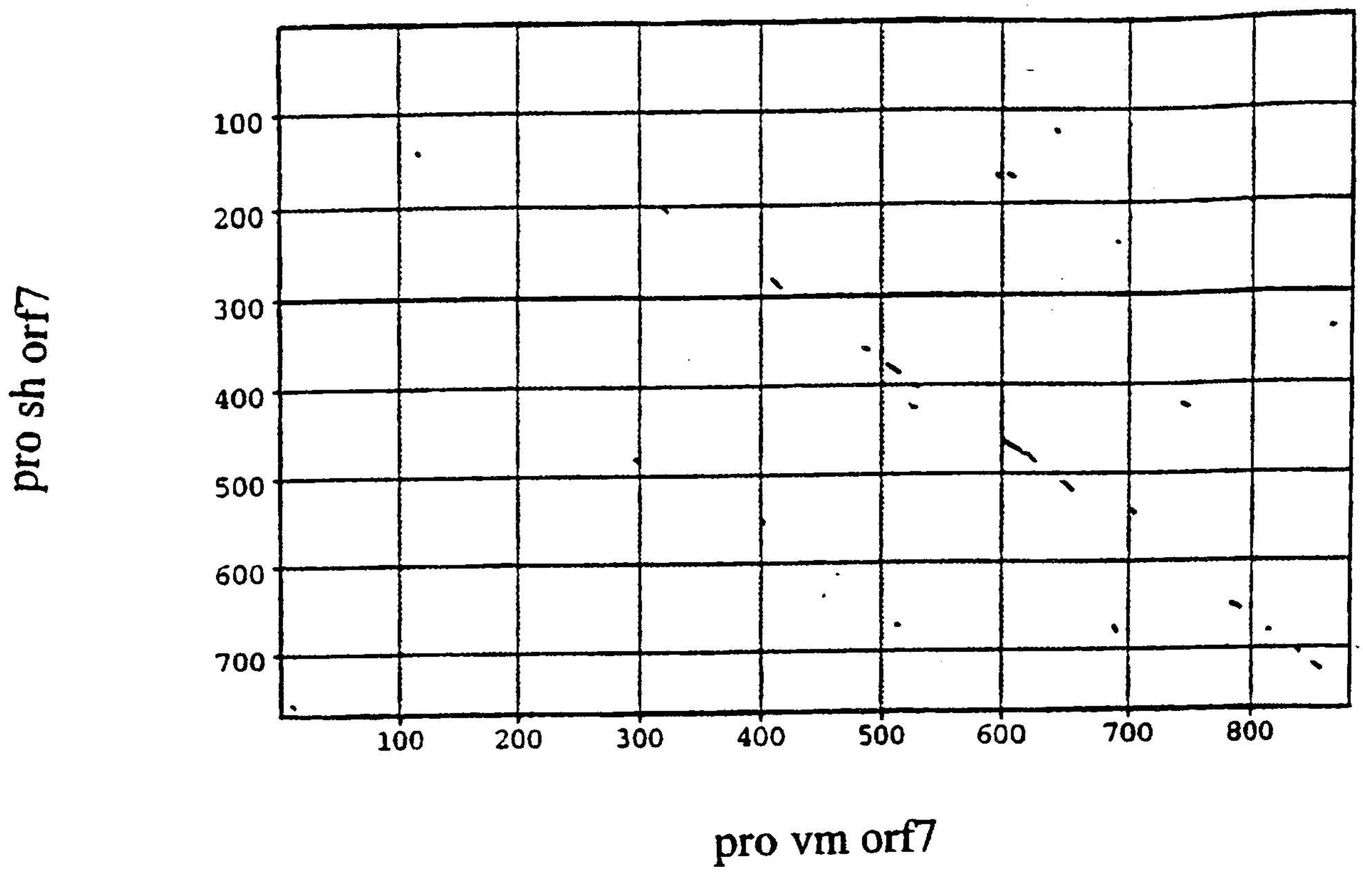

100
200
300
400
500
600
700
100
200
300
400
500
600
700
800
pro sh orf7
pro vm orf7

FIG. 10

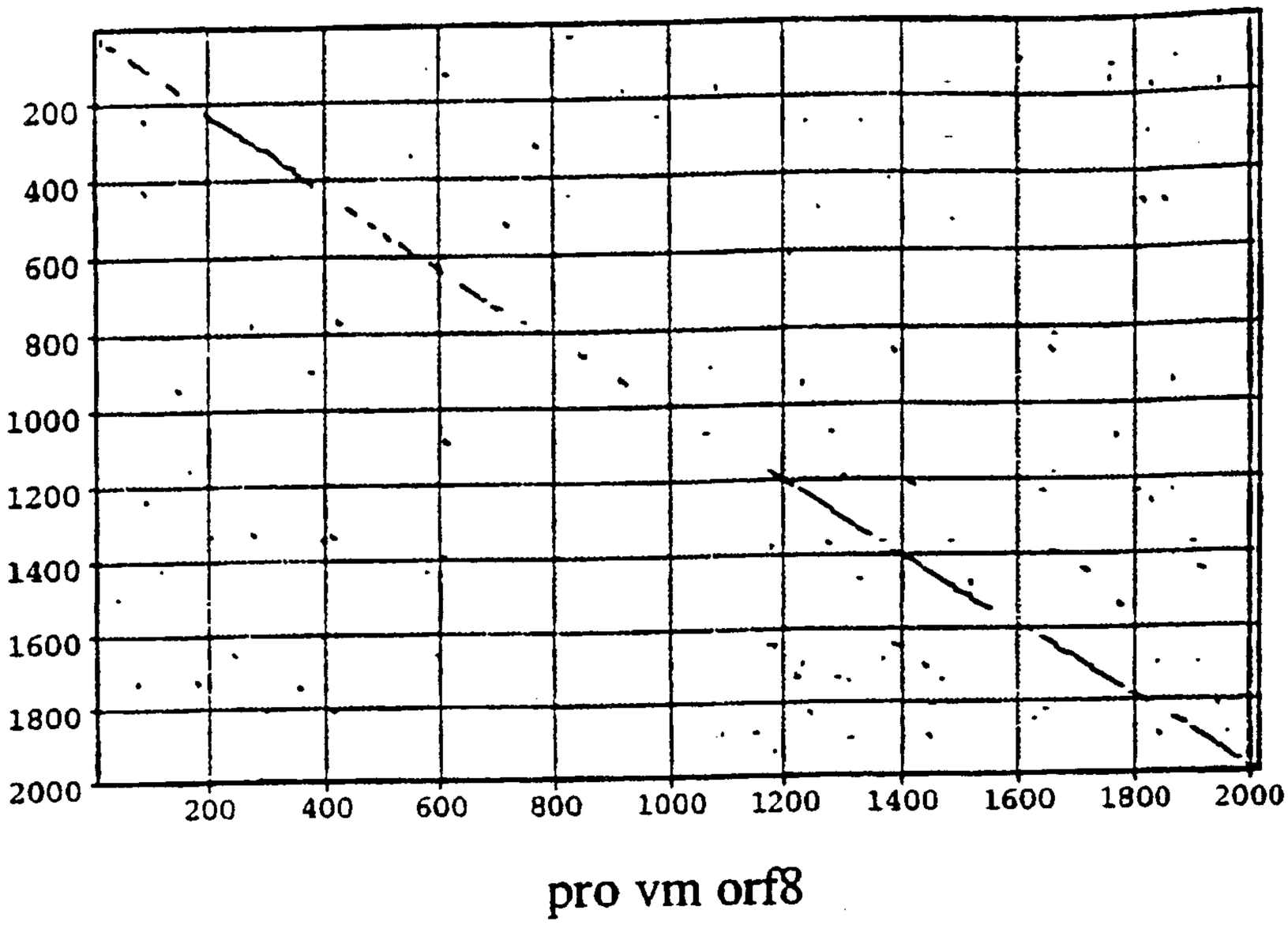

200
400
600
800
1000
1200
1400
1600
1800
2000
pro sh orf8
pro vm orf8

FIG. 11

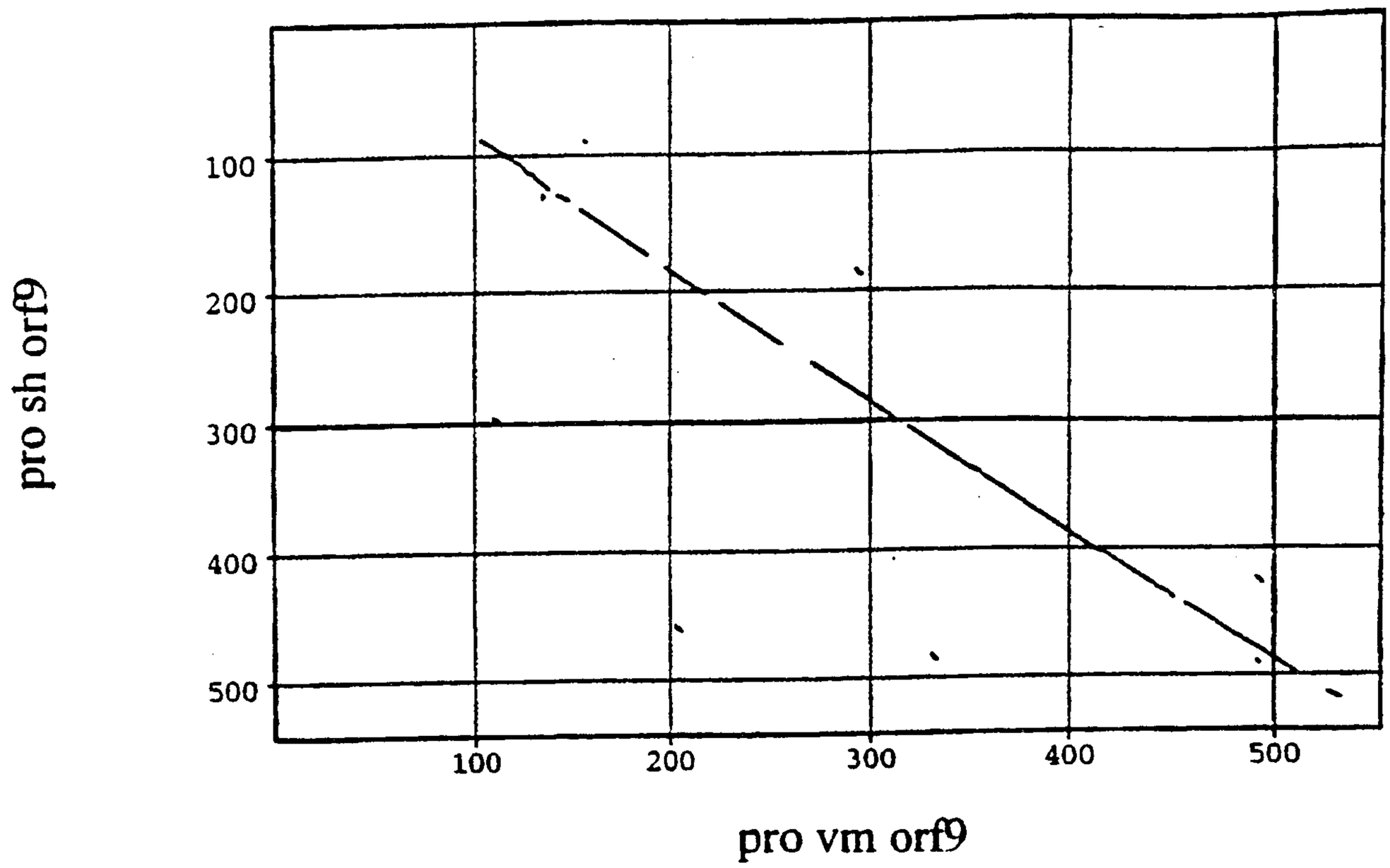
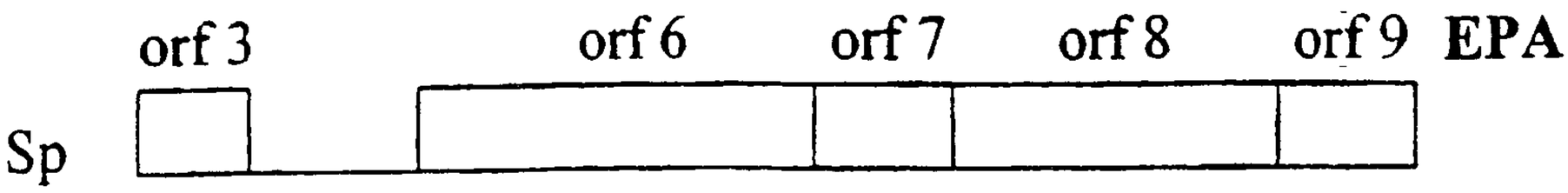
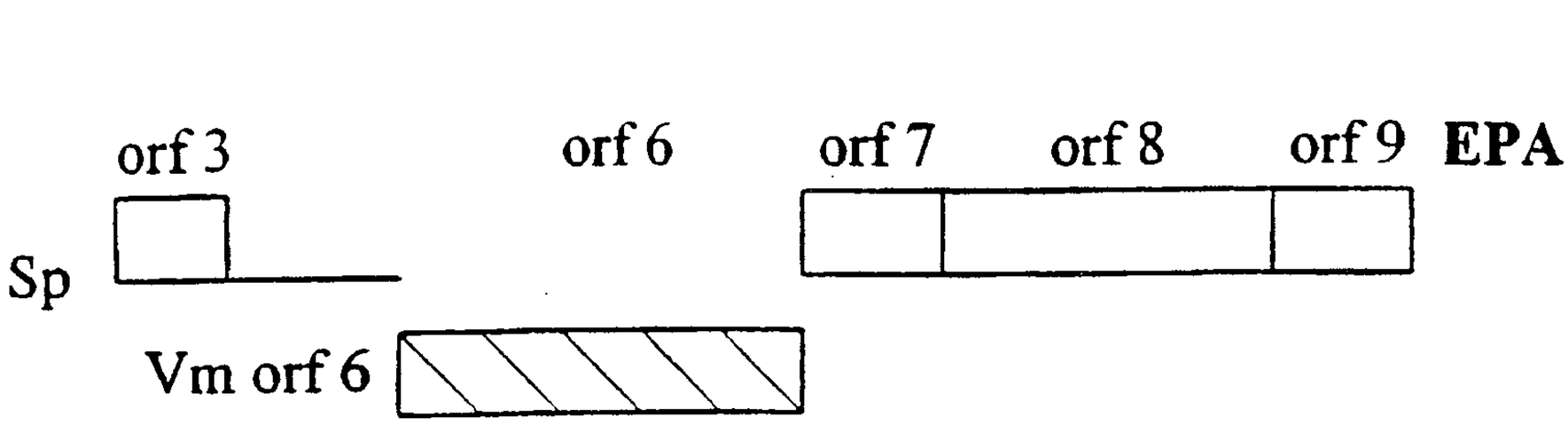
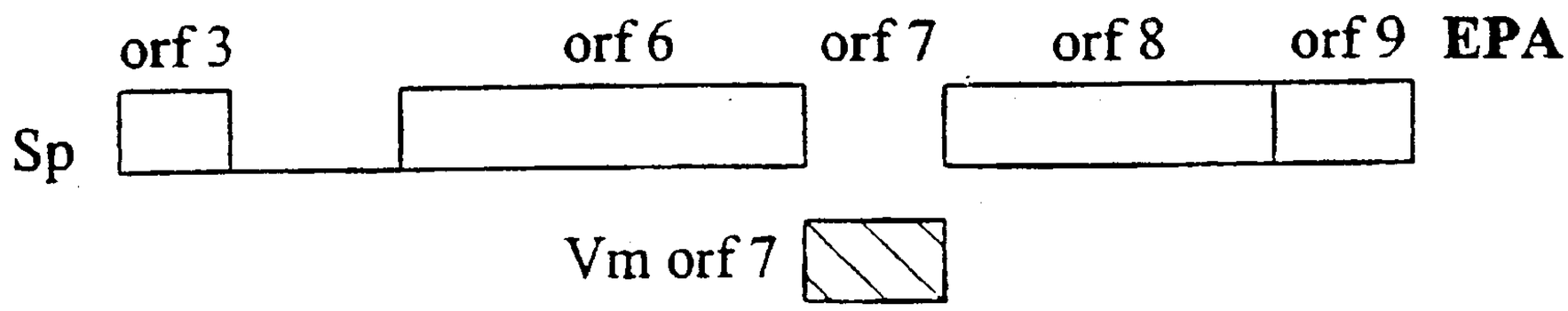


FIG. 12


orf 3
orf 6
orf 7
orf 8
orf 9
EPA
Sp


orf 3
orf 6
orf 7
orf 8
orf 9
EPA
Sp
Vm orf 6


orf 3
orf 6
orf 7
orf 8
orf 9
EPA
Sp
Vm orf 7

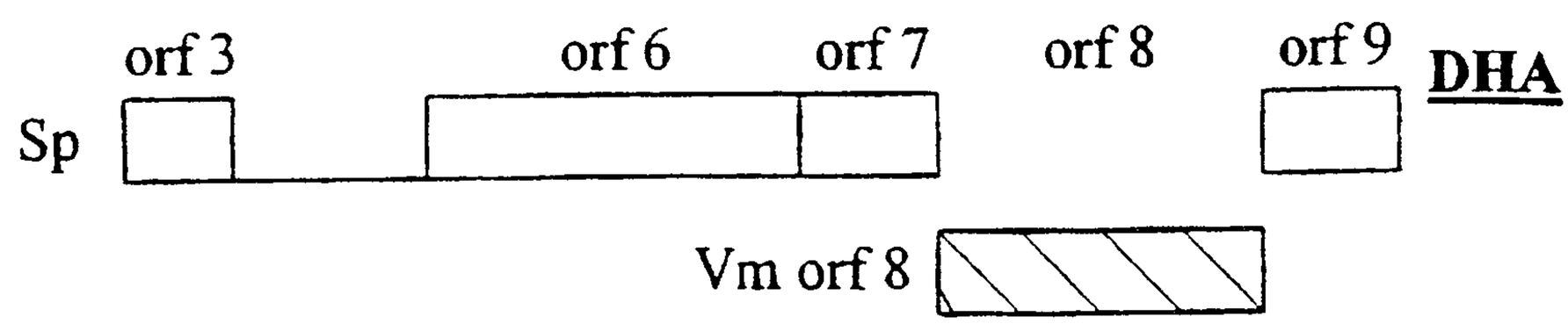

orf 3
orf 6
orf 7
orf 8
orf 9
DHA
Sp
Vm orf 8

FIG. 13

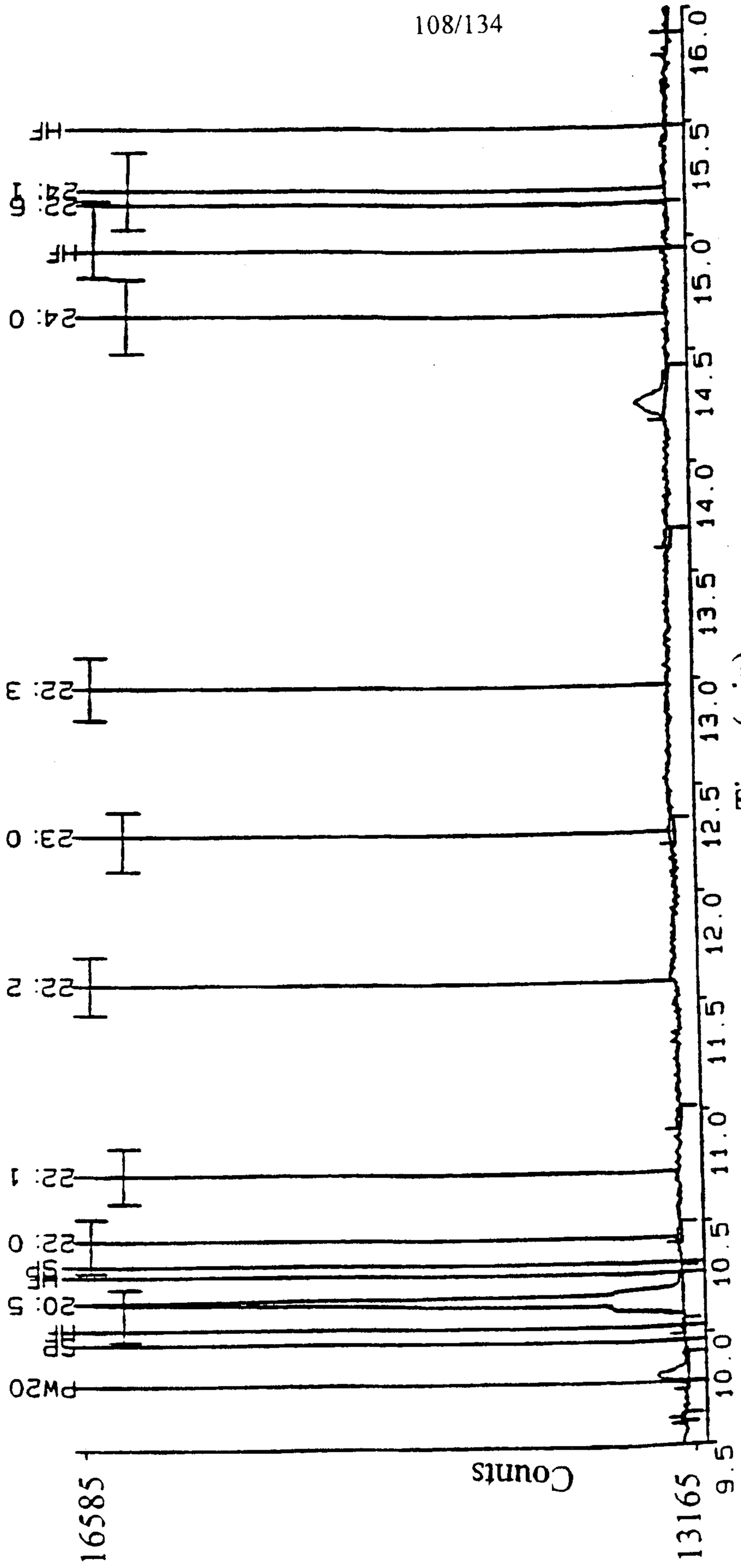

Counts
16585
13165
Time (min)
9.5
10.0
10.5
11.0
11.5
12.0
12.5
13.0
13.5
14.0
14.5
15.0
15.5
16.0
pW20
mP
20: 5
mF
22: 0
mF
24: 0
22: 3
23: 0
22: 2
22: 1
mF
22: 0

FIG. 14

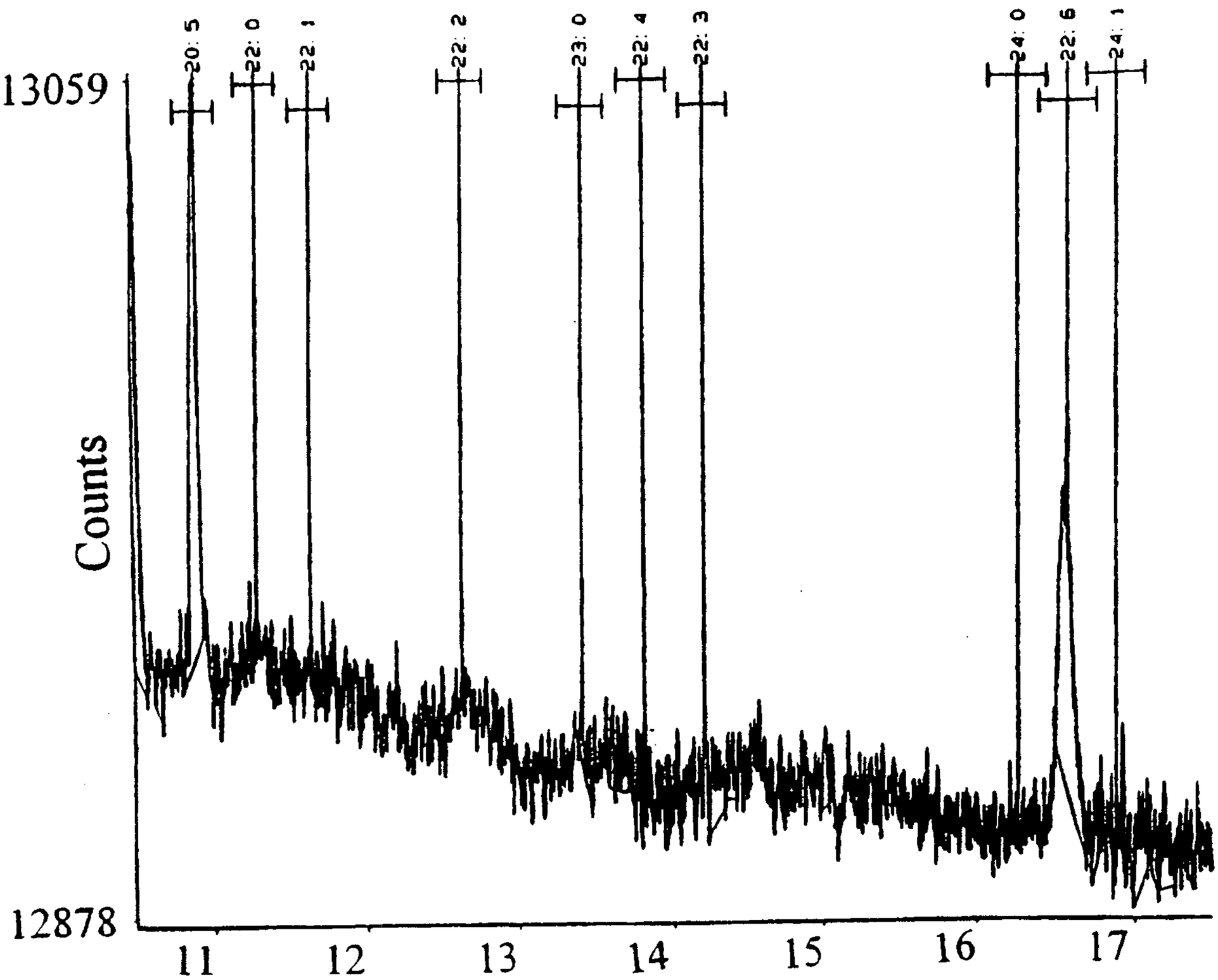

13059
20:5
22:0
22:1
22:2
23:0
22:4
22:3
24:0
22:6
24:1
Counts
12878
11
12
13
14
15
16
17
Time (min)

FIG. 15

EPA (%Fatty acids)	*DHA (%Fatty acids)*	*20 deg C*
0.00	0.06	pEPAD8
0.60	**0.70**	*4*
0.64	**0.66**	*5*
0.33	**0.22**	*6s*
0.45	**0.59**	*6l*
		23 deg C
0.02	0.06	*pEPAD8*
0.32	**0.62**	*4*
0.27	**0.22**	*6s*
0.18	**0.65**	*6l*

FIGURE 16

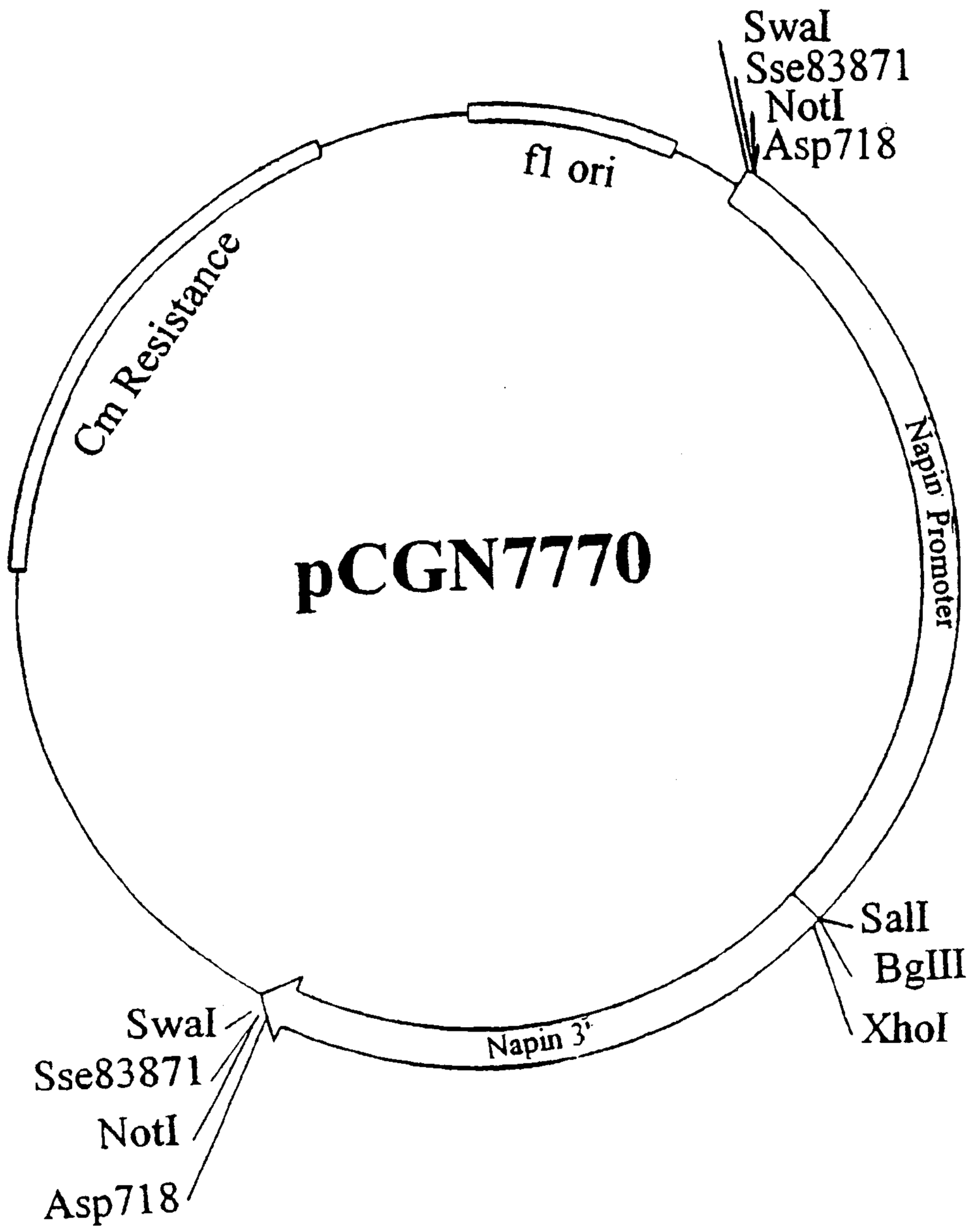

SwaI
Sse83871
NotI
Asp718
f1 ori
Cm Resistance
pCGN7770
Napin Promoter
SalI
BglII
XhoI
Napin 3'
SwaI
Sse83871
NotI
Asp718

FIG. 17

pCGN8535

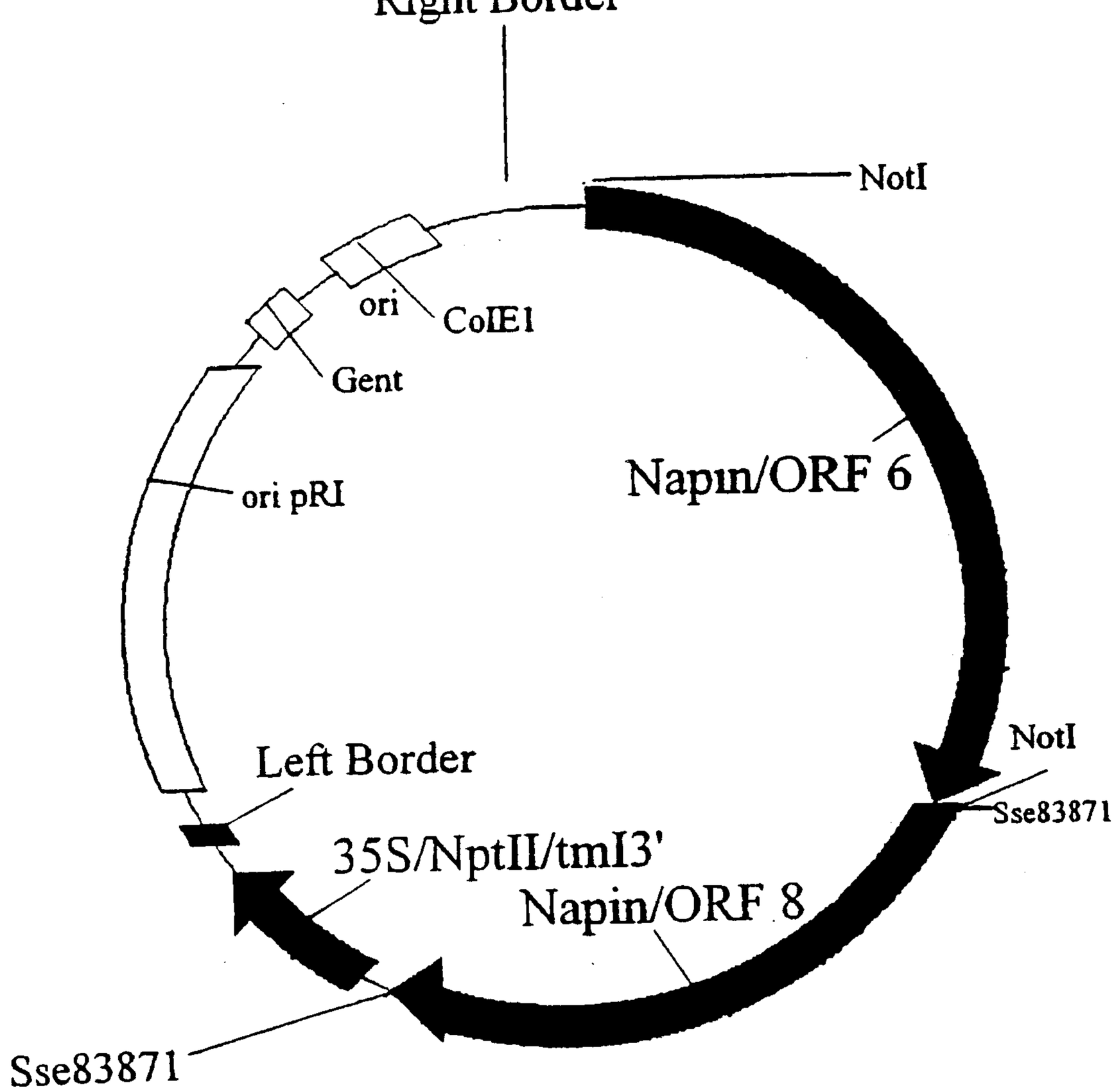


FIG. 18

pCGN8537

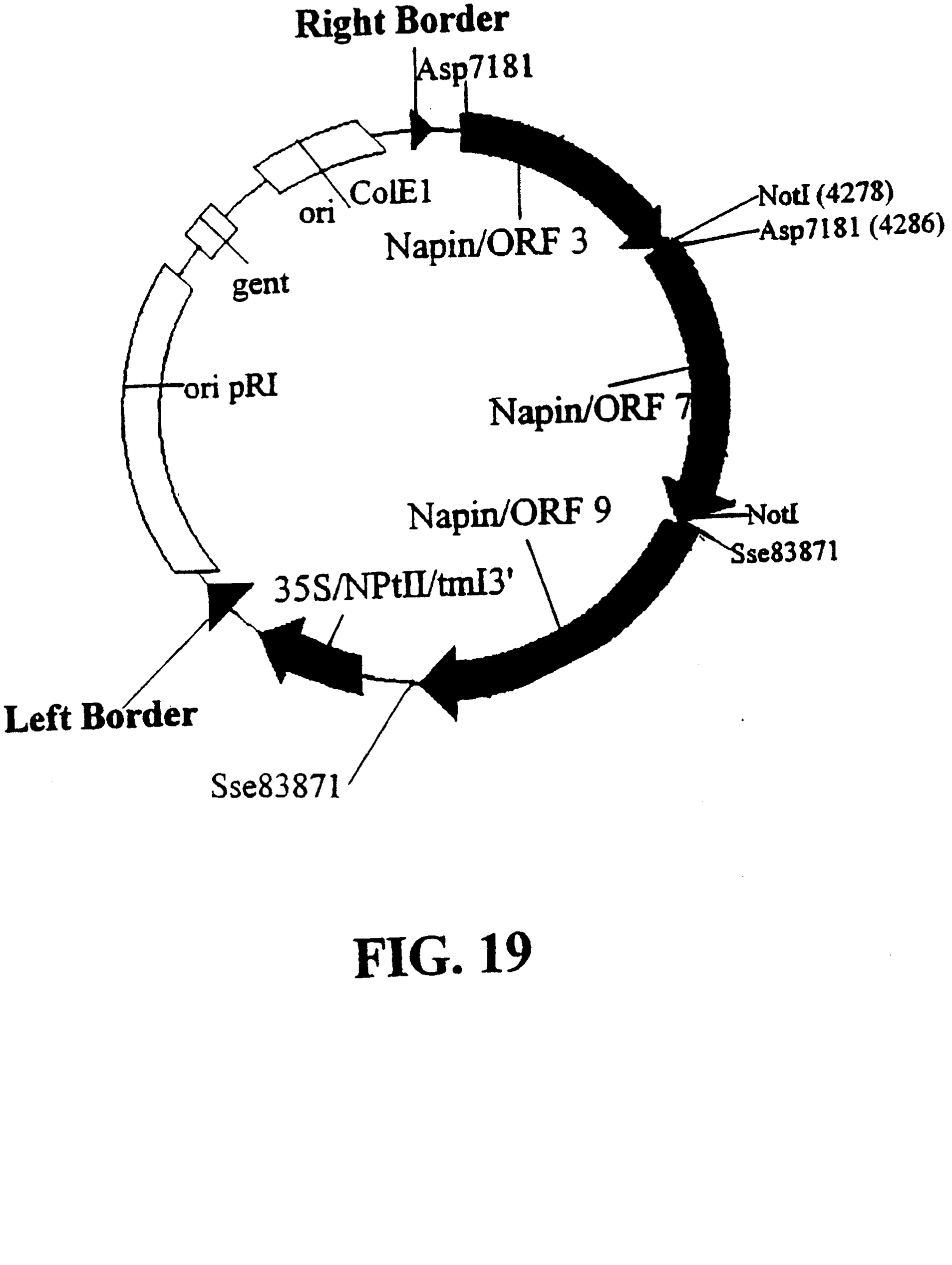


FIG. 19

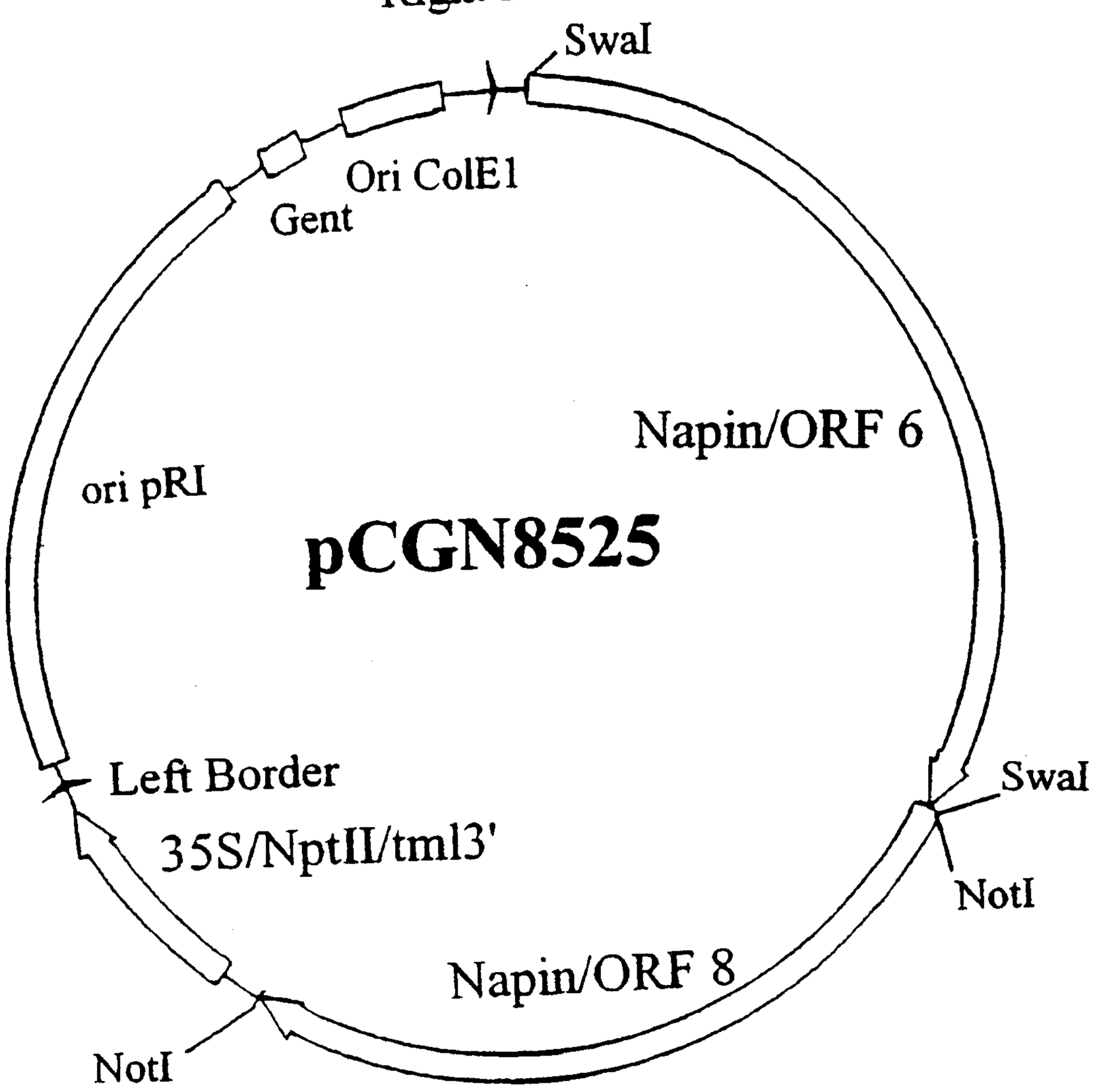

Right Border
SwaI
Ori ColE1
Gent
Napin/ORF 6
ori pRI
pCGN8525
Left Border
35S/NptII/tml3'
SwaI
NotI
Napin/ORF 8
NotI

FIG. 20

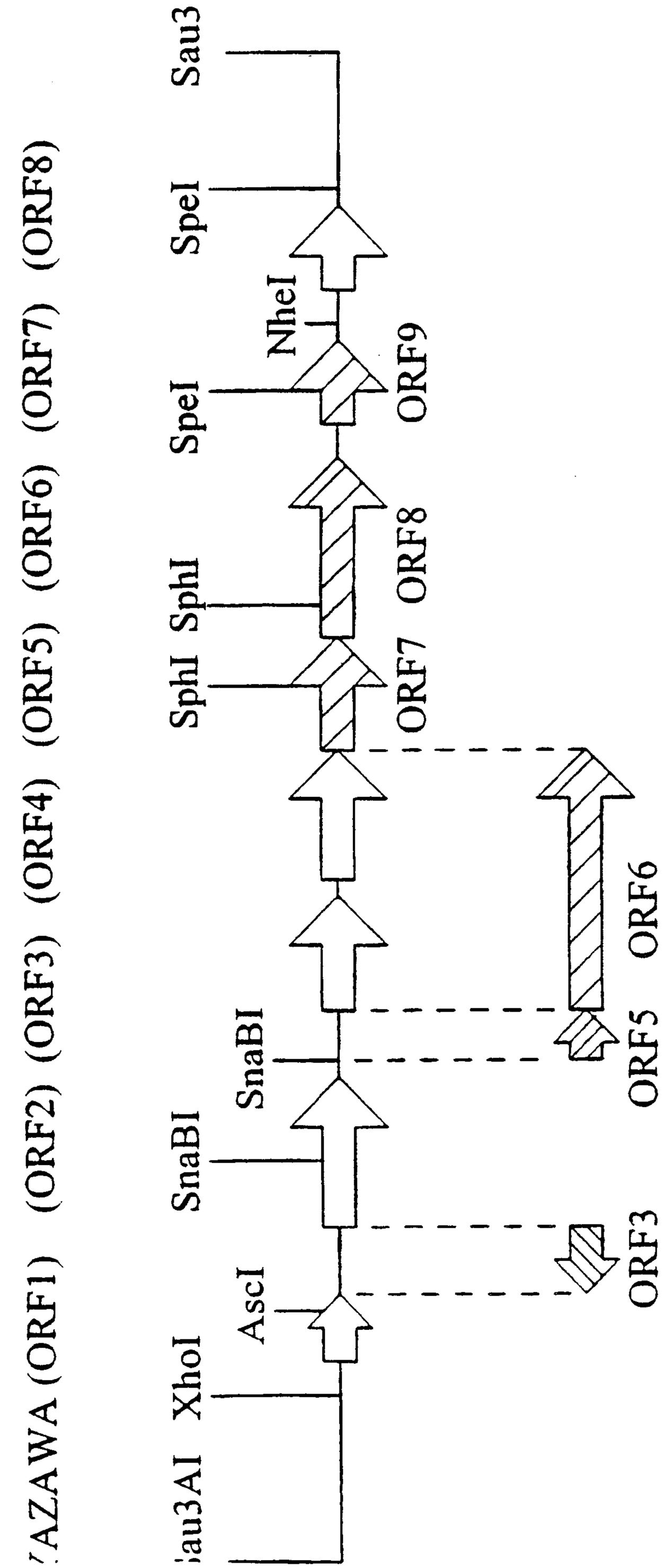

Sau3
SpeI
NheI
SpeI
ORF9
SphI SphI
ORF7 ORF8
SnaBI
ORF5 ORF6
SnaBI
AscI
ORF3
XhoI
Sau3AI
(ORF1) (ORF2) (ORF3) (ORF4) (ORF5) (ORF6) (ORF7) (ORF8)
AZAWA

FIG. 21

pCGN8560

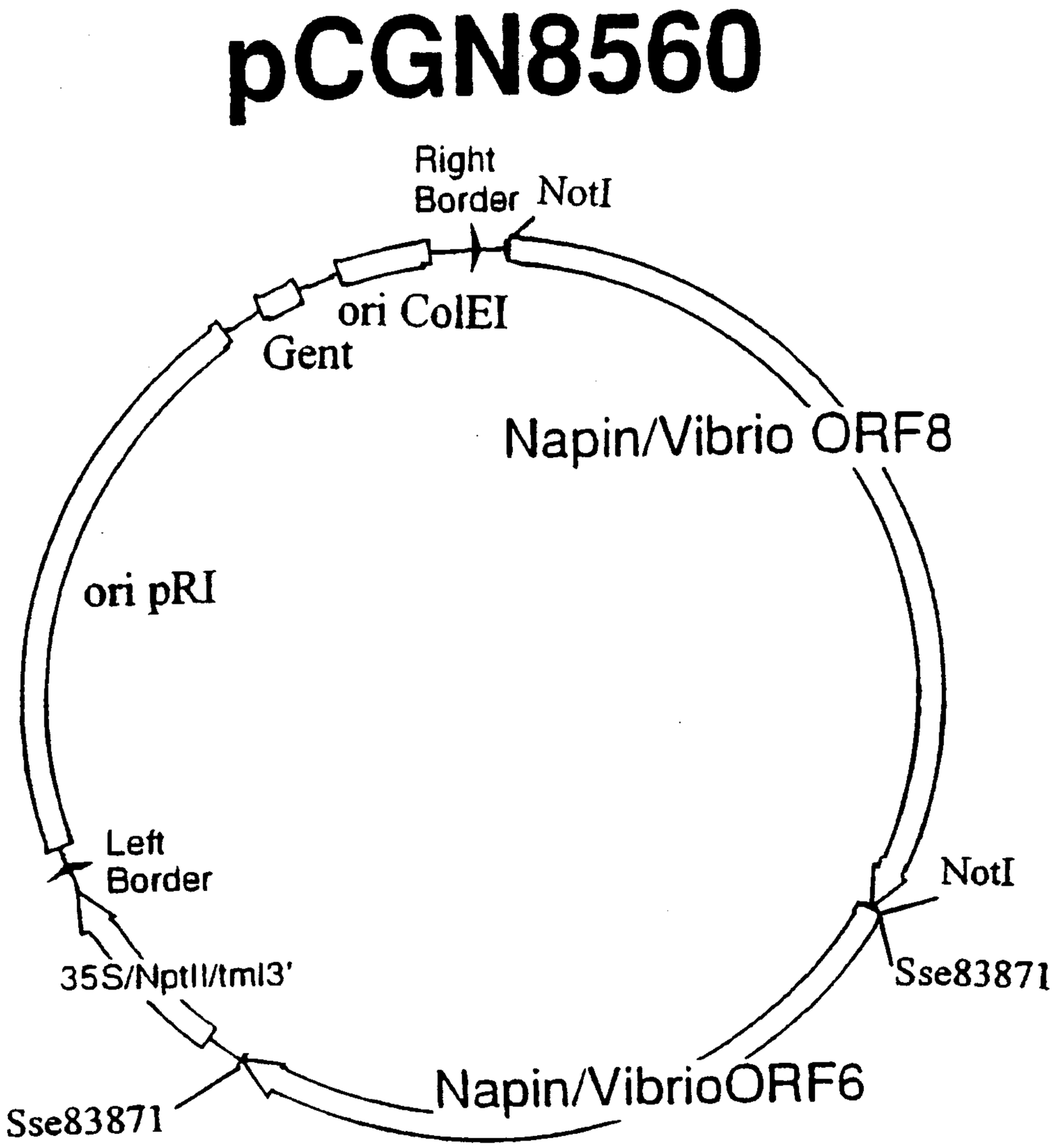


FIG. 22

pCGN8556

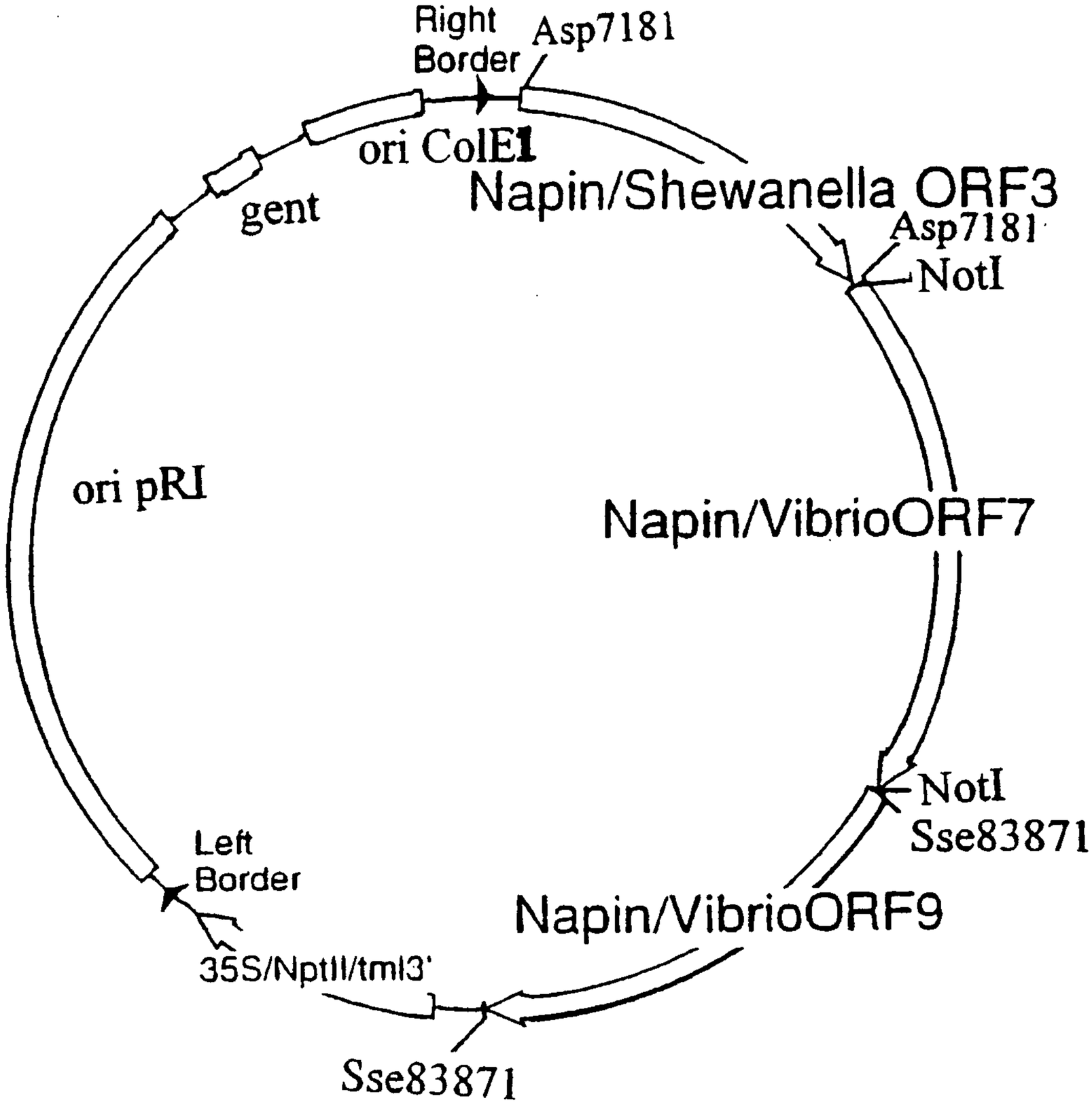


FIG. 23

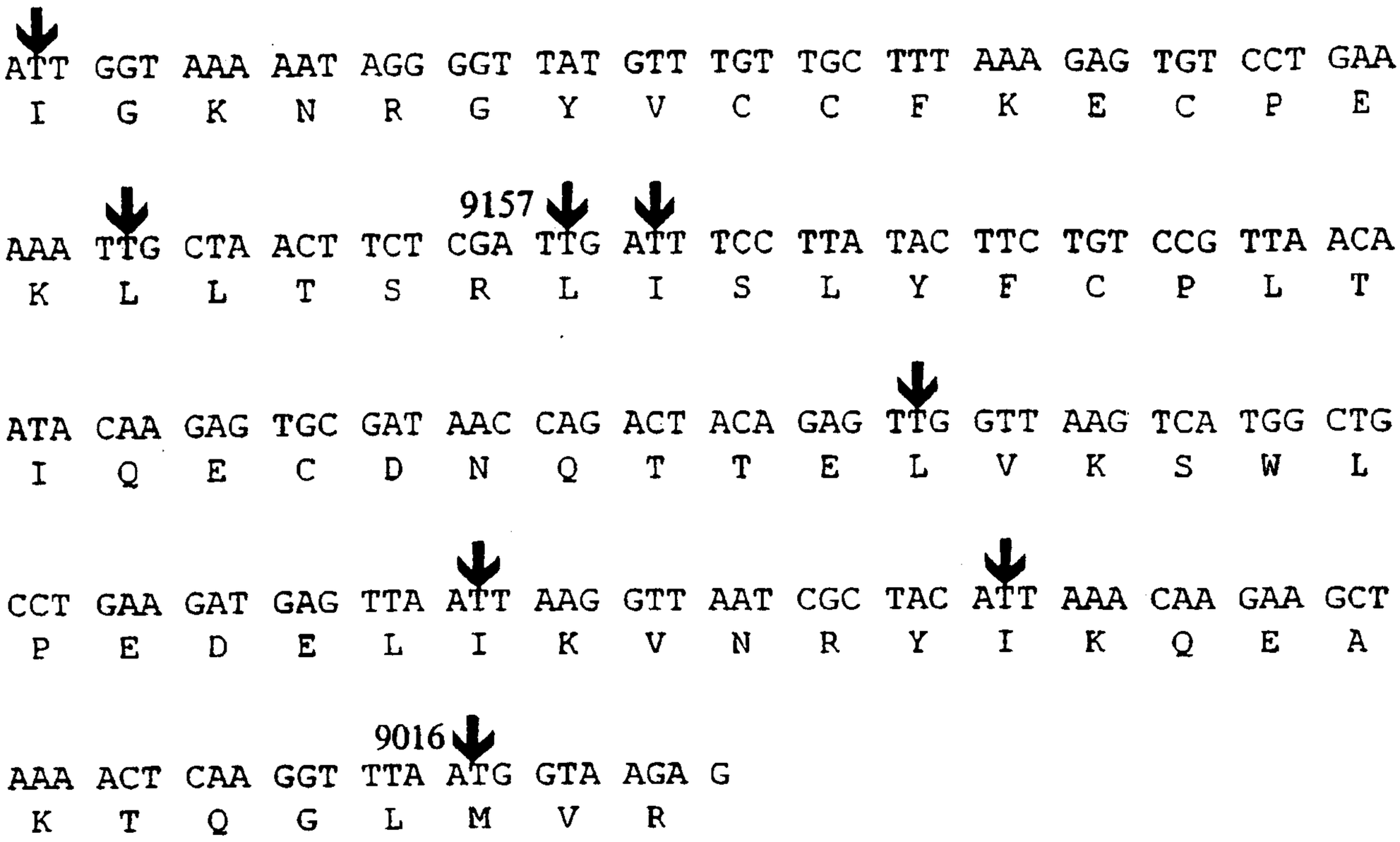

ATT GGT AAA AAT AGG GGT TAT GTT TGT TGC TTT AAA GAG TGT CCT GAA
I G K N R G Y V C C F K E C P E
9157
AAA TTG CTA ACT TCT CGA TTG ATT TCC TTA TAC TTC TGT CCG TTA ACA
K L L T S R L I S L Y F C P L T
ATA CAA GAG TGC GAT AAC CAG ACT ACA GAG TTG GTT AAG TCA TGG CTG
I Q E C D N Q T T E L V K S W L
CCT GAA GAT GAG TTA ATT AAG GTT AAT CGC TAC ATT AAA CAA GAA GCT
P E D E L I K V N R Y I K Q E A
9016
AAA ACT CAA GGT TTA ATG GTA AGA G
K T Q G L M V R

FIG. 24

```
AGCGAAATGC TTATCAAGAA ATTCCAAGAT CAATACATCA CTGGGAAGAA AATTCATTCC   60
CTGGTTCACT GGGTAACGTT ATTTCCGGCC GTATTGCTAA CCGCTTCGAC CTTGGTGGCA  120
TGAACTGTGT CGTTGATGCA GCATGTGCAG GCCCTCTTGC TGCATTGCGT ATGGCATTAA  180
GCGAGCTTGT TGAAGGCCGC AGCGAAATGA TGATTACAGG TGGTGTGTGT ACCGATAACT  240
CACCAACCAT GTACATGAGC TTCTCTAAAA CACCGGCATT CACGACAAAC GAAACAATTC  300
AACCATTCGA TATTGACTCG AAAGGTATGA TGATTGGTGA AGGTATCGGT ATGATTGCGC  360
TTAAACGTCT TGAAGACGCA GAGCGTGATG GCGACCGTAT CTATTCCGTG ATTAAAGGTG  420
TTGGGTGCAT CTTCAGACGG TAATTTATTA AGAGTANTTA TGCGCNTCGT CCTGAAGGTC  480
AGGCTAAGGC ACTTAAACGT GCTTACGACG ATGCAGGTTT CGCACCGCAC ACACTTGGCT  540
TACTTGAAGC CCACGGCACA GGCACAGCAG CAGGTGATGT GGCAGAATTC AGTGGTCTTA  600
ACTCTGTATT CAGTGAAGGC AATGACGAAA AGCAACACAT CGCATTAGGT TCAGTGAAAT  660
CACAGATTGG TCACACTAAA TCAACAGCGG GTACTGCGGG TCTAATCAAA GCGTCTTTAG  720
CACTGCACCA TAAAGTACTG CCGCCAACAA TCAATGTAAC CAGCCCTAAC CCTAAACTGA  780
ATATTGAAGA CTCGCCTTTC TACCTCAATA CACAGACGCG TCCATGGATG CAACGTGTCG  840
ATGGTACACC GCGTCGTGCT GGTATTAGCT CATTTGGTTT TGGTG                   885
```

FIG. 25

```
                              20                  40                  60
                     *        *         *         *         *         *
3-2(-VECTO   CCAAGCTAAA GCACTTAACC GTGCTTATGA AGATGCCGGT TTTGCCCCTG AAACATGTGG

jmpl str +   CCAAGCTAAA GCACTTAACC GTGCCTATGA TGATGCCGGT TTTGCCCCTG AAACATGTGG
             |||||||||| |||||||||  ||||  |||||  |||||  |||  |||||  ||   |||||||  |
3-2(-VECTO   CCAAGCTAAA GCACTTAACC GTGCTTATGA AGATGCCGGT TTTGCCCCTG AAACATGTGG

                              80                  100                 120
                     *        *         *         *         *         *
3-2(-VECTO   TCTAATTGAA GGCCATGGTA CGGGTACCAA AGCGGGTGAT GCCGCAGAAT TTGCTGGCTT

jmpl str +
             TCTAATTGAA GGCCATGGTA C
             ||||||||||  |   ||  ||  |  |
3-2(-VECTO   TCTAATTGAA GGCCATGGTA C

jmpl str +

                                                AGA ACGCAAAGTT GCCGCACTGT TTGGTCGCCA
                                                |  |  ||     |  |  ||||||  |  ||||||||
3-2(-VECTO                                      CAA AGCGGGTGAT GCCGCACTGT TTGGTCGCTT
```

FIG. 26-1

```
                                    140                 160                 180
                                  *   *   *   *   *   *   *   *   *   *   *   *
3-2(-VECTO  GACCAAACAC TTTGGCGCCG CCAGTGATGA AAAGCAATAT ATCGCCTTAG GCTCAGTTAA

jmp1 str +                                                C ATTGCGCTAG GTTCAGTTAA
                                                          | | ||  |||| ||||||||
3-2(-VECTO                                                T ATCGCCTTAG GCTCAGTTAA

jmp1 str +
            AGGTTCACAA
                  |||
3-2(-VECTO  GACCTAACAC

                                    200                 220                 240
                                  *   *   *   *   *   *   *   *   *   *   *   *
3-2(-VECTO  ATCGCAAATT GGTCATACTA AATCTGCGGC TGGCTCTGCG GGTATGATTA AGGCGGCATT

jmp1 str +                                                CG GCTTCGATTT TGGCGGCATG
                                                          || | |  ||    |    ||||
3-2(-VECTO                                                CG CGTATGATTA AGGCGGCATT

jmp1 str +  ATCACAAATT GGTCATACTA AATCAACTGC AGGT
            ||| |||||| |||||||||| ||||  | ||  ||
3-2(-VECTO  ATCGCAAATT GGTCATACTA AATCTGCGGC TGGC
```

FIG. 26-2

```
jmpl st +
                                                GCACTGCT GCAAGCATGA ACGCGTCGTT
                                                ||  |||  |  |  ||||  ||||||||
3-2(-VECTO                                      GCTCTGCG GCTATCATTA ACGCGGCATT

                                260                 280                 300
                          *          *          *          *          *          *
3-2(-VECTO  AGCGCTGCAT CATAAAATCT TACCTGCAAC GATCCATATC GATAAACCAA GTGAAGCCTT

jmpl st +
            AACGGTG
            | |   |
3-2(-VECTO  AGCGCTG

jmpl st +
              T
              |
3-2(-VECTO    A

jmpl st +
                                     TCCCTGGTGC TAACCATATC AGCAAACCA
                                     |   |||     | |||||||    ||| ||
3-2(-VECTO                           TACCTGCAAC GATCCATATC GATAAACCA

                                320                 340                 360
                          *          *          *          *          *          *
3-2(-VECTO  GGATATCAAA AACAGCCCGT TATACCTAAA CAGCGAAACG CGTCCTTGGA TGCCACGTGA
```

FIG. 26-3

```
jmpl str +                CTCACCTT TGTATCTAAA CACTGAGACT TCGTCCATGG TTACCACGTGT
                          |   |  | | || ||||| ||  || ||   ||||| |||  | |||||||
3-2(-VECTO                CAGCCCGT TATACCTAAA CAGCGAAACG GCGTCCTTGG ATGCCACGTGA

                                380                 400
                          *          *         *         *
3-2(-VECTO  AGATGGTATT CCACGTCGTG CAGGTATTAG CTCATTTGGT TTTGGTGGC
jmpl str +  TGATGGTACG CCGCGCCGCG CGGGTATTAG CTCATTTGGT TTTGGTGGC>
             |||||||   || || || | | |||||||| |||||||||| |||||||||
3-2(-VECTO  AGATGGTATT CCACGTCGTG CAGGTATTAG CTCATTTGGT TTTGGTGGC
```

FIG. 26-4

CGCTGCCGCCGCGTCTCGCCGCGCCGCGCCGCGCCGCCGCCGCTCGCGCGCACGCC
CGCGCGTCTCGCCGCGCCTGCTGTCTCGAACGAGCTTCTCGAGAAGGCCGAGACCGTCG
TCATGGAGGTCCTCGCCGCCAAGACTGGCTACGAGACTGACATGATCGAGTCCGACATG
GAGCTCGAGACTGAGCTCGGCATTGACTCCATCAAGCGTGTCGAGATCCTCTCCGAGGT
TCAGGCCATGCTCAACGTCGAGGCCAAGGACGTCGACGCTCTCAGCCGCACTCGCACTG
TGGGTGAGGTCGTCAACGCCATGAAGGCTGAGATCGCTGGTGGCTCTGCCCCGGCGCCT
GCCGCCGCTGCCCCAGGTCCGGCTGCTGCCGCCCCTGCGCCTGCTGTCTCGAGCGAGCT
TCTCGAGAAGGCCGAGACTGTCGTCATGGAGGTCCTCGCCGCCAAGACTGGCTACGAGA
CTGACATGATTGAGTCCGACATGGAGCTCGAGACCGAGCTCGGCATTGACTCCATCAAG
CGTGTCGAGATTCTCTCCGAGGTTCAGGCCATGCTCAACGTCGAGGCCAAGGACGTCGA
CGCTCTCAGCCGCACTCGCACTGTTGGTGAGGTCGTCGATGCCATGAAGGCTGAGATCG
CTGGCAGCTCCGCCTCGGCGCCTGCCGCCGCTGCTCCTGCTCCGGCTGCTGCCGCTCCT
GCGCCCGCTGCCGCCGCCCCTGCTGTCTCGAACGAGCTTCTCGAGAAAGCCGAGACTGT
CGTCATGGAGGTCCTCGCCGCCAAGACTGGCTACGAGACTGACATGATCGAGTCCGACA
TGGAGCTCGAGACTGAGCTCGGCATTGACTCCATCAAGCGTGTCGAGATCCTCTCCGAG
GTTCAGGCCATGCTCAACGTCGAGGCCAAGGACGTCGATGCCCTCAGCCGCACCCGCAC
TGTTGGCGAGGTTGTCGATGCCATGAAGGCCGAGATCGCTGGTGGCTCTGCCCCGGCGC
CTGCCGCCGCTGCCCCTGCTCCGGCTGCCGCCGCCCCTGCTGTCTCGAACGAGCTTCTT
GAGAAGGCCGAGACTGTCGTCATGGAGGTCCTCGCCGCCAAGACTGGCTACGAGACCGA
CATGATCGAGTCCGACATGGAGCTCGAGACCGAGCTCGGCATTGACTCCATCAAGCGTG
TCGAGATTCTCTCCGAGGTTCAGGCCATGCTCAACGTCGAGGCCAAGGACGTCGATGCT
CTCAGCCGCACTCGCACTGTTGGCGAGGTCGTCGATGCCATGAAGGCTGAGATCGCCGG
CAGCTCCGCCCCGGCGCCTGCCGCCGCTGCTCCTGCTCCGGCTGCTGCCGCTCCTGCGC
CCGCTGCCGCTGCCCCTGCTGTCTCGAGCGAGCTTCTCGAGAAGGCCGAGACCGTCGTC
ATGGAGGTCCTCGCCGCCAAGACTGGCTACGAGACTGACATGATTGAGTCCGACATGGA
GCTCGAGACTGAGCTCGGCATTGACTCCATCAAGCGTGTCGAGATCCTCTCCGAGGTTC
AGGCCATGCTCAACGTCGAGGCCAAGGACGTCGATGCCCTCAGCCGCACCCGCACTGTT
GGCGAGGTTGTCGATGCCATGAAGGCCGAGATCGCTGGTGGCTCTGCCCCGGCGCCTGC
CGCCGCTGCCCCTGCTCCGGCTGCCGCCGCCCCTGCTGTCTCGAACGAGCTTCTTGAGA
AGGCCGAGACCGTCGTCATGGAGGTCCTCGCCGCCAAGACTGGCTACGAGACCGACATG
ATCGAGTCCGACATGGAGCTCGAGACCGAGCTCGGCATTGACTCCATCAAGCGTGTCGA
GATTCTCTCCGAGGTTCAGGCCATGCTCAACGTCGAGGCCAAGGACGTCGACGCTCTCA
GCCGCACTCGCACTGTTGGCGAGGTCGTCGATGCCATGAAGGCTGAGATCGCTGGTGGC
TCTGCCCCGGCGCCTGCCGCCGCTGCTCCTGCCTCGGCTGGCGCCGCGCCTGCGGTCAA
GATTGACTCGGTCCACGGCGCTGACTGTGATGATCTTTCCCTGATGCACGCCAAGGTGG
TTGACATCCGCCGCCCGGACGAGCTCATCCTGGAGCGCCCCGAGAACCGCCCCGTTCTC
GTTGTCGATGACGGCAGCGAGCTCACCCTCGCCCTGGTCCGCGTCCTCGGCGCCTGCGC
CGTTGTCCTGACCTTTGAGGGTCTCCAGCTCGCTCAGCGCGCTGGTGCCGCTGCCATCC
GCCACGTGCTCGCCAAGGATCTTTCCGCGGAGAGCGCCGAGAAGGCCATCAAGGAGGCC
GAGCAGCGCTTTGGCGCTCTCGGCGGCTTCATCTCGCAGCAGGCGGAGCGCTTCGAGCC
CGCCGAAATCCTCGGCTTCACGCTCATGTGCGCCAAGTTCGCCAAGGCTTCCCTCTGCA
CGGCTGTGGCTGGCGGCCGCCCGGCCTTTATCGGTGTGGCGCGCCTTGACGGCCGCCTC

Figure 27 A-1

GGATTCACTTCGCAGGGCACTTCTGACGCGCTCAAGCGTGCCCAGCGTGGTGCCATCTT
TGGCCTCTGCAAGACCATCGGCCTCGAGTGGTCCGAGTCTGACGTCTTTTCCCGCGGCG
TGGACATTGCTCAGGGCATGCACCCCGAGGATGCCGCCGTGGCGATTGTGCGCGAGATG
GCGTGCGCTGACATTCGCATTCGCGAGGTCGGCATTGGCGCAAACCAGCAGCGCTGCAC
GATCCGTGCCGCCAAGCTCGAGACCGGCAACCCGCAGCGCCAGATCGCCAAGGACGACG
TGCTGCTCGTTTCTGGCGGCGCTCGCGGCATCACGCCTCTTTGCATCCGGGAGATCACG
CGCCAGATCGCGGGCGGCAAGTACATTCTGCTTGGCCGCAGCAAGGTCTCTGCGAGCGA
ACCGGCATGGTGCGCTGGCATCACTGACGAGAAGGCTGTGCAAAAGGCTGCTACCCAGG
AGCTCAAGCGCGCCTTTAGCGCTGGCGAGGGCCCCAAGCCCACGCCCCGCGCTGTCACT
AAGCTTGTGGGCTCTGTTCTTGGCGCTCGCGAGGTGCGCAGCTCTATTGCTGCGATTGA
AGCGCTCGGCGGCAAGGCCATCTACTCGTCGTGCGACGTGAACTCTGCCGCCGACGTGG
CCAAGGCCGTGCGCGATGCCGAGTCCCAGCTCGGTGCCCGCGTCTCGGGCATCGTTCAT
GCCTCGGGCGTGCTCCGCGACCGTCTCATCGAGAAGAAGCTCCCCGACGAGTTCGACGC
CGTCTTTGGCACCAAGGTCACCGGTCTCGAGAACCTCCTCGCCGCCGTCGACCGCGCCA
ACCTCAAGCACATGGTCCTCTTCAGCTCGCTCGCCGGCTTCCACGGCAACGTCGGCCAG
TCTGACTACGCCATGGCCAACGAGGCCCTTAACAAGATGGGCCTCGAGCTCGCCAAGGA
CGTCTCGGTCAAGTCGATCTGCTTCGGTCCCTGGGACGGTGGCATGGTGACGCCGCAGC
TCAAGAAGCAGTTCCAGGAGATGGGCGTGCAGATCATCCCCCGCGAGGGCGGCGCTGAT
ACCGTGGCGCGCATCGTGCTCGGCTCCTCGCCGGCTGAGATCCTTGTCGGCAACTGGCG
CACCCCGTCCAAGAAGGTCGGCTCGGACACCATCACCCTGCACCGCAAGATTTCCGCCA
AGTCCAACCCCTTCCTCGAGGACCACGTCATCCAGGGCCGCCGCGTGCTGCCCATGACG
CTGGCCATTGGCTCGCTCGCGGAGACCTGCCTCGGCCTCTTCCCCGGCTACTCGCTCTG
GGCCATTGACGACGCCCAGCTCTTCAAGGGTGTCACTGTCGACGGCGACGTCAACTGCG
AGGTGACCCTCACCCCGTCGACGGCGCCCTCGGGCCGCGTCAACGTCCAGGCCACGCTC
AAGACCTTTTCCAGCGGCAAGCTGGTCCCGGCCTACCGCGCCGTCATCGTGCTCTCCAA
CCAGGGCGCGCCCCCGGCCAACGCCACCATGCAGCCGCCCTCGCTCGATGCCGATCCGG
CGCTCCAGGGCTCCGTCTACGACGGCAAGACCCTCTTCCACGGCCCGGCCTTCCGCGGC
ATCGATGACGTGCTCTCGTGCACCAAGAGCCAGCTTGTGGCCAAGTGCAGCGCTGTCCC
CGGCTCCGACGCCGCTCGCGGCGAGTTTGCCACGGACACTGACGCCCATGACCCCTTCG
TGAACGACCTGGCCTTTCAGGCCATGCTCGTCTGGGTGCGCCGCACGCTCGGCCAGGCT
GCGCTCCCCAACTCGATCCAGCGCATCGTCCAGCACCGCCCGGTCCCGCAGGACAAGCC
CTTCTACATTACCCTCCGCTCCAACCAGTCGGGCGGTCACTCCCAGCACAAGCACGCCC
TTCAGTTCCACAACGAGCAGGGCGATCTCTTCATTGATGTCCAGGCTTCGGTCATCGCC
ACGGACAGCCTTGCCTTCTAA

Figure 27 A-2

TGCCGTCTTTGAGGAGCATGACCCCTCCAACGCCGCCTGCACGGGCCACGACTCCATTT
CTGCGCTCTCGGCCCGCTGCGGCGGTGAAAGCAACATGCGCATCGCCATCACTGGTATG
GACGCCACCTTTGGCGCTCTCAAGGGACTCGACGCCTTCGAGCGCGCCATTTACACCGG
CGCTCACGGTGCCATCCCACTCCCAGAAAAGCGCTGGCGCTTTCTCGGCAAGGACAAGG
ACTTTCTTGACCTCTGCGGCGTCAAGGCCACCCCGCACGGCTGCTACATTGAAGATGTT
GAGGTCGACTTCCAGCGCCTCCGCACGCCCATGACCCCTGAAGACATGCTCCTCCCTCA
GCAGCTTCTGGCCGTCACCACCATTGACCGCGCCATCCTCGACTCGGGAATGAAAAAGG
GTGGCAATGTCGCCGTCTTTGTCGGCCTCGGCACCGACCTCGAGCTCTACCGTCACCGT
GCTCGCGTCGCTCTCAAGGAGCGCGTCCGCCCTGAAGCCTCCAAGAAGCTCAATGACAT
GATGCAGTACATTAACGACTGCGGCACATCCACATCGTACACCTCGTACATTGGCAACC
TCGTCGCCACGCGCGTCTCGTCGCAGTGGGGCTTCACGGGCCCCTCCTTTACGATCACC
GAGGGCAACAACTCCGTCTACCGCTGCGCCGAGCTCGGCAAGTACCTCCTCGAGACCGG
CGAGGTCGATGGCGTCGTCGTTGCGGGTGTCGATCTCTGCGGCAGTGCCGAAAACCTTT
ACGTCAAGTCTCGCCGCTTCAAGGTGTCCACCTCCGATACCCCGCGCGCCAGCTTTGAC
GCCGCCGCCGATGGCTACTTTGTCGGCGAGGGCTGCGGTGCCTTTGTGCTCAAGCGTGA
GACTAGCTGCACCAAGGACGACCGTATCTACGCTTGCATGGATGCCATCGTCCCTGGCA
ACGTCCCTAGCGCCTGCTTGCGCGAGGCCCTCGACCAGGCGCGCGTCAAGCCGGGCGAT
ATCGAGATGCTCGAGCTCAGCGCCGACTCCGCCCGCCACCTCAAGGACCCGTCCGTCCT
GCCCAAGGAGCTCACTGCCGAGGAGGAAATCGGCGGCCTTCAGACGATCCTTCGTGACG
ATGACAAGCTCCCGCGCAACGTCGCAACGGGCAGTGTCAAGGCCACCGTCGGTGACACC
GGTTATGCCTCTGGTGCTGCCAGCCTCATCAAGGCTGCGCTTTGCATCTACAACCGCTA
CCTGCCCAGCAACGGCGACGACTGGGATGAACCCGCCCCTGAGGCGCCCTGGGACAGCA
CCCTCTTTGCGTGCCAGACCTCGCGCGCTTGGCTCAAGAACCCTGGCGAGCGTCGCTAT
GCGGCCGTCTCGGGCGTCTCCGAGACGCGCTCGTGCTATTCCGTGCTCCTCTCCGAAGC
CGAGGGCCACTACGAGCGCGAGAACCGCATCTCGCTCGACGAGGAGGCGCCCAAGCTCA
TTGTGCTTCGCGCCGACTCCCACGAGGAGATCCTTGGTCGCCTCGACAAGATCCGCGAG
CGCTTCTTGCAGCCCACGGGCGCCGCCCCGCGCGAGTCCGAGCTCAAGGCGCAGGCCCG
CCGCATCTTCCTCGAGCTCCTCGGCGAGACCCTTGCCCAGGATGCCGCTTCTTCAGGCT
CGCAAAAGCCCCTCGCTCTCAGCCTCGTCTCCACGCCCTCCAAGCTCCAGCGCGAGGTC
GAGCTCGCGGCCAAGGGTATCCCGCGCTGCCTCAAGATGCGCCGCGATTGGAGCTCCCC
TGCTGGCAGCCGCTACGCGCCTGAGCCGCTCGCCAGCGACCGCGTCGCCTTCATGTACG
GCGAAGGTCGCAGCCCTTACTACGGCATCACCCAAGACATTCACCGCATTTGGCCCGAA
CTCCACGAGGTCATCAACGAAAAGACGAACCGTCTCTGGGCCGAAGGCGACCGCTGGGT
CATGCCGCGCGCCAGCTTCAAGTCGGAGCTCGAGAGCCAGCAGCAAGAGTTTGATCGCA
ACATGATTGAAATGTTCCGTCTTGGAATCCTCACCTCAATTGCCTTCACCAATCTGGCG
CGCGACGTTCTCAACATCACGCCCAAGGCCGCCTTTGGCCTCAGTCTTGGCGAGATTTC
CATGATTTTTGCCTTTTCCAAGAAGAACGGTCTCATCTCCGACCAGCTCACCAAGGATC
TTCGCGAGTCCGACGTGTGGAACAAGGCTCTGGCCGTTGAATTTAATGCGCTGCGCGAG
GCCTGGGGCATTCCACAGAGTGTCCCCAAGGACGAGTTCTGGCAAGGCTACATTGTGCG
CGGCACCAAGCAGGATATCGAGGCGGCCATCGCCCCGGACAGCAAGTACGTGCGCCTCA
CCATCATCAATGATGCCAACACCGCCCTCATTAGCGGCAAGCCCGACGCCTGCAAGGCT
GCGATCGCGCGTCTCGGTGGCAACATTCCTGCGCTTCCCGTGACCCAGGGCATGTGCGG
CCACTGCCCCGAGGTGGGACCTTATACCAAGGATATCGCCAAGATCCATGCCAACCTTG

Figure 27 B-1

AGTTCCCCGTTGTCGACGGCCTTGACCTCTGGACCACAATCAACCAGAAGCGCCTCGTG
CCACGCGCCACGGGCGCCAAGGACGAATGGGCCCCTTCTTCCTTTGGCGAGTACGCCGG
CCAGCTCTACGAGAAGCAGGCTAACTTCCCCCAAATCGTCGAGACCATTTACAAGCAAA
ACTACGACGTCTTTGTCGAGGTTGGGCCCAACAACCACCGTAGCACCGCAGTGCGCACC
ACGCTTGGTCCCCAGCGCAACCACCTTGCTGGCGCCATCGACAAGCAGAACGAGGATGC
TTGGACGACCATCGTCAAGCTTGTGGCTTCGCTCAAGGCCCACCTTGTTCCTGGCGTCA
CGATCTCGCCGCTGTACCACTCCAAGCTTGTGGCGGAGGCTCAGGCTTGCTACGCTGCG
CTCTGCAAGGGTGAAAAGCCCAAGAAGAACAAGTTTGTGCGCAAGATTCAGCTCAACGG
TCGCTTCAACAGCAAGGCGGACCCCATCTCCTCGGCCGATCTTGCCAGCTTTCCGCCTG
CGGACCCTGCCATTGAAGCCGCCATCTCGAGCCGCATCATGAAGCCTGTCGCTCCCAAG
TTCTACGCGCGTCTCAACATTGACGAGCAGGACGAGACCCGAGATCCGATCCTCAACAA
GGACAACGCGCCGTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTC
CGTCGCCTGCTCCTTCGGCCCCCGTGCAAAAGAAGGCTGCTCCCGCCGCGGAGACCAAG
GCTGTTGCTTCGGCTGACGCACTTCGCAGTGCCCTGCTCGATCTCGACAGTATGCTTGC
GCTGAGCTCTGCCAGTGCCTCCGGCAACCTTGTTGAGACTGCGCCTAGCGACGCCTCGG
TCATTGTGCCGCCCTGCAACATTGCGGATCTCGGCAGCCGCGCCTTCATGAAAACGTAC
GGTGTTTCGGCGCCTCTGTACACGGGCGCCATGGCCAAGGGCATTGCCTCTGCGGACCT
CGTCATTGCCGCCGGCCGCCAGGGCATCCTTGCGTCCTTTGGCGCCGGCGGACTTCCCA
TGCAGGTTGTGCGTGAGTCCATCGAAAAGATTCAGGCCGCCCTGCCCAATGGCCCGTAC
GCTGTCAACCTTATCCATTCTCCCTTTGACAGCAACCTCGAAAAGGGCAATGTCGATCT
CTTCCTCGAGAAGGGTGTCACCTTTGTCGAGGCCTCGGCCTTTATGACGCTCACCCCGC
AGGTCGTGCGGTACCGCGCGGCTGGCCTCACGCGCAACGCCGACGGCTCGGTCAACATC
CGCAACCGTATCATTGGCAAGGTCTCGCGCACCGAGCTCGCCGAGATGTTCATGCGTCC
TGCGCCCGAGCACCTTCTTCAGAAGCTCATTGCTTCCGGCGAGATCAACCAGGAGCAGG
CCGAGCTCGCCCGCCGTGTTCCCGTCGCTGACGACATCGCGGTCGAAGCTGACTCGGGT
GGCCACACCGACAACCGCCCCATCCACGTCATTCTGCCCCTCATCATCAACCTTCGCGA
CCGCCTTCACCGCGAGTGCGGCTACCCGGCCAACCTTCGCGTCCGTGTGGGCGCCGGCG
GTGGCATTGGGTGCCCCCAGGCGGCGCTGGCCACCTTCAACATGGGTGCCTCCTTTATT
GTCACCGGCACCGTGAACCAGGTCGCCAAGCAGTCGGGCACGTGCGACAATGTGCGCAA
GCAGCTCGCGAAGGCCACTTACTCGGACGTATGCATGGCCCCGGCTGCCGACATGTTCG
AGGAAGGCGTCAAGCTTCAGGTCCTCAAGAAGGGAACCATGTTTCCCTCGCGCGCCAAC
AAGCTCTACGAGCTCTTTTGCAAGTACGACTCGTTCGAGTCCATGCCCCCCGCAGAGCT
TGCGCGCGTCGAGAAGCGCATCTTCAGCCGCGCGCTCGAAGAGGTCTGGGACGAGACCA
AAAACTTTTACATTAACCGTCTTCACAACCCGGAGAAGATCCAGCGCGCCGAGCGCGAC
CCCAAGCTCAAGATGTCGCTGTGCTTTCGCTGGTACCTGAGCCTGGCGAGCCGCTGGGC
CAACACTGGAGCTTCCGATCGCGTCATGGACTACCAGGTCTGGTGCGGTCCTGCCATTG
GTTCCTTCAACGATTTCATCAAGGGAACTTACCTTGATCCGGCCGTCGCAAACGAGTAC
CCGTGCGTCGTTCAGATTAACAAGCAGATCCTTCGTGGAGCGTGCTTCTTGCGCCGTCT
CGAAATTCTGCGCAACGCACGCCTTTCCGATGGCGCTGCCGCTCTTGTGGCCAGCATCG
ATGACACATACGTCCCGGCCGAGAAGCTGTAAGTAAGCTCTCATATATGTTAGTTGCGT
GAGACCGACACGAAGATAATATCACATACGCTTTTGTTTGTTCTTTCAATTATTTGTCT
GTGCTTCATGTTGCTCCTCAGTATCTAGCTGGCGGCTCTTATCTTCTTTTAAAATATCT
GGACAAGGACAAAAACAAGAATAAAGGCGAGAAGATGTGAATTTCATTTCGACTTGAGA

Figure 27 B-2

ACTCGAAGAGCATTGATGCGGTTAGTATATGGGTATTTTCCAGACACTTTTCATCATCA
TCATCATCATCATCATTATGAAGAAGTAGTAGCTGATAAAGTAGACTCACTGTTTGCAG
CGAGAAAAAAAAAAAAAAAAAAA

Figure 27 B-3

CGAGCAGAGGCCGGCCGCGAGCCCGAGCCCGCGCCGCAGATCACTAGTACCGCTGCGGA
ATCACAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCCACGAGAGG
GAGATAAAGAAAAAGCGGCAGAGACGATGGCGCTCCGTGTCAAGACGAACAAGAAGCCA
TGCTGGGAGATGACCAAGGAGGAGCTGACCAGCGGCAAGACCGAGGTGTTCAACTATGA
GGAACTCCTCGAGTTCGCAGAGGGCGACATCGCCAAGGTCTTCGGACCCGAGTTCGCCG
TCATCGACAAGTACCCGCGCCGCGTGCGCCTGCCCGCCCGCGAGTACCTGCTCGTGACC
CGCGTCACCCTCATGGACGCCGAGGTCAACAACTACCGCGTCGGCGCCCGCATGGTCAC
CGAGTACGATCTCCCCGTCAACGGAGAGCTCTCCGAGGGCGGAGACTGCCCCTGGGCCG
TCCTGGTCGAGAGTGGCCAGTGCGATCTCATGCTCATCTCCTACATGGGCATTGACTTC
CAGAACCAGGGCGACCGCGTCTACCGCCTGCTCAACACCACGCTCACCTTTTACGGCGT
GGCCCACGAGGGCGAGACCCTCGAGTACGACATTCGCGTCACCGGCTTCGCCAAGCGTC
TCGACGGCGGCATCTCCATGTTCTTCTTCGAGTACGACTGCTACGTCAACGGCCGCCTC
CTCATCGAGATGCGCGATGGCTGCGCCGGCTTCTTCACCAACGAGGAGCTCGACGCCGG
CAAGGGCGTCGTCTTCACCCGCGGCGACCTCGCCGCCCGCGCCAAGATCCCAAAGCAGG
ACGTCTCCCCCTACGCCGTCGCCCCCTGCCTCCACAAGACCAAGCTCAACGAAAAGGAG
ATGCAGACCCTCGTCGACAAGGACTGGGCATCCGTCTTTGGCTCCAAGAACGGCATGCC
GGAAATCAACTACAAACTCTGCGCGCGTAAGATGCTCATGATTGACCGCGTCACCAGCA
TTGACCACAAGGGCGGTGTCTACGGCCTCGGTCAGCTCGTCGGTGAAAAGATCCTCGAG
CGCGACCACTGGTACTTTCCCTGCCACTTTGTCAAGGATCAGGTCATGGCCGGATCCCT
CGTCTCCGACGGCTGCAGCCAGATGCTCAAGATGTACATGATCTGGCTCGGCCTCCACC
TCACCACCGGACCCTTTGACTTCCGCCCGGTCAACGGCCACCCCAACAAGGTCCGCTGC
CGCGGCCAAATCTCCCCGCACAAGGGCAAGCTCGTCTACGTCATGGAGATCAAGGAGAT
GGGCTTCGACGAGGACAACGACCCGTACGCCATTGCCGACGTCAACATCATTGATGTCG
ACTTCGAAAAGGGCCAGGACTTTAGCCTCGACCGCATCAGCGACTACGGCAAGGGCGAC
CTCAACAAGAAGATCGTCGTCGACTTTAAGGGCATCGCTCTCAAGATGCAGAAGCGCTC
CACCAACAAGAACCCCTCCAAGGTTCAGCCCGTCTTTGCCAACGGCGCCGCCACTGTCG
GCCCCGAGGCCTCCAAGGCTTCCTCCGGCGCCAGCGCCAGCGCCAGCGCCGCCCCGGCC
AAGCCTGCCTTCAGCGCCGATGTTCTTGCGCCCAAGCCCGTTGCCCTTCCCGAGCACAT
CCTCAAGGGCGACGCCCTCGCCCCCAAGGAGATGTCCTGGCACCCCATGGCCCGCATCC
CGGGCAACCCGACGCCCTCTTTTGCGCCCTCGGCCTACAAGCCGCGCAACATCGCCTTT
ACGCCCTTCCCCGGCAACCCCAACGATAACGACCACACCCCGGGCAAGATGCCGCTCAC
CTGGTTCAACATGGCCGAGTTCATGGCCGGCAAGGTCAGCATGTGCCTCGGCCCCGAGT
TCGCCAAGTTCGACGACTCGAACACCAGCCGCAGCCCCGCTTGGGACCTCGCTCTCGTC
ACCCGCGCCGTGTCTGTGTCTGACCTCAAGCACGTCAACTACCGCAACATCGACCTCGA
CCCCTCCAAGGGTACCATGGTCGGCGAGTTCGACTGCCCCGCGGACGCCTGGTTCTACA
AGGGCGCCTGCAACGATGCCCACATGCCGTACTCGATCCTCATGGAGATCGCCCTCCAG
ACCTCGGGTGTGCTCACCTCGGTGCTCAAGGCGCCCCTGACCATGGAGAAGGACGACAT
CCTCTTCCGCAACCTCGACGCCAACGCCGAGTTCGTGCGCGCCGACCTCGACTACCGCG
GCAAGACTATCCGCAACGTCACCAAGTGCACTGGCTACAGCATGCTCGGCGAGATGGGC
GTCCACCGCTTCACCTTTGAGCTCTACGTCGATGATGTGCTCTTTTACAAGGGCTCGAC
CTCGTTCGGCTGGTTCGTGCCCGAGGTYTTTGCCGCCCAGGCCGGCCTCGACAACGGCC
GCAAGTCGGAGCCCTGGTTCATTGAGAACAAGGTTCCGGCCTCGCAGGTCTCCTCCTTT
GACGTGCGCCCCAACGGCAGCGGCCGCACCGCCATCTTCGCCAACGCCCCCAGCGGCGC

Figure 27 C-1

CCAGCTCAACCGCCGCACGGACCAGGGCCAGTACCTCGACGCCGTCGACATTGTCTCCG
GCAGCGGCAAGAAGAGCCTCGGCTACGCCCACGGTTCCAAGACGGTCAACCCGAACGAC
TGGTTCTTCTCGTGCCACTTTTGGTTTGACTCGGTCATGCCCGGAAGTCTCGGTGTCGA
GTCCATGTTCCAGCTCGTCGAGGCCATCGCCGCCCACGAGGATCTCGCTGGCAAAGCAC
GGCATTGCCAACCCCACCTTTGTGCACGCCCCCGGGCAAGATCAAGCTGGAAGTACCGC
GGSCAGCTCACGCCCAAGAGCAAGAAGATGGACTCGGAGGTCCACATCGTGTCCGTGGA
CGCCCACGACGGCGTTGTCGACCTCGTCGCCGACGGCTTCCTCTGGGCCGACAGCCTCC
GCGTCTACTCGGTGAGCAACATTCGCGTGCGCATCGCCTCCGGTGAGGCCCCTGCCGCC
GCCTCCTCCGCCGCCTCTGTGGGCTCCTCGGCTTCGTCCGTCGAGCGCACGCGCTCGAG
CCCCGCTGTCGCCTCCGGCCCGGCCCAGACCATCGACCTCAAGCAGCTCAAGACCGAGC
TCCTCGAGCTCGATGCCCCGCTCTACCTCTCGCAGGACCCGACCAGCGGCCAGCTCAAG
AAGCACACCGACGTGGCCTCCGGCCAGGCCACCATCGTGCAGCCCTGCACGCTCGGCGA
CCTCGGTGACCGCTCCTTCATGGAGACCTACGGCGTCGTCGCCCCGCTGTACACGGGCG
CCATGGCCAAGGGCATTGCCTCGGCGGACCTCGTCATCGCCGCCGGCAAGCGCAAGATC
CTCGGCTCCTTTGGCGCCGGCGGCCTCCCCATGCACCACGTGCGCGCCGCCCTCGAGAA
GATCCAGGCCGCCCTGCCTCAGGGCCCCTACGCCGTCAACCTCATCCACTCGCCTTTTG
ACAGCAACCTCGAGAAGGGCAACGTCGATCTCTTCCTCGAGAAGGGCGTCACTGTGGTG
GAGGCCTCGGCATTCATGACCCTCACCCCGCAGGTCGTGCGCTACCGCGCCGCCGGCCT
CTCGCGCAACGCCGACGGTTCGGTCAACATCCGCAACCGCATCATCGGCAAGGTCTCGC
GCACCGAGCTCGCCGAGATGTTCATCCGCCCGGCCCCGGAGCACCTCCTCGAGAAGCTC
ATCGCCTCGGGCGAGATCACCCAGGAGCAGGCCGAGCTCGCGCGCCGCGTTCCCGTCGC
CGACGATATCGCTGTCGAGGCTGACTCGGGCGGCCACACCGACAACCGCCCCATCCACG
TCATCCTCCCGCTCATCATCAACCTCCGCAACCGCCTGCACCGCGAGTGCGGCTACCCC
GCGCACCTCCGCGTCCGCGTTGGCGCCGGCGGTGGCGTCGGCTGCCCGCAGGCCGCCGC
CGCCGCGCTCACCATGGGCGCCGCCTTCATCGTCACCGGCACTGTCAACCAGGTCGCCA
AGCAGTCCGGCACCTGCGACAACGTGCGCAAGCAGCTCTCGCAGGCCACCTACTCGGAT
ATCTGCATGGCCCCGGCCGCCGACATGTTCGAGGAGGGCGTCAAGCTCCAGGTCCTCAA
GAAGGGAACCATGTTCCCCTCGCGCGCCAACAAGCTCTACGAGCTCTTTTGCAAGTACG
ACTCCTTCGACTCCATGCCTCCTGCCGAGCTCGAGCGCATCGAGAAGCGTATCTTCAAG
CGCGCACTCCAGGAGGTCTGGGAGGAGACCAAGGACTTTTACATTAACGGTCTCAAGAA
CCCGGAGAAGATCCAGCGCGCCGAGCACGACCCCAAGCTCAAGATGTCGCTCTGCTTCC
GCTGGTACCTTGGTCTTGCCAGCCGCTGGGCCAACATGGGCGCCCCGGACCGCGTCATG
GACTACCAGGTCTGGTGTGGCCCGGCCATTGGCGCCTTCAACGACTTCATCAAGGGCAC
CTACCTCGACCCCGCTGTCTCCAACGAGTACCCCTGTGTCGTCCAGATCAACCTGCAAA
TCCTCCGTGGTGCCTGCTACCTGCGCCGTCTCAACGCCCTGCGCAACGACCCGCGCATT
GACCTCGAGACCGAGGATGCTGCCTTTGTCTACGAGCCCACCAACGCGCTCTAAGAAAG
TGAACCTTGTCCTAACCCGACAGCGAATGGCGGGAGGGGCGGGCTAAAAGATCGTATT
ACATAGTATTTTTCCCCTACTCTTTGTGAAAAAAAAAAAAAAAAAA

Figure 27 C-2

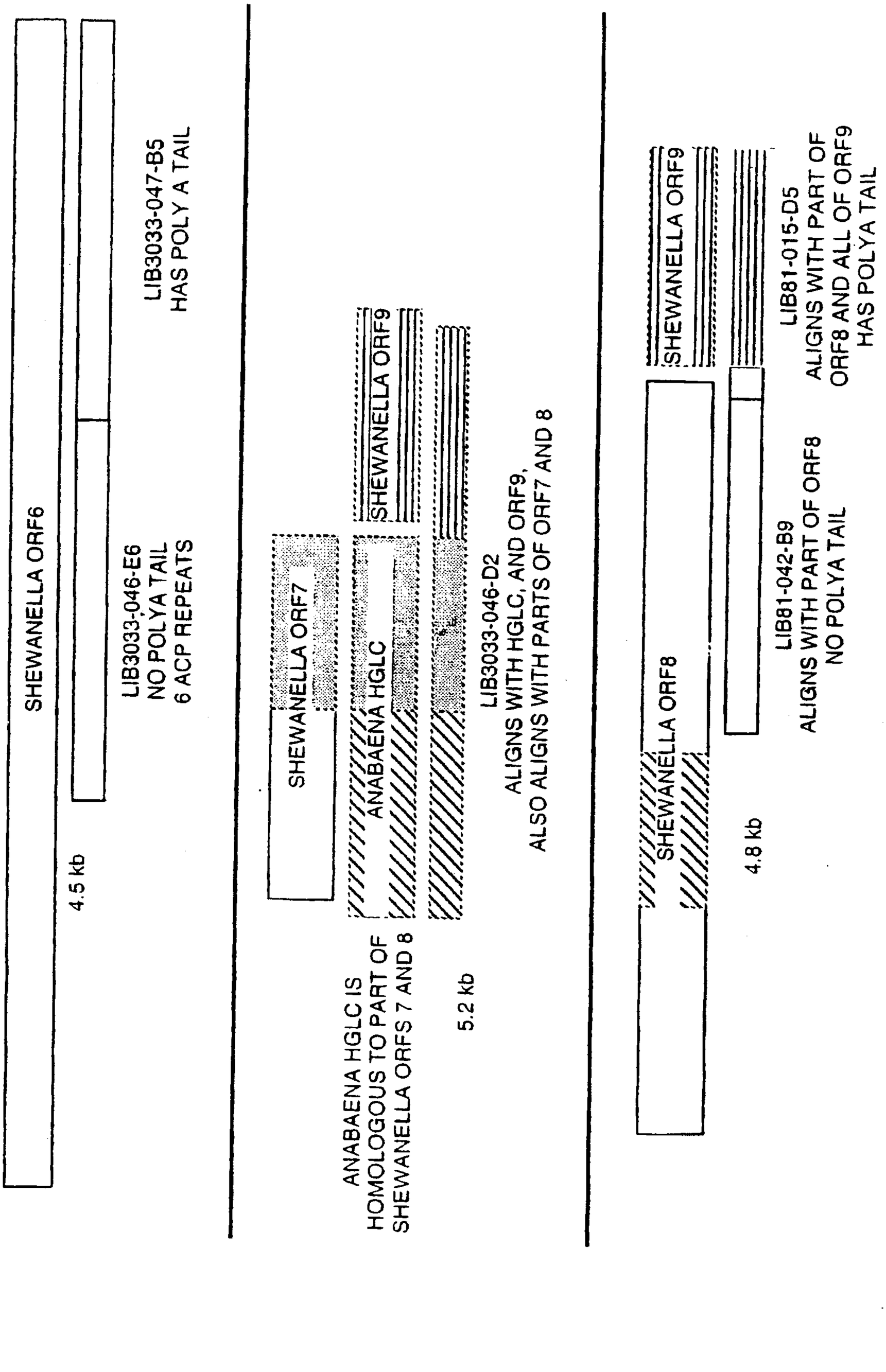

SHEWANELLA ORF6
LIB3033-046-E6
NO POLYA TAIL
6 ACP REPEATS
LIB3033-047-B5
HAS POLYA TAIL
4.5 kb
SHEWANELLA ORF7
ANABAENA HGLC
SHEWANELLA ORF9
ANABAENA HGLC IS
HOMOLOGOUS TO PART OF
SHEWANELLA ORFS 7 AND 8
5.2 kb
LIB3033-046-D2
ALIGNS WITH HGLC, AND ORF9,
ALSO ALIGNS WITH PARTS OF ORF7 AND 8
SHEWANELLA ORF9
SHEWANELLA ORF8
LIB81-042-B9
ALIGNS WITH PART OF ORF8
NO POLYA TAIL
LIB81-015-D5
ALIGNS WITH PART OF
ORF8 AND ALL OF ORF9
HAS POLYA TAIL
4.8 kb

Figure 28

RCRRVSPRRAAPPPPLARTPARLAAPAVSNELLEKAETVVMEVLAAKTGYETDMIESDM
ELETELGIDSIKRVEILSEVQAMLNVEAKDVDALSRTRTVGEVVNAMKAEIAGGSAPAP
AAAAPGPAAAAPAPAVSSELLEKAETVVMEVLAAKTGYETDMIESDMELETELGIDSIK
RVEILSEVQAMLNVEAKDVDALSRTRTVGEVVDAMKAEIAGSSASAPAAAAPAPAAAAP
APAAAAPAVSNELLEKAETVVMEVLAAKTGYETDMIESDMELETELGIDSIKRVEILSE
VQAMLNVEAKDVDALSRTRTVGEVVDAMKAEIAGGSAPAPAAAAPAPAAAAPAVSNELL
EKAETVVMEVLAAKTGYETDMIESDMELETELGIDSIKRVEILSEVQAMLNVEAKDVDA
LSRTRTVGEVVDAMKAEIAGSSAPAPAAAAPAPAAAAPAPAAAAPAVSSELLEKAETVV
MEVLAAKTGYETDMIESDMELETELGIDSIKRVEILSEVQAMLNVEAKDVDALSRTRTV
GEVVDAMKAEIAGGSAPAPAAAAPAPAAAAPAVSNELLEKAETVVMEVLAAKTGYETDM
IESDMELETELGIDSIKRVEILSEVQAMLNVEAKDVDALSRTRTVGEVVDAMKAEIAGG
SAPAPAAAAPASAGAAPAVKIDSVHGADCDDLSLMHAKVVDIRRPDELILERPENRPVL
VVDDGSELTLALVRVLGACAVVLTFEGLQLAQRAGAAAIRHVLAKDLSAESAEKAIKEA
EQRFGALGGFISQQAERFEPAEILGFTLMCAKFAKASLCTAVAGGRPAFIGVARLDGRL
GFTSQGTSDALKRAQRGAIFGLCKTIGLEWSESDVFSRGVDIAQGMHPEDAAVAIVREM
ACADIRIREVGIGANQQRCTIRAAKLETGNPQRQIAKDDVLLVSGGARGITPLCIREIT
RQIAGGKYILLGRSKVSASEPAWCAGITDEKAVQKAATQELKRAFSAGEGPKPTPRAVT
KLVGSVLGAREVRSSIAAIEALGGKAIYSSCDVNSAADVAKAVRDAESQLGARVSGIVH
ASGVLRDRLIEKKLPDEFDAVFGTKVTGLENLLAAVDRANLKHMVLFSSLAGFHGNVGQ
SDYAMANEALNKMGLELAKDVSVKSICFGPWDGGMVTPQLKKQFQEMGVQIIPREGGAD
TVARIVLGSSPAEILVGNWRTPSKKVGSDTITLHRKISAKSNPFLEDHVIQGRRVLPMT
LAIGSLAETCLGLFPGYSLWAIDDAQLFKGVTVDGDVNCEVTLTPSTAPSGRVNVQATL
KTFSSGKLVPAYRAVIVLSNQGAPPANATMQPPSLDADPALQGSVYDGKTLFHGPAFRG
IDDVLSCTKSQLVAKCSAVPGSDAARGEFATDTDAHDPFVNDLAFQAMLVWVRRTLGQA
ALPNSIQRIVQHRPVPQDKPFYITLRSNQSGGHSQHKHALQFHNEQGDLFIDVQASVIA
TDSLAF

Figure 29 A

AVFEEHDPSNAACTGHDSISALSARCGGESNMRIAITGMDATFGALKGLDAFERAIYTG
AHGAIPLPEKRWRFLGKDKDFLDLCGVKATPHGCYIEDVEVDFQRLRTPMTPEDMLLPQ
QLLAVTTIDRAILDSGMKKGGNVAVFVGLGTDLELYRHRARVALKERVRPEASKKLNDM
MQYINDCGTSTSYTSYIGNLVATRVSSQWGFTGPSFTITEGNNSVYRCAELGKYLLETG
EVDGVVVAGVDLCGSAENLYVKSRRFKVSTSDTPRASFDAAADGYFVGEGCGAFVLKRE
TSCTKDDRIYACMDAIVPGNVPSACLREALDQARVKPGDIEMLELSADSARHLKDPSVL
PKELTAEEEIGGLQTILRDDDKLPRNVATGSVKATVGDTGYASGAASLIKAALCIYNRY
LPSNGDDWDEPAPEAPWDSTLFACQTSRAWLKNPGERRYAAVSGVSETRSCYSVLLSEA
EGHYERENRISLDEEAPKLIVLRADSHEEILGRLDKIRERFLQPTGAAPRESELKAQAR
RIFLELLGETLAQDAASSGSQKPLALSLVSTPSKLQREVELAAKGIPRCLKMRRDWSSP
AGSRYAPEPLASDRVAFMYGEGRSPYYGITQDIHRIWPELHEVINEKTNRLWAEGDRWV
MPRASFKSELESQQQEFDRNMIEMFRLGILTSIAFTNLARDVLNITPKAAFGLSLGEIS
MIFAFSKKNGLISDQLTKDLRESDVWNKALAVEFNALREAWGIPQSVPKDEFWQGYIVR
GTKQDIEAAIAPDSKYVRLTIINDANTALISGKPDACKAAIARLGGNIPALPVTQGMCG
HCPEVGPYTKDIAKIHANLEFPVVDGLDLWTTINQKRLVPRATGAKDEWAPSSFGEYAG
QLYEKQANFPQIVETIYKQNYDVFVEVGPNNHRSTAVRTTLGPQRNHLAGAIDKQNEDA
WTTIVKLVASLKAHLVPGVTISPLYHSKLVAEAQACYAALCKGEKPKKNKFVRKIQLNG
RFNSKADPISSADLASFPPADPAIEAAISSRIMKPVAPKFYARLNIDEQDETRDPILNK
DNAPSSSSSSSSSSSSSPSPAPSAPVQKKAAPAAETKAVASADALRSALLDLDSMLA
LSSASASGNLVETAPSDASVIVPPCNIADLGSRAFMKTYGVSAPLYTGAMAKGIASADL
VIAAGRQGILASFGAGGLPMQVVRESIEKIQAALPNGPYAVNLIHSPFDSNLEKGNVDL
FLEKGVTFVEASAFMTLTPQVVRYRAAGLTRNADGSVNIRNRIIGKVSRTELAEMFMRP
APEHLLQKLIASGEINQEQAELARRVPVADDIAVEADSGGHTDNRPIHVILPLIINLRD
RLHRECGYPANLRVRVGAGGGIGCPQAALATFNMGASFIVTGTVNQVAKQSGTCDNVRK
QLAKATYSDVCMAPAADMFEEGVKLQVLKKGTMFPSRANKLYELFCKYDSFESMPPAEL
ARVEKRIFSRALEEVWDETKNFYINRLHNPEKIQRAERDPKLKMSLCFRWYLSLASRWA
NTGASDRVMDYQVWCGPAIGSFNDFIKGTYLDPAVANEYPCVVQINKQILRGACFLRRL
EILRNARLSDGAAALVASIDDTYVPAEKL

Figure 29 B

RAEAGREPEPAPQITSTAAESQQQQQQQQQQQQQQQPREGDKEKAAETMALRVKTNKKPCWEMT
KEELTSGKTEVFNYEELLEFAEGDIAKVFGPEFAVIDKYPRRVRLPAREYLLVTRVTLMDAEVN
NYRVGARMVTEYDLPVNGELSEGGDCPWAVLVESGQCDLMLISYMGIDFQNQGDRVYRLLNTTL
TFYGVAHEGETLEYDIRVTGFAKRLDGGISMFFFEYDCYVNGRLLIEMRDGCAGFFTNEELDAG
KGVVFTRGDLAARAKIPKQDVSPYAVAPCLHKTKLNEKEMQTLVDKDWASVFGSKNGMPEINYK
LCARKMLMIDRVTSIDHKGGVYGLGQLVGEKILERDHWYFPCHFVKDQVMAGSLVSDGCSQMLK
MYMIWLGLHLTTGPFDFRPVNGHPNKVRCRGQISPHKGKLVYVMEIKEMGFDEDNDPYAIADVN
IIDVDFEKGQDFSLDRISDYGKGDLNKKIVVDFKGIALKMQKRSTNKNPSKVQPVFANGAATVG
PEASKASSGASASASAAPAKPAFSADVLAPKPVALPEHILKGDALAPKEMSWHPMARIPGNPTP
SFAPSAYKPRNIAFTPFPGNPNDNDHTPGKMPLTWFNMAEFMAGKVSMCLGPEFAKFDDSNTSR
SPAWDLALVTRAVSVSDLKHVNYRNIDLDPSKGTMVGEFDCPADAWFYKGACNDAHMPYSILME
IALQTSGVLTSVLKAPLTMEKDDILFRNLDANAEFVRADLDYRGKTIRNVTKCTGYSMLGEMGV
HRFTFELYVDDVLFYKGSTSFGWFVPEVFAAQAGLDNGRKSEPWFIENKVPASQVSSFDVRPNG
SGRTAIFANAPSGAQLNRRTDQGQYLDAVDIVSGSGKKSLGYAHGSKTVNPNDWFFSCHFWFDS
VMPGSLGVESMFQLVEAIAAHEDLAGKARHCQPHLCARPRARSSWKYRGQLTPKSKKMDSEVHI
VSVDAHDGVVDLVADGFLWADSLRVYSVSNIRVRIASGEAPAAASSAASVGSSASSVERTRSSP
AVASGPAQTIDLKQLKTELLELDAPLYLSQDPTSGQLKKHTDVASGQATIVQPCTLGDLGDRSF
METYGVVAPLYTGAMAKGIASADLVIAAGKRKILGSFGAGGLPMHHVRAALEKIQAALPQGPYA
VNLIHSPFDSNLEKGNVDLFLEKGVTVVEASAFMTLTPQVVRYRAAGLSRNADGSVNIRNRIIG
KVSRTELAEMFIRPAPEHLLEKLIASGEITQEQAELARRVPVADDIAVEADSGGHTDNRPIHVI
LPLIINLRNRLHRECGYPAHLRVRVGAGGGVGCPQAAAAAALTMGAAFIVTGTVNQVAKQSGTCD
NVRKQLSQATYSDICMAPAADMFEEGVKLQVLKKGTMFPSRANKLYELFCKYDSFDSMPPAELE
RIEKRIFKRALQEVWEETKDFYINGLKNPEKIQRAEHDPKLKMSLCFRWYLGLASRWANMGAPD
RVMDYQVWCGPAIGAFNDFIKGTYLDPAVSNEYPCVVQINLQILRGACYLRRLNALRNDPRIDL
ETEDAAFVYEPTNAL

Figure 29 C