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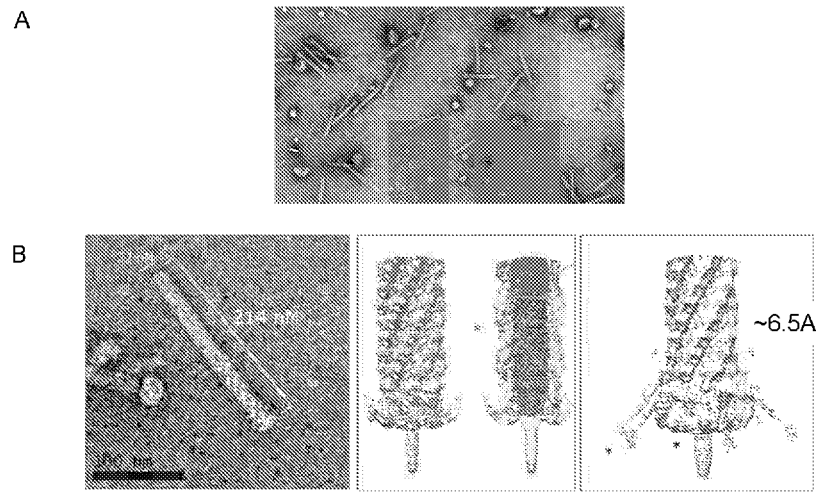
(54) Title: LEADER SEQUENCE

FIGURE 3



(57) Abstract: The present invention provides use of a *Photorhabdus Virulence* Cassettes (PVC) effector leader sequence, for packaging a payload into a PVC Needle Complex, and related methods for manufacturing a packaged PVC Needle Complex. The payload is one or more selected from a polypeptide, a nucleic acid, or a combination thereof, and the leader sequence and the payload form an effector fusion that is distinct from a wild-type PVC effector protein.

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Leader Sequence

The present invention relates to a leader sequence, and use of a leader sequence for packaging molecules into protein complexes.

Biological molecules (e.g. peptides, proteins and nucleic acids) have great potential as broadly applicable therapeutics. Indeed, there has been a trend in recent years for the pharmaceutical industry to move away from 'small molecule' drugs, toward more complex macromolecular therapeutics (aka. "biologics"). Such biologics include protein-based therapeutics (notably antibodies, hormones, growth factors and cytokines) and nucleic acid-based treatments (such as short-interfering RNAs, DNA/RNA vaccines and gene therapies).

While the biologics market has developed significantly in recent years, the low availability of effective delivery systems (and practicable methods for manufacturing such delivery systems) has limited the diversity of molecular targets of such bio-therapeutics, especially when the target is cytosolic. Indeed, the majority of approved peptide therapeutics on the market act by targeting extracellular components, such as membrane receptors or secreted molecules (e.g. present in the interstitial space). For example, humira (the most successful therapeutic monoclonal antibody) targets the extracellularly secreted cytokine TNFα. Insulin acts by binding its cognate receptor present on the cell membrane (the same being true of other hormone peptide therapeutics).

Similar problems exist in the agricultural industry, where protein-based pesticides are typically toxins which must target an extracellular component of a cell of a pest. By way of example, *Bacillus thuringiensis* toxins are commonly used natural pesticides which must bind membrane receptors to exert their toxic effects.

Methods for cytosolic delivery of biological molecules have been developed for laboratory research, which generally involve delivering the molecules within lipid vehicles which fuse with the plasma membrane of a cell, before emptying their payload into the cytosol. However, such methods find limited use in medicine and veterinary, e.g. due to the non-specific nature in which they deliver molecules to cells.

Bacterial secretion systems have been explored as potential delivery systems, given their natural ability to secrete (or more particularly 'inject') molecules into target cells. The most studied of such secretion systems is the Type III secretion system (T3SS), a "protein appendage" found in several Gram-negative bacteria. However, a significant drawback of these systems is that they remain associated with the bacterial membrane at all times, requiring use of actual bacterial cells (comprising the secretion system) as the delivery system. As such, it is difficult to fully control what molecules are transferred from the bacteria to the target cell (even when the biologic of interest is overexpressed), as these secretion systems function by providing a connection (e.g. channel) between the bacteria's cytosol and the target cell's cytosol, through which other components (potentially harmful to the host) may flow.

Therefore, there exists not only a need for improved delivery systems, but also means for producing such systems which find compatibility with molecules (payloads) having a range of sizes and molecular properties.

The present invention solves one or more of the above-mentioned problems.

The present invention is predicated on the surprising finding that toxigenic *Photorhabdus Virulence Cassettes* (PVC) effector proteins of *Photorhabdus* bacteria comprise a previously unknown "leader sequence" (or "leader peptide"), which functions to package (or "load") PVC effectors into a so called PVC Needle Complex(e.g. "nanosyringe"), which subsequently delivers the PVC effector to a target cell where it exerts its toxigenic effect(s) (the PVC effectors representing a payload of such nanosyringes). Moreover, the inventors have found that such leader sequences can be practically utilized to direct a payload linked thereto to be packaged into a PVC Needle Complex (and related/ homologous complexes), a well characterized molecular delivery system of *Photorhabdus*. Thus, the newly discovered leader sequence surprisingly functions to load the PVC Needle Complex with a molecular payload (or "warhead").

Further to this finding, the inventors have developed an advantageous, practical utility for such leader sequence for packaging/ loading 'heterologous' payloads (including non-*Photorhabdus* molecules) into PVC Needle Complexes, independent of the size, molecular properties or provenance of the heterologous payload.

In a first aspect the invention provides use of a *Photorhabdus Virulence Cassettes* (PVC) effector leader sequence, for packaging a payload into a PVC Needle Complex;

wherein the payload is one or more selected from a polypeptide, a nucleic acid, or a combination thereof (preferably a polypeptide); and

wherein the leader sequence and the payload form an effector fusion that is distinct from a wild-type PVC effector protein.

In one aspect, an aspect of the invention provides use of a PVC effector leader sequence, for packaging a payload into a PVC Needle Complex;

wherein the payload is one or more selected from a polypeptide, a nucleic acid, or a combination thereof (preferably a polypeptide); and

wherein the leader sequence and the payload form a fusion that is distinct from a PVC effector protein (e.g. wild-type PVC effector protein).

In other words, the invention provides in one aspect a method for packaging a payload into a PVC Needle Complex with a PVC effector leader sequence, comprising contacting an (effector) fusion with a PVC Needle Complex, wherein the payload is one or more selected from a polypeptide, a nucleic acid, or a combination thereof (preferably a polypeptide); and wherein the leader sequence and the payload form the (effector) fusion, that is distinct from a PVC effector protein (e.g. wild-type PVC effector protein).

The terms "fusion" and "effector fusion", in the context of a (effector) fusion formed by the leader sequence and the payload (and that is distinct from a wild-type PVC effector protein) are used interchangeably herein.

This use (of the leader sequence) was demonstrated, as outlined in the examples, by expressing an effector fusion (tagged with a detection label) and a PVC Needle Complex in a cell (e.g. host bacterial cell) wherein the effector fusion is packaged into the PVC Needle Complex (via the leader sequence), isolating the PVC Needle Complex, then detecting the presence or absence of the payload within the PVC Needle Complex (e.g. a disrupted version thereof) via Western blot detection of the detection label. The presence of the payload is detected when fused to a leader sequence only, but not when the payload lacks a leader sequence.

The term "PVC effector leader sequence" means the leader region (polypeptide region) from a PVC effector polypeptide which is capable of packaging a payload (e.g. effector) into a PVC Needle Complex, and is preferably amino acids 1-50 of a PVC effector, or amino acids 2-50 when omitting the initial methionine. The inventors have demonstrated that the leader sequence is encompassed within (or may consist essentially of) amino acids 1-50 of a multitude of identified PVC effector polypeptide sequences. However, leader sequences having alternative lengths and positioning within a PVC effector are intended to be encompassed (e.g. with the proviso that said leader sequence is capable of packaging a payload into a PVC Needle Complex).

The remaining (non-leader sequence) portion of a PVC effector is referred to an "effector portion" (e.g. payload) herein. The effector portion preferably comprises or consists essentially of amino acids 51-C terminus of a PVC effector protein.

Thus, in one embodiment, a PVC effector leader sequence is encompassed within amino acids 1-50 or 2-50 (preferably 1-50) of a PVC effector polypeptide.

In embodiment, a PVC effector leader sequence comprises (or consists essentially of) amino acids 1-50 or 2-50 (preferably 1-50) of a PVC effector polypeptide.

The term "wild-type PVC effector protein" is used synonymously with the term "endogenous PVC effector protein", or simply "PVC effector protein", and refers to an (e.g. intact) PVC effector sequence having an endogenous leader sequence (i.e. endogenous to the given PVC effector, preferably amino acids 1-50 of the PVC effector) associated with the effector portion (e.g. the payload, preferably amino acids 51-C terminus of a PVC effector protein). Examples of wild-type PVC effectors may comprise (or consist essentially of) an amino acid sequence of one or more sequence selected from SEQ ID NO.: 1 – SEQ ID NO.: 46. The fusion/ effector fusion of the invention described herein is thus distinct from a PVC effector protein (e.g. wild-type PVC effector protein), as the leader sequence is not fused to an effector portion with which it may be fused in the case of a wild-type PVC effector protein. By way of example, the fusion/ effector fusion may comprise the leader sequence of the "Pnf" PVC effector protein (e.g. the leader of SEQ ID NO.: 78) fused to the effector portion of the hvnA (gene *Plu1649*) PVC effector protein (e.g. amino acids 51-295 of SEQ ID NO.: 46), but is not intended to refer to the leader sequence of the "Pnf" PVC effector protein (e.g. the leader of SEQ ID NO.: 78) fused to the effector portion of the Pnf PVC effector protein (e.g. amino acids 51-340 of SEQ ID NO.: 32).

On the other hand, the fusion/ effector fusion may comprise the leader sequence of, e.g., the "Pnf" PVC effector protein (e.g. the leader of SEQ ID NO.: 78) fused to a non-effector portion, for example a non-*Photorhabdus* protein such as Cre recombinase. Thus, the leader sequence finds utility in packaging a range of e.g. heterologous (non-wild-type) agents into a PVC Needle Complex, opening the possibility to use the PVC Needle Complex as a modular, diverse delivery system for delivering not only natural effectors, but also 'unnatural' payloads to a cell for the first time. As such, it is possible to manufacture a PVC Needle Complex having a payload of choice.

Another aspect of the invention provides a method for manufacturing a PVC Needle Complex comprising a payload (e.g. in other words, a method for manufacturing a packaged PVC Needle Complex), the method comprising:

a. contacting (e.g. within a host cell) a PVC Needle Complex with an effector fusion comprising a PVC effector leader sequence fused to a payload;
b. wherein the payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof (preferably a polypeptide); and
c. wherein the effector fusion is distinct from a wild-type PVC effector protein.

An aspect of the invention provides a method for manufacturing a PVC Needle Complex comprising a payload (e.g. in other words, a method for manufacturing a packaged PVC Needle Complex), the method comprising:

a. contacting (e.g. within a host cell) a PVC Needle Complex with a fusion, the fusion comprising a PVC effector leader sequence fused to a payload, wherein the leader sequence and the payload form a fusion that is distinct from a PVC effector protein (e.g. wild-type PVC effector protein); and
b. wherein the payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof (preferably a polypeptide).

In one embodiment, said contacting may occur within a cell (e.g. bacterial host cell), in a cell lysate, or in a purified cell lysate (preferably within a cell). In one embodiment, said contacting may occur within a cell free expression system. Similar, a use described herein may comprise a contacting step (between the fusion/ effector fusion and PVC Needle Complex) occurring within a cell (e.g. bacterial host cell), in a cell lysate, cell free expression system, or in a purified cell lysate (preferably within a cell, more preferably a bacterial host cell).

A cassette (operon) encoding the PVC Needle Complex may be operably linked to a first promoter, and a gene encoding the fusion/ effector fusion (payload) may be operably linked to a second (preferably different) promoter. In one embodiment, said first and/or second promoter is an inducible promoter (e.g. an arabinose inducible promoter such a pBAD, and/or an IPTG inducible promoter). Thus, the invention embraces an expression system wherein an operon encoding the PVC is present within a first vector/ plasmid (optionally operably linked to a first promoter), and the sequence encoding the effector fusion (leader sequence fused to payload) is present within a second (preferably different) plasmid (optionally linked to a second promoter).

In one embodiment, the PVC Needle Complex and/or (preferably and) effector fusion may be expressed in one or more host selected from a bacterial cell, a yeast cell, an insect cell and/or a mammalian cell. In a preferable embodiment, the PVC Needle Complex and effector fusion may be expressed together in a host cell selected from a bacterial cell, a yeast cell, an insect cell and a mammalian cell (preferably a bacterial cell). Suitable mammalian cells include a HEK293 cell and/or a CHO cell.

The PVC Needle Complex and/or (preferably and) the effector fusion (payload) may be expressed in a heterologous bacterial expression system (preferably *E. coli*). In one embodiment, the PVC Needle Complex and/or (preferably and) the PVC effector may be expressed in a *Photorhabdus* cell, optionally wherein the PVC operon of the *Photorhabdus* cell is endogenous to the cell (and optionally wherein the PVC operon is operably linked to an inducible promoter which may be incorporated into the genome to be operably linked to the PVC operon via genetic engineering). For example, an inducible promoter may be introduced into the genome of a *Photorhabdus* cell 5' to a PVC (operon), preferably by recombineering as described in the examples (e.g. Example 3).

The payload may be, for example, a therapeutic payload, such that a PVC Needle Complex finds utility in medical treatment.

In a further aspect, the invention provides a (packaged) PVC Needle Complex, for use in a method of treatment;

a. wherein the PVC Needle Complex comprises (e.g. is packaged with) an effector fusion which comprises (or consists essentially of) a PVC effector leader sequence fused to a payload;
b. wherein said payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof (preferably a polypeptide); and
c. wherein the effector fusion is distinct from a wild-type PVC effector protein.

A further aspect of the invention provides a (packaged) PVC Needle Complex, for use in a method of treatment;

a. wherein the PVC Needle Complex holds (e.g. is packaged with) a fusion which comprises (or consists essentially of) a PVC effector leader sequence fused to a payload;
b. wherein said payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof (preferably a polypeptide); and
c. wherein the fusion is distinct from a PVC effector protein (e.g. wild-type PVC effector protein).

In one aspect, the invention provides a method of treating a subject, the method comprising administering a (packaged) PVC Needle Complex to a subject (e.g. a patient);

a. wherein the PVC Needle Complex comprises (e.g. is packaged with) an effector fusion which comprises (or consists essentially of) a PVC effector leader sequence fused to a payload;
b. wherein said payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof (preferably a polypeptide); and
c. wherein the effector fusion is distinct from a wild-type PVC effector protein.

In other words, an aspect of the invention provides a method of treating a subject, the method comprising administering a (packaged) PVC Needle Complex to a subject (e.g. a patient);

a. wherein the PVC Needle Complex holds (e.g. is packaged with) a fusion which comprises (or consists essentially of) a PVC effector leader sequence fused to a payload;
b. wherein said payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof (preferably a polypeptide); and
c. wherein the fusion is distinct from a PVC effector protein (e.g. wild-type PVC effector protein).

In a preferable embodiment, the payload is a polypeptide.

The subject may be a mammalian subject, preferably a human subject.

The terms "PVC Needle Complex holds an effector fusion" and "PVC Needle Complex comprising an effector fusion" means a PVC Needle Complex having a packaged effector fusion, or in other words, a PVC Needle Complex that is packaged with an effector fusion.

The term "packaged effector fusion", "fusion" and "effector fusion" (e.g. wherein the fusion/ effector fusion is distinct from a wild-type PVC effector protein) embraces a combination of a PVC effector leader sequence and a payload which remains in contact (e.g. fused) subsequent to packaging into PVC Needle Complex (e.g. the leader sequence has not been cleaved off the payload), as well as combination of a PVC effector leader sequence and a payload which are no longer in direct contact (e.g. no longer fused, such as following cleavage of the leader sequence from the payload).

The term "treat" or "treating" as used herein encompasses prophylactic treatment (e.g. to prevent onset of a disease) as well as corrective treatment (treatment of a subject already suffering from a disease). Preferably "treat" or "treating" as used herein means corrective treatment. The term "treat" or "treating" encompasses treating both the disease and a symptom thereof. In some embodiments "treat" or "treating" refers to a symptom of a disease.

Therefore, a PVC Needle Complex may be administered to a subject in a therapeutically effective amount or a prophylactically effective amount.

A "therapeutically effective amount" is any amount of the (packaged/ laden) PVC Needle Complex, which when administered alone or in combination (e.g. with another therapeutic, administered parallel or in series and acting additively or synergistically) to a subject for treating a disease (or a symptom thereof) is sufficient to effect such treatment of the disease, or symptom thereof.

A "prophylactically effective amount" is any amount of the (packaged/ laden) PVC Needle Complex that, when administered alone or in combination (e.g. with another therapeutic, administered parallel or in series and acting additively or synergistically) to a subject inhibits or delays the onset or reoccurrence of a disease (or a symptom thereof). In some

embodiments, the prophylactically effective amount prevents the onset or reoccurrence of a disease entirely. "Inhibiting" the onset means either lessening the likelihood of disease onset (or symptom thereof), or preventing the onset entirely.

In a related aspect, there is provided a (packaged) PVC Needle Complex comprising (e.g. that holds/ that is packaged with) an effector fusion;

a. wherein said effector fusion comprises (or consists essentially of) a PVC effector leader sequence fused to a payload (or in other words, wherein said effector fusion is formed by a PVC effector leader sequence and a payload);
b. wherein said payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof; and
c. wherein the effector fusion is distinct from a wild-type PVC effector protein.

In other words, one aspect of the invention provides a (packaged) PVC Needle Complex that holds (e.g. is packaged with) a fusion;

a. wherein said fusion comprises (or consists essentially of) a PVC effector leader sequence fused to a payload (or in other words, wherein said fusion is formed by a PVC effector leader sequence and a payload);
b. wherein said payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof (preferably a polypeptide); and
c. wherein the fusion is distinct from a PVC effector protein (e.g. wild-type PVC effector protein).

In a preferable embodiment, the (packaged) PVC Needle Complex is an isolated (e.g. non-natural) PVC Needle Complex.

As explained below, the PVC Needle Complex typically functions in nature to deliver toxigenic PVC effectors to insect targets. By expanding greatly the number and variety of payloads which may be packaged into a PVC Needle Complex, the invention concomitantly expands the number and variety of invertebrates (e.g. pests), such as amoeba, nematodes, helminths and insects, which may be targeted and killed.

In a further aspect of the invention, there is provided a method for suppressing a pest, the method comprising:

a. contacting a pest, or a target area comprising a pest, with a (packaged) PVC Needle Complex comprising (e.g. holding/ packaged with) an effector fusion;
b. wherein the effector fusion comprises (or consists essentially of) a PVC effector leader sequence fused to a payload (or in other words, wherein said effector fusion is formed by a PVC effector leader sequence and a payload);
c. wherein said payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof (preferably a polypeptide); and
d. wherein the effector fusion is distinct from a wild-type PVC effector protein.

An aspect of the invention provides a method for suppressing a pest, the method comprising:

a. contacting a pest, or a target area comprising a pest, with a (packaged) PVC Needle Complex holding (e.g. packaged with) a fusion;

b. wherein the fusion comprises (or consists essentially of) a PVC effector leader sequence fused to a payload (or in other words, wherein said fusion is formed by a PVC effector leader sequence and a payload);
c. wherein said payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof (preferably a polypeptide); and
d. wherein the fusion is distinct from a PVC effector protein (e.g. wild-type PVC effector protein).

The terms "PVC Needle Complex holds an effector fusion" and "PVC Needle Complex comprising an effector fusion" means a PVC Needle Complex having a packaged effector fusion.

The term "target area" refers to an area where a pest is present and/or where a pest may be (e.g. is expected to be, or suspected of being) present.

Thus, in one embodiment, a target area may be contacted before, and/or when a pest is present. The target area may be in the vicinity of (e.g. close proximity to) a pest. Alternatively, the target area may be an area that a user wishes to protect from a pest. For example, a target area may comprise a plant and/or plant product.

The term "suppressing a pest" embraces "pest control", "inhibiting the growth of a pest", "inhibiting the proliferation of pest", and/or "mortality of a pest".

Examples of such pest include one or more insect(s), mite(s), sowbug(s), pillbug(s), centipede(s), mollusk(s), millipede(s), protist(s), fungus (fungi), helminth(s) and/or bloodborne parasite(s). The pest may be at any stage of development e.g. may be a larvae and/or adult pest (e.g. imago).

The invention may be used to target a variety of agricultural, commercial, home and garden pests.

In one embodiment the pest is an insect, a mite, a sowbug, a pillbug, a centipede, a mollusk and/or a millipede. Suitably the pest may be an insect and/or a mite (preferably insect).

Examples of suitable insects include, an insect of the order Lepidoptera, Coleoptera, Diptera, Blattodea, Hymenoptera, Isoptera, Orthoptera, Thysanura, and/or Dermaptera. In one embodiment an insect of the order Lepidoptera may be one or more of a moth and/or a butterfly. Suitable moths include *Manduca Sexta* and/or *Galleria mellonella*.

In one embodiment an insect of the order Coleoptera may be one or more of a European chafer grub, a northern masked chafer grub, a southern masked chafer grub, a Japanese beetle grub, a June beetle grub, a black vine weevil, a strawberry root weevil, a clay-colored weevil, a Colorado potato beetle, and/or a wireworm. In another embodiment an insect of the order Diptera may be one or more of a leatherjacket (e.g. larvae of a crane fly), an onion maggot, a cabbage maggot, a carrot rust fly maggot, a fungus gnat, and/or a mosquito. In another embodiment an insect of the order Blattodea may be a cockroach, suitably one or more cockroach selected from an American cockroach, and/or a German cockroach.

In one embodiment an insect of the order Hymenoptera may be an ant. Suitably, the ant may be one or more of a carpenter ant, an odorous house ant, a pavement ant, an Argentine ant, a Pharaoh ant, a tawny crazy ant, a harvester ant, a red imported fire ant, a Southern fire ant, a European fire ant, and/or a little fire ant. In another embodiment an insect of the order Hymenoptera may be a yellowjacket.

In one embodiment an insect of the order Isoptera may be a termite. Suitably the termite may be one or more of a damp wood termite, a dry wood termite, and/or a subterranean termite. In another embodiment an insect of the order Orthoptera may be one or more of a cricket, a grasshopper, and/or a locust. In one embodiment an insect of the order Thysanura may be a silverfish. In another embodiment an insect of the order Dermaptera may be an earwig.

Examples of suitable molluscs include a slug and/or a snail.

In one embodiment, the pest is a protist. In one embodiment, said protist is one or more selected from *Chaos carolinense*, *Amoeba proteus*, *Naegleria fowleri*, *Dictyostelium discoideum, Entamoeba histolytica, Trichomonas vaginalis, Blastocystis hominis, Leishmania Spp.,* and *Giardia lamblia.* In one embodiment, said protist is one or more selected from *Fonticula alba, Dictyostelium discoideum, Chlamydomonas reinhardtii, Crytomonas paramedium, Paulinella chromatophora, Nannochloropsis gaditana,* and/or *Tetrahymena Spp.*

In one embodiment, the pest is a fungus. In one embodiment, said fungus is one or more fungus selected from *Encephalitozoan cuniculi, Nasema apis, Namema ceranae, Vittaforma carneae, Enterocytosoan bieneusi, Spraguea lophii, Vavra culiculis, Edharzardia aedes, Nematocida parisii, Razella Spp., Parasitella parasitica, Lichteimia ramose, Sporisorium scitamineum, Trametes versicolor,* and/or *Punctularia strigosozonata.*

In one embodiment, said fungus is a *Candida* spp. Said *Candida* spp. may be one or more selected from *C. albicans, C. ascalaphidarum, C. amphixiae, C. Antarctica, C. argentea, C. atlantica, C. atmosphaerica, C. auris, C. blattae, C. bromeliacearum, C. carpophila, C. carvajalis, C. cerambycidarum, C. chauliodes, C. corydalis, C. dosseyi, C. dubliniensis, C. ergatensis, C. fructus, C. glabrata, C. fermentati, C. guilliermondii, C. haemulonii, C. humilis, C. insectamens, C. insectorum, C. intermedia, C. jeffresii, C. kefyr, C. keroseneae, C. krusei, C. lusitaniae, C. lyxosophila, C. maltose, C. marina, C. membranifaciens, C. mogii, C. oleophila, C. oregonensis, C. parapsilosis, C. quercitrusa, C. rugose, C. sake, C. shehatea, C. temnochilae, C. tenuis, C. theae, C. tolerans, C. tropicalis, C. tsuchiyae, C. sinolaborantium, C. sojae, C. subhashii, C. viswanathii, C. utilis, C. ubatubensis,* and/or *C. zemplinina.* Suitably, said *Candida* spp. may be *C. albicans.*

In another embodiment, the pest is a helminth. Said helminth may be one or more selected from the phyla *Annelida, Platyhelminthes, Nematoda* and/or *Acanthocephala.* In one embodiment, said helminth is a parasitic flatworm. Said parasitic flatworm may be one or more selected from a *Cestoda, a Trematoda* and/or a *Monogenea.* In one embodiment, said helminth is a parasitic nematode. Said parasitic nematode may be one or more selected an

ascarid (*Ascaris*), a filaria, a hookworm, a pinworm (*Enterobius*), and/or a whipworm (*Trichuris trichiura*).

In one embodiment, the pest is a bloodborne parasite. Said bloodborne parasite may be one or more selected from *Trypanosoma* Spp (e.g. *Trypanosoma brucei* and/or *T. cruzi*), *Babesia* Spp (e.g. *Babesia microti), Leishmania* Spp, *Plasmodium* Spp (e.g. *P. falciparum*), and/or *Toxoplasma* Spp. (e.g. *Toxoplasma gondii*).

The PVC Needle Complex for pest control is suitably environmentally safe (e.g. an environmentally safe pesticidal composition).

Other advantageous utilities include delivering a payload to a cell, for example, during laboratory research. Such cell may be part of an *in vitro* cell line, or may be a cell of an animal (e.g. a research animal model). Additionally or alternatively, the cell may be comprised within an *ex vivo* system, such as an organoid.

Another aspect of the invention provides an *in vitro* (and/or *ex vivo*) method for delivering a payload into a cell, the method comprising:

a. contacting a cell with a (packaged) PVC Needle Complex comprising (e.g. holding/ packaged with) an effector fusion;
b. wherein the effector fusion comprises (or consists essentially of) a PVC effector leader sequence fused to a payload (or in other words, wherein said effector fusion is formed by a PVC effector leader sequence and a payload);
c. wherein said payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof (preferably a polypeptide); and
d. wherein the effector fusion is distinct from a wild-type PVC effector protein.

An aspect of the invention provides an *in vitro* (and/or *ex vivo*) method for delivering a payload into a cell, the method comprising:

a. contacting a cell with a (packaged) PVC Needle Complex holding (e.g. packaged with) a fusion;
b. wherein the fusion comprises (or consists essentially of) a PVC effector leader sequence fused to a payload (or in other words, wherein said fusion is formed by a PVC effector leader sequence and a payload);
c. wherein said payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof (preferably a polypeptide); and
d. wherein the fusion is distinct from a PVC effector protein (e.g. wild-type PVC effector protein).

In one aspect, the invention provides an effector fusion comprising (or consisting essentially of) a PVC effector leader sequence fused to a payload (or in other words, an effector fusion formed by a PVC effector leader sequence and a payload);

a. wherein said payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof; and
b. wherein the effector fusion is distinct from a wild-type PVC effector protein.

An aspect of the invention provides a fusion comprising (or consisting essentially of) a PVC effector leader sequence fused to a payload (or in other words, a fusion formed by a PVC effector leader sequence and a payload);

a. wherein said payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof (preferably a polypeptide); and
b. wherein the fusion is distinct from a PVC effector protein (e.g. wild-type PVC effector protein).

In one embodiment, the fusion/ effector fusion is an isolated fusion/ effector fusion (e.g. an isolated, non-naturally occurring fusion/ effector fusion).

The present invention embraces a nucleic acid comprising a nucleotide sequence which encodes the fusion/ effector fusion, and/or an expression vector comprising said nucleic acid. Also embraced is a host cell comprising said nucleic acid and/or expression vector.

As discussed above, the present inventors have discovered and practically utilised the leader sequence(s) described herein for the first time.

Thus, another aspect of the invention provides an isolated PVC effector leader sequence (e.g. wherein the isolated PVC effector leader sequence is capable of packaging a payload into a PVC Needle Complex).

In a related aspect there is provided an isolated nucleic acid comprising a nucleotide sequence which encodes a PVC effector leader sequence.

The isolated PVC effector leader sequence may be recombinant, synthetic, and/or purified. The isolated nucleic encoding a PVC effector leader sequence may be recombinant, synthetic, and/or purified.

Further details on the background of the invention, and terminology used herein, is provided below.

Photorhabdus is a bacterium of the genus Enterobacteriacae, represented by three formally recognized (to date) species – namely *P. luminescens*, *P. asymbiotica,* and *P. temperata*. Important strains include *P. asymbiotica* subsp. *australis,* and *P. luminescens* subsp *laumondii.* Currently available genome sequences are available on GenBank (*Photorhabdus asymbiotica* ATCC43949 complete genome – GenBank Accession Number: FM162591.1; *Photorhabdus laumondii* subsp. *laumondii* strain TT01 chromosome, complete genome – GenBank Accession number: CP024901.1).

Reference to "*Photorhabdus luminescens* subsp. *laumondii*" may be used interchangeably with "*Photorhabdus luminescens* subsp. *laumondii* TT01", "*Photorhabdus laumondii* subsp. *laumondii* strain TT01" and "*P. luminescens* TT01" herein.

The genome sequence for a further strain of *P. asymbiotica*, namely *P. asymbiotica* Kingscliff, is described in Wilkinson *et. al.* (FEMS Microbiology Letters, Volume 309, Issue 2, August 2010, Pages 136–143), incorporated herein by reference. Further genome

sequences are described in Thanwisai *et. al.* (PLoS ONE 7(9): e43835), incorporated herein by reference.

Each of these species comprise at least one operon known as a *Photorhabdus* Virulence Cassette (PVC) operon, encoding a PVC Needle Complex, which may be referred to as a "nanosyringe" herein. Given that *Photorhabdus* is typically found in nature as an insecticidal bacterium following regurgitation from a (symbiont) entomopathogenic *Heterorhabditis* sp. nematode (e.g. in order to avoid competition for food and resources from insects), it is understood that the PVC Needle Complex functions in nature to suppress insects. Indeed, it has been shown that an isolated PVC Needle Complex (holding/ packaged with a natural effector toxin, such as Pnf) can be used to kill insect larvae – see Example 2. The *Photorhabdus* Virulence Cassettes represent one of at least four well-characterised toxin delivery systems of *Photorhabdus*. Other major classes of *Photorhabdus* protein insecticidal toxins include the "Toxin Complexes" (Tcs), the "binary PirAB toxins", and the "makes caterpillars floppy" (Mcf) toxins.

The term "*Photorhabdus* Virulence Cassette" (PVC) (used synonymously with the term "PVC operon" herein) means a discrete operon of a *Photorhabdus* genome comprising genes encoding for polypeptide subunits which, when expressed, assemble to provide the macromolecular PVC Needle Complex. The molecular architecture of these cassettes have been well characterized and described, for example in The Molecular Biology of *Photorhabdus* Bacteria (Springer International Publishing AG 2017, ISBN: 978-3-319-52714-7, Chapter 10, pages 159-177), incorporated herein by reference. A PVC (operon) typically comprises around sixteen genes (*pvc1-pvc16*) encoding structural proteins which assemble to provide a "PVC Needle Complex", which are typically followed by one or more genes at the 3' end which encode PVC effector genes, having toxic activity (and typically being homologues of typical T3SS-like effectors). A *Photorhabdus* genome typically comprises a plurality of such cassettes (e.g. at least four), which are often associated with different effector payloads, or even a plurality of effector payloads.

Three classes of PVC structural operons (Classes I, II and III) have been observed in the genomes of *Photorhabdus,* and members of other genera. PVCs within each class are similar in terms of the number and type of genes encoding structural proteins they contain (see Figure 1(B)). In more detail, Class I PVCs (which may be referred to as a "prototypical PVC" herein) comprise 16 conserved genes (*pvc1-16).* Class II lack *pvc13* host cell binding fibres and *pvc3*, which (without wishing to be bound by theory) the inventors believe may be a minor specialised sheath subunit that attaches pvc13 fibre proteins onto the PVC Needle Complex (nanosyringe). As such, it is believed this class may be "non-specific", injecting payloads into multiple (potential any) cell types. Class III is similar to Class I, but has an additional *Pvc0* gene at the start of the operon (of unknown function) and two additional genes encoded between *pvc13* and *pvc14* that resemble "invasion" type protein genes. This class is typically seen in the human clinical isolate strains of *Photorhabdus* – the inventors have shown that optimal transcription of PVC Class III may occur when the strain (harboring the PVC operon encoding a PVC Class III operon) is grown at 37°C and exposed to human serum, suggesting this class may be a mammalian adapted version of a PVC Needle Complex.

An example cassette (PVC) is shown in Figure 1(D), which shows a map of the model "Class I" PVC operon of *Photorhabdus asymbiotica* ATCC43949 (obtainable from the ATCC, accession number: ATCC 43949), said operon being associated with the downstream effector gene "PAU_03332" (encoding a Pnf protein effector, e.g. SEQ ID NO.: 32). This model operon is referred to as *Pa*^{ATCC43949} PVC*pnf*. This operon comprises sixteen structural genes (*pvc1-16*), and two genes (3' end) encoding effectors (in this case the *pvc17* / Rhs-like, encoding an Rhs-like effector, and *pvc21*, encoding a Pnf effector). Said genes *pvc1-16* correspond to genes PAU_03353 to PAU_03338 of the sequence of GenBank accession no. FM162591.1, and are represented by the sequence of SEQ ID NO.: 93.

An example PVC operon (e.g. encoding the structural genes, but not a/the PVC effector) is provided in SEQ ID NO: 93 (which is encodes the operon shown schematically in Figure1(D)), with other examples being SEQ ID NO: 94 and in SEQ ID NO: 95. These sequences begin at the ATG start codon of the first structural gene (*pvc1*) of the PVC cassette / operon, and end at the TAA stop codon of the final structural gene (*pvc16*).

A PVC Needle Complex from any one of Classes I-III may be used for a variety of applications. However, PVC Needle Complexes of a certain class may be particularly suitable for delivery to a defined cell type. For example, a PVC Needle Complex for delivery of a payload to a mammalian cell may suitably be a member of Class III. A PVC Needle Complex for delivery of a payload to an insect cell (e.g. to an insect) may suitably be a member of Class I (such as *P. asymbiotica* PVC*pnf*, encoded by SEQ ID NO.: 93, e.g. as expressed in *E. coli* from a cosmid clone).

Thus, as will be understood by the skilled person, the term "PVC Needle Complex" (used synonymously with the terms "PVC Needle Complex delivery system" and "nanosyringe" herein) means a macromolecular protein complex comprising polypeptide subunits encoded by a PVC (operon) of a *Photorhabdus* bacterium. A PVC Needle Complex is assembled in a nanosyringe structure, having a physical structure (superficially) similar to the antibacterial R-type pyocins (see Figure 3). Functional and molecular studies have shown that a PVC Needle Complex becomes packaged (loaded) with a PVC effector protein(s) (i.e. the PVC effector proteins are packaged therein, or thereon), the packaged PVC Needle Complex is released from the bacterium, and then injects the PVC effector into a target cell such that the PVC effector protein may exert toxicity.

The term "PVC Needle Complex" preferably encompasses PVC Needle Complex-like structures/complexes, encoded by operon(s) comprising genes which are homologous to genes of a *Photorhabdus* PVC operon. PVC-like elements are not restricted to *Photorhabdus,* and a well characterized homologous operon (to a PVC operon) is present on the pADAP plasmid of the insect pathogenic bacteria *Serratia entomophila*. Furthermore, an analogous, and (at least partially) homologous, PVC-like 'injectosome' Needle Complex system is employed by the bacterium *Pseudoalteromonas luteoviolacea* (e.g. used to control the metamorphosis of the marine worm Hydroides elegans). Structures exist in other Enterobacteriaceae (such as *Yersinia* Spp.) which are encoded by operons having homology to a PVC operon, and may be used with a leader sequence described herein. Each of these (PVC-like) structures are embraced by the term "PVC Needle Complex" as used herein.

Thus, a PVC Needle Complex is a "nanosyringe" complex, with the polypeptide encoded by the effector gene being packaged (loaded) within, or at the end (tip) of, the PVC Needle Complex, thus representing a "payload" or "warhead" of the PVC Needle Complex. The present inventors have demonstrated that the PVC Needle Complex itself (with the payload still loaded) is freely released (e.g. secreted) from *Photorhabdus* cells, before interacting with the membrane of a target cell and injecting the payload into the cell's cytosol. Indeed, the inventors have successfully expressed and loaded PVC Needle Complexes in heterologous expression systems, before isolating/ purifying the PVC Needle Complexes and using them to suppress (e.g. kill) insect larvae (see Example 2). Thus, the PVC Needle Complexes act as long-range protein delivery systems.

In one embodiment, the PVC Needle Complex is encoded by a sequence having at least 75% sequence identity (preferably at least 85% sequence identify; more preferably at least 95% sequence identity) to a sequence selected from SEQ ID NO.: 93, SEQ ID NO.: 94, and SEQ ID NO.: 95 (for example, SEQ ID NO.: 93).

In one embodiment, the PVC Needle Complex is encoded by a sequence selected from SEQ ID NO.: 93, SEQ ID NO.: 94, and SEQ ID NO.: 95 (for example, SEQ ID NO.: 93).

Leader/ signal sequences are typically peptides, often of 10-30 amino acids long present at the N-terminus of the majority of (newly) expressed proteins that are destined towards the secretory pathway (e.g. for directing said proteins to a protein-conducting channel on the cell membrane). Many proteins require a signal sequence for Golgi or endoplasmic reticulum entry.

The term "leader sequence" (used interchangeably with the terms "leader peptide", "signal sequence", "targeting signal", "localization signal", "localization sequence", and "transit peptide" herein), used in the context of a "PVC effector leader sequence" herein, means a polypeptide sequence which functions to direct the PVC effector into the interior, or the end (tip), of a PVC Needle Complex – as such, the leader sequence functions to package a PVC effector into a PVC Needle Complex. The PVC Needle Complex can subsequently deliver (e.g. inject) the PVC effector into a target cell. The PVC Needle Complex may be an assembled PVC Needle Complex. The term "PVC Needle Complex" may refer to a fragment of a PVC Needle Complex (e.g. wherein the leader sequence contacts said fragment, and optionally the PVC Needle Complex assembles around the leader sequence-payload 'effector fusion').

A PVC leader sequence is typically present in the N-terminus (characterized by or encompassed within the first 50 amino acids) of a PVC effector or homologue thereof. However, the invention embraces leader sequences of PVC effectors and PVC effector homologues, which may be found in regions other than the N-terminal region of such PVC effectors/ homologues (e.g. in the C-terminal region).

In one embodiment, the leader sequence comprises (or consists essentially of) amino acid residues 1-50 of a PVC effector (e.g. PVC effector protein). Reference to "amino acid residues 1-50" embraces "amino acid residues 2-50", wherein the N-terminal methionine is omitted e.g. has been cleaved. The leader sequence may be a fragment of the N-terminal

50 amino acids of a PVC effector (e.g. a fragment comprising or consisting essentially of ≤ 45, ≤ 35, ≤ 25, or ≤ 15 amino acids), with the proviso that the fragment is capable of packaging a payload into a PVC Needle Complex.

In one embodiment, a leader sequence (e.g. isolated leader sequence) of the invention comprises (or consists essentially of) an amino acid sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% sequence identity to one or more sequence selected from SEQ ID NO.: 47 - SEQ ID NO.: 92 (preferably SEQ ID NO.: 50, SEQ ID NO.: 68, SEQ ID NO.: 71, SEQ ID NO.: 76, SEQ ID NO.: 78, or SEQ ID NO.: 92) – e.g. with the proviso that the leader sequence is capable of packaging a payload into a PVC Needle Complex. In a preferable embodiment, a leader sequence comprises (or consists essentially of) an amino acid sequence having at least 60% sequence identity to one or more sequence selected from SEQ ID NO.: 47 - SEQ ID NO.: 92 (preferably SEQ ID NO.: 50, SEQ ID NO.: 68, SEQ ID NO.: 71, SEQ ID NO.: 76, SEQ ID NO.: 78, or SEQ ID NO.: 92) – e.g. with the proviso that the leader sequence is capable of packaging a payload into a PVC Needle Complex. In a more preferable embodiment, a leader sequence comprises (or consists essentially of) an amino acid sequence of one or more selected from SEQ ID NO.: 47 - SEQ ID NO.: 92 (preferably SEQ ID NO.: 50, SEQ ID NO.: 68, SEQ ID NO.: 71, SEQ ID NO.: 76, SEQ ID NO.: 78, or SEQ ID NO.: 92). In one embodiment, a leader sequence comprises (or consists essentially of) an amino acid sequence selected from SEQ ID NO.: 47 - SEQ ID NO.: 92 (preferably SEQ ID NO.: 50, SEQ ID NO.: 68, SEQ ID NO.: 71, SEQ ID NO.: 76, SEQ ID NO.: 78, or SEQ ID NO.: 92).

In one embodiment, a leader sequence comprises (or consists essentially of) an amino acid sequence selected from SEQ ID NO.: 50, SEQ ID NO.: 68, SEQ ID NO.: 71, SEQ ID NO.: 76, SEQ ID NO.: 78, and SEQ ID NO.: 92.

In one embodiment, the leader sequence comprises (or consists essentially of) an amino acid sequence of SEQ ID NO.: 50. In one embodiment, the leader sequence comprises (or consists essentially of) an amino acid sequence of SEQ ID NO.: 68. In one embodiment, the leader sequence comprises (or consists essentially of) an amino acid sequence of SEQ ID NO.: 71. In one embodiment, the leader sequence comprises (or consists essentially of) an amino acid sequence of SEQ ID NO.: 76. In one embodiment, the leader sequence comprises (or consists essentially of) an amino acid sequence of SEQ ID NO.: 78. In one embodiment, the leader sequence comprises (or consists essentially of) an amino acid sequence of SEQ ID NO.: 92.

Without wishing to be bound by theory, it is believed that the leader sequences share a "chemical composition consensus", based on amino acid properties. More particularly, the leader sequences comprise similar charge patterns, the pattern comprising 2x negatively charged regions, each followed by a positively charged region (e.g. [-ve] [+ve] [-ve] [+ve]) – see Figure 9. This is consistent with leader sequences of toxins of the type 2 secretion system, which comprise a charge / property pattern of [+ve] [Hydrophobic] [+ve] [C]. A further theory posits that the leader sequences share a typical "helix-turn-helix" structure. Another theory is that the leader sequences form a structure recognised by an ATPase enzyme (e.g. encoded by the gene PAU_03339 (*pvc15*) in the model operon of Figure 1(D)) present in the interior, or at the end (e.g. tip), of a PVC Needle Complex.

The term "PVC effector" (used synonymously with the term "PVC operon-encoded effector", and "PVC effector protein") means an effector polypeptide encoded by a *Photorhabdus* PVC operon, more particularly (and typically) found shortly downstream (3') of the structural genes of said operon (preferably shortly or immediately downstream of *pvc16*, and typically within 5kb). The term "PVC effector" preferably embraces homologues thereof. Thus, the leader sequence may also be from a polypeptide encoded by a gene which is a homologue of gene encoding a PVC effector – see Table 1 for examples of such homologues. Indeed, identification of PVC effectors is aided by detecting homology of a gene downstream of *pvc16* with a known toxin polypeptide (e.g. a gene which encodes said toxin polypeptide). As will be understood by the skilled person, the term "homologue" preferably means a gene that descended from the same ancestral gene, and shares similar function – such gene (or polypeptide encoded thereby) is homologous to a gene encoding the PVC effector. A homologue may be from the genome of a *Photorhabdus* species or from a species other than a *Photorhabdus* species. Examples of suitable homologues are outlined in Table 1.

The present inventors have elucidated and characterised, in detail, genes that encode PVC effectors of these PVC Needle Complexes in the three most common (best characterised) strains of *Photorhabdus*, as well as the *P. asymbiotica* Thai strain PB68.1. This was conducted based on analysing proximity of genetic linkage to the 3' end of the PVC structural genes of the operons, and predicted function of the protein sequence of the effector (e.g. a homologue of a known effector/ toxin protein). In more detail, the PVC effectors (e.g. genes encoding the PVC effectors) were typically identified as open reading frames (ORF) having homology to genes encoding known toxin polypeptides (e.g. homologues as outlined in Table 1), and being typically present within a distance of 1 kilobase to 5 kilobase (kb) (e.g. within 1 kb) downstream of the final structural gene of a PVC operon (e.g. *pvc16*) (typically with few or no intervening genes). Typically, there are no "non-toxin-like" ORFs between the end of the operon (encoding the PVC Needle Complex) and the PVC effector gene(s). Although there may be (e.g. one, or two) other small predicted genes present in these regions, these other genes are not assigned as PVC effectors (due to lack of homology to a known effector/ toxin gene, as described above).

In order to assign a putative PVC effector gene (e.g. ORF within a distance of 5kb, for example within 1kb downstream of the final structural gene of a PVC operon) as a PVC effector gene, the inventors used a combination of BlastP and HHPRED (https://toolkit.tuebingen.mpg.de/#/tools/hhpred). Putative PVC effector genes were assigned as PVC effector genes based on direct homology to known toxin encoding genes, similarity to a toxin protein family, proximity to the PVC operon (e.g. within 1-5kb downstream of the final structural gene of a PVC operon, *pvc16*) and/or based on domain similarities of predicted secondary structures to that of known toxins.

Thus, a PVC effector (gene) may be identified (within a *Photorhabdus* genome) by (i) identifying *pvc16* (e.g. via sequence homology to a known *pvc16*), (ii) identifying an ORF 3' to *pvc16*, preferably ≤5kb downstream of *pvc16*), and (iii) confirming said ORF encodes a PVC effector through identification of sequence homology to a known gene encoding a toxin polypeptide (for example, a toxin protein described in the column of Table 1 labelled "Homologue(s)").

By way of example, the PVC effector gene PAU_03337 (referred to herein as "*sepC*" due to homology to virulent *sep* genes) is positioned 325 base pairs (bp) downstream of *pvc16* (PAU_03338) of the PVC operon referred to herein as PVC*pnf* (e.g. of SEQ ID NO. 93), which is found in *P. asymbiotica* ATCC43949. That is, the start codon of PAU_03337 begins 325 bp downstream of the end of the stop codon of PAU_03338.

This can be illustrated by reference to the *P. asymbiotica* ATCC43949 complete genome, accessible via GenBank accession no. FM162591.1 (see also *e.g.* Wilkinson *et al,* BMC Genomics volume 10, article number: 302 (2009), incorporated herein by reference), in which effector gene PAU_03337 is annotated as being positioned in the genome as follows: complement (3913237..3914247) – that is, at nucleotide positions 3913237..3914247; and PAU_03338 is annotated as being positioned in the genome as follows: complement (3914573..3915454). No other ORF (encoding an effector or otherwise) is found between these two genes.

A further PVC effector gene associated with the PVC operon referred to herein as PVC*pnf* (e.g. of SEQ ID NO. 93), namely PAU_03332 (referred to herein as *"pnf"*), is positioned 3535bp downstream of *pvc16* (PAU_03338).

The PVC effector gene PAU_02095 (referred to herein as "*Rhs-like toxin effector*" due to homology to virulent Rhs toxin genes) is positioned 3961bp downstream of *pvc16* (PAU_02099) of a PVC operon referred to herein as PVC*lopT* (e.g. of SEQ ID NO. 94), which is found in *P. asymbiotica* ATCC43949. That is, the start codon of PAU_02095 begins 3961bp downstream of the end of the stop codon of PAU_02099.

In a further example, the PVC effector of gene PAU_02009 (referred to as *"cif"* herein due to predicted function as a cell cycle inhibiting factor/ ATP/GTP binding protein) is positioned 157bp downstream of *pvc16* (PAU_02008) of the associated PVC operon, referred to herein as PVC*cif*, found in *P. asymbiotica* ATCC43949.

In yet further examples: with regard to a PVC operon of *P. luminescens* TT01 referred to as a PVC*unit4* operon herein, PVC effector gene *"pvc17"* (e.g. "*plu1651*") is positioned 104bp downstream of *pvc16* (gene "*plu1655*"); and with regard to a PVC operon of *Photorhabdus temperata* subsp. *temperata* Meg1 referred to as a PVC*cif* operon herein, PVC effector gene "CIF toxin effector" (e.g. MEG1DRAFT_03529) is positioned 4216bp downstream of the relevant *pvc16* gene.

These examples, illustrate that a gene encoding a PVC effector is typically positioned within a distance of ≤ 5 kb downstream of the final gene of a PVC operon (e.g. of *pvc16*), more typically within a distance of ≤ 1 kb downstream of the final gene of a PVC operon.

In summary, there exists 46 PVC effectors that have been identified in these four strains (based on currently available sequence data) (see Table 1). The first 50 amino acids of each of these PVC effectors represent (or encompass) their endogenous leader sequence, and the inventors have demonstrated the leader sequences may be cloned and fused to a variety of payloads to be packaged into a PVC Needle Complex – see Examples 3 and 4. Thus, a PVC effector (as translated) comprises at least two principle domains: the leader sequence

(amino acids 1 to 50) and the actual effector polypeptide (amino acids 51 to C-terminal amino acid) - the latter of which may be referred to as the "effector" (e.g. "effector portion") or "payload" herein.

Although the *Photorhabdus* genome sequence(s) continues to be revised, this consolidated list of PVC effector genes represents a comprehensive description of such effectors, and is based on currently available sequence data of the most common (best characterised) *Photorhabdus* strains, and provides the skilled person with an understanding of the term "PVC effector" as well as the sequences of these PVC effectors (as well as how to search/mine for further PVC effectors, e.g. in alternative (genome) sequences). As described above, the inventors have found that the PVC effector proteins comprise a leader sequence which is necessary (and sufficient) for directing the PVC effector protein (e.g. payload) to be packaged/ loaded into a PVC Needle Complex.

Table 1

Gene (Locus Tag)	Predicted Function	Accession No. (polypeptide sequence)	Homologue(s)	SEQ ID NO.:
PAK_1985	Cell cycle inhibiting factor / ATP/GTP binding protein.	WP_036768136	Cif type III effector	1
PAK_1987	Cytidine deaminase toxin-like.	WP_036768135	YwqJ family	2
PAK_1988	RHS repeat toxin like / Cholera enterotoxin (A chain) ADP Ribosyltransferase like	WP_036768134	RHS repeat-protein	3
PAK_2075	CNF; cytotoxic necrotizing factor (zinc metallo-peptidase) / Neurotoxin A; botulinum	WP_036768069 (exemplary, not 100% identical)	CNF1 family	4
PAK_2077	LopT cysteine proteinase (peptidase C58 family).	WP_036768068	YopT type III effector from Yersinia.	5
PAK_2892	Pvc17; putative nematode symbiosis protein	WP_065822933 (exemplary, not 100% identical)	n/a	6
PAK_2893	Similar to Type III secretion protein GogB	WP_065822917 (exemplary, not 100% identical)	GogB type III effector from Salmonella.	7
PAK_2894	RHS-repeat protein. Function unknown.	WP_036774164	RHS-repeat protein.	8
PAK_3525	CNF/PaTox domain like tyrosine glycosylase UDP-GlcNAc	WP_036768627.1 (exemplary, not 100% identical)	PaTox from *Photorhabdus asymbiotica* ATCC43949	9
PAT_00148	Cif-like; Cell cycle inhibiting factor / ATP/GTP binding protein.	WP_065823029	Cif type III effector	10
PAT_00149	YwqJ -Cytidine deaminase toxin-like.	WP_065823017.1	YwqJ family	11
PAT_00150	RHS repeat toxin like / Cholera enterotoxin (A chain) ADP	WP_065823018.1	RHS repeat protein	12

	Ribosyltransferase like			
PAT_00152	Domain similar to Colicin A and Glucosly Transferase	WP_065823019	n/a	13
PAT_02308	Pvc17; putative nematode symbiosis protein	WP_065822933	n/a	14
PAT_02309	Similar to Type III secretion protein GogB	WP_065822917	GogB type III effector from Salmonella.	15
PAT_02310	RHS-repeat protein. Function unknown.	WP_065822916	RHS repeat protein	16
PAT_02956	cytotoxic necrotizing factor (zinc metallopeptidase) / Neurotoxin A; botulinum	WP_065822174	CNF1 family	17
PAT_02957	LopT cysteine proteinase (peptidase C58 family). Similar to YopT type III toxin of Yersinia.	WP_065822175	YopT type III effector from Yersinia.	18
PAT_03171	YwqJ-Cytidine deaminase toxin-like.	WP_065823264	YwqJ family	19
PAT_03172	Cytotoxic necrotizing factor 1, Rho deamidase	WP_065823265	CNF1 family	20
PAT_03177	Calmodulin-sensitive adenylate cyclase	WP_065823268	CyaA family	21
PAU_02009	Cif-like; Cell cycle inhibiting factor / ATP/GTP binding protein.	CAQ84101	Cif type III effector	22
PAU_02010	TccC3 / RHS repeat toxin like.	CAQ84102	RHS repeat protein	23
PAU_02095	TccC2 / RHS repeat toxin like. Neutral metalloproteinase II.	CAQ84187	RHS repeat protein	24
PAU_02096	LopT cysteine proteinase (peptidase C58 family). Similar to YopT type III toxin of Yersinia.	CAQ84188	YopT type III effector from Yersinia.	25
PAU_02097	RHS-repeat protein. Function unknown.	CAQ84189	RHS repeat protein	26
PAU_02098	Dermonecrotic toxin; Pasteurella multocida toxin-like / RtxA-like (Glucosyltransferase)	CAQ84190	RtxA family from Vibrio	27
PAU_2230	PaTox; tyrosine glycosylase and cysteine protease domains.	CAQ84322	Type III effector SseI from Salmonella	28
PAU_02805	Pvc17; putative nematode symbiosis protein	CAQ84177	n/a	29
PAU_02806	Similar to Type III secretion protein GogB	CAQ84895	GogB type III effector from Salmonella.	30
PAU_02807	Similar to Type III secretion protein GogB	CAQ84179	GogB type III effector from Salmonella.	31
PAU_03332	Pnf; Rho GTPase deaminidase and tranglutination.	CAQ85420	CNF1 family from *E. coli*	32

PAU_03337	CyaA-like; Adenylylcyclase toxin (anthrax EF-like).	CAQ85425	Antrax Edema Factor, *Pseudomonas* ExoY toxin	33
Plu1651	Pvc17. Putative nematode symbiosis protein. Induces endotokia matricida in *C. elegans* (experimental)	WP_011145938	n/a	34
Plu1671	RHS repeat toxin like. ADP-ribosyltransferase	WP_011145957	RHS repeat protein	35
Plu1672	RHS repeat toxin like. ADP-ribosyltransferase	WP_011145958	RHS repeat protein	36
Plu1690 / PLU_RS08490	RHS repeat toxin like. Rho deamidase	WP_011145974	RHS repeat protein	37
Plu1691	RHS repeat toxin like. ADP-ribosyltransferase	WP_011145975	RHS repeat protein	38
Plu1712	CyaA calmodulin-sensitive adenylate cyclase like.	WP_011145994	CyaA family	39
Plu1713	Weak similarity to Diphtheria toxin catalytic domain.	WP_011145995	n/a	40
Plu1714	RHS repeat toxin like. Neutral metallo-proteinase II.	WP_041380028	RHS repeat protein	41
Plu2400	Dermonecrotic toxin-like; Pasteurella multocida toxin-like / RtxA-like Glucosyltransferase.	WP_011146635	RtxA family from Vibrio	42
Plu2401	LopT cysteine proteinase (peptidase C58 family). Similar to YopT type III toxin of Yersinia.	WP_011146636	YopT type III effector from Yersinia.	43
Plu2514	Similar to *Xenorhabdus* Mcf-domain / weak acid phosphatase.	WP_011146737	n/a	44
Plu2515	Cif-like; Cell cycle inhibiting factor / ATP/GTP binding protein.	WP_011146738	Cif type III effector	45
Plu1649	N-acyl homoserine lactonase like	WP_133148775	Weak similarity to HvnA of Vibrio	46

The accession numbers provided in Table 1 are provided for exemplary purposes, providing example amino acid sequences of (or having high similarity to) PVC effectors described herein. The sequences of said accession numbers may be accessed through GenBank (https://www.ncbi.nlm.nih.gov/genbank/).

The locus tag (beginning with "PAU" or "Plu") corresponds to the locus tag assigned to the effector in genome sequences available through GenBank above. Locus tags beginning with "PAT" (referring to strain *P. asymbiotica* Thai strain PB68.1) and "PAK" (referring to strain *P. asymbiotica* Kingscliff) have been assigned by the present inventors upon identification of the PVC effector genes within the genomes of said strains (in a consistent manner with the locus tags of publicly available sequences).

This locus tags may be used herein to refer to the corresponding PVC effector polypeptide.

In one embodiment, the PVC effector is encoded by one or more gene (with the SEQ ID NO. of the encoded PVC effector protein in parentheses) selected from PAK_1985 (SEQ ID NO: 1), PAK_1987 (SEQ ID NO: 2), PAK_1988 (SEQ ID NO: 3), PAK_2075 (SEQ ID NO: 4), PAK_2077 (SEQ ID NO: 5), PAK_2892 (SEQ ID NO: 6), PAK_2893 (SEQ ID NO: 7), PAK_2894 (SEQ ID NO: 8), PAK_3525 (SEQ ID NO: 9), PAT_00148 (SEQ ID NO: 10), PAT_00149 (SEQ ID NO: 11), PAT_00150 (SEQ ID NO: 12), PAT_00152 (SEQ ID NO: 13), PAT_02308 (SEQ ID NO: 14), PAT_02309 (SEQ ID NO: 15), PAT_02310 (SEQ ID NO: 16), PAT_02956 (SEQ ID NO: 17), PAT_02957 (SEQ ID NO: 18), PAT_03171 (SEQ ID NO: 19), PAT_03172 (SEQ ID NO: 20), PAT_03177 (SEQ ID NO: 21), PAU_02009 (SEQ ID NO: 22), PAU_02010 (SEQ ID NO: 23), PAU_02095 (SEQ ID NO: 24), PAU_02096 (SEQ ID NO: 25), PAU_02097 (SEQ ID NO: 26), PAU_02098 (SEQ ID NO: 27), PAU_02230 (SEQ ID NO: 28), PAU_02805 (SEQ ID NO: 29), PAU_02806 (SEQ ID NO: 30), PAU_02807 (SEQ ID NO: 31), PAU_03332 (SEQ ID NO: 32), PAU_03337 (SEQ ID NO: 33), Plu1651 (SEQ ID NO: 34), Plu1671 (SEQ ID NO: 35), Plu1672 (SEQ ID NO: 36), Plu1690 (SEQ ID NO: 37), Plu1691 (SEQ ID NO: 38), Plu1712 (SEQ ID NO: 39), Plu1713 (SEQ ID NO: 40), Plu1714 (SEQ ID NO: 41), Plu2400 (SEQ ID NO: 42), Plu2401 (SEQ ID NO: 43), Plu2514 (SEQ ID NO: 44), Plu2515 (SEQ ID NO: 45), Plu1649 (SEQ ID NO: 46), or a combination thereof.

In one embodiment, the PVC effector is encoded by one or more gene (with the SEQ ID NO. of the encoded PVC effector protein in parentheses) selected from PAU_02009 (SEQ ID NO: 22), PAU_02010 (SEQ ID NO: 23), PAU_02095 (SEQ ID NO: 24), PAU_02096 (SEQ ID NO: 25), PAU_02097 (SEQ ID NO: 26), PAU_02098 (SEQ ID NO: 27), PAU_02230 (SEQ ID NO: 28), PAU_02805 (SEQ ID NO: 29), PAU_02806 (SEQ ID NO: 30), PAU_02807 (SEQ ID NO: 31), PAU_03332 (SEQ ID NO: 32), PAU_03337 (SEQ ID NO: 33), Plu1651 (SEQ ID NO: 34), Plu1671 (SEQ ID NO: 35), Plu1672 (SEQ ID NO: 36), Plu1690 (SEQ ID NO: 37), Plu1691 (SEQ ID NO: 38), Plu1712 (SEQ ID NO: 39), Plu1713 (SEQ ID NO: 40), Plu1714 (SEQ ID NO: 41), Plu2400 (SEQ ID NO: 42), Plu2401 (SEQ ID NO: 43), Plu2514 (SEQ ID NO: 44), Plu2515 (SEQ ID NO: 45), Plu1649 (SEQ ID NO: 46), or a combination thereof. These gene names correspond to the 'locus tags' of PVC effector genes in the *Photorhabdus* genome sequences accessible via GenBank, as described above. The PAT and PAK locus tags were generated by the present inventors, such that terminology is consistent with the PAU and Plu locus tags of publicly available genome sequences.

Thus, the PVC effector may be encoded by one or more gene listed above.

In one embodiment, the PVC effector is encoded by one or more gene (with the SEQ ID NO. of the encoded PVC effector in parentheses) selected from PAK_02075 (SEQ ID NO: 4), PAU_02009 (SEQ ID NO: 22), PAU_02096 (SEQ ID NO: 25), PAU_02806 (SEQ ID NO: 30), PAU_03332 (SEQ ID NO: 32), Plu1651 (SEQ ID NO: 34), Plu1649 (SEQ ID NO: 46), or a combination thereof.

In a preferable embodiment, the PVC effector is encoded by one or more gene (with the SEQ ID NO. of the encoded PVC effector in parentheses) selected from PAU_02806 (SEQ ID NO: 30), PAU_03332 (SEQ ID NO: 32), Plu1651 (SEQ ID NO: 34), Plu1649 (SEQ ID NO: 46), or a combination thereof.

The PVC effector may have a sequence having at least 80% sequence identity (preferably at least 90% sequence identity; more preferably 100% sequence identity) to an amino acid sequence selected from SEQ ID NO: 1 - SEQ ID NO: 46. For example, the PVC effector may have a sequence having at least 80% sequence identity (preferably at least 90% sequence identity; more preferably 100% sequence identity) to an amino acid sequence selected from SEQ ID NO: 22 - SEQ ID NO: 46.

The present inventors have identified the leader sequences of the gogB1 (PAU_02806) and Pnf (PAU_03332) PVC effectors as being particularly efficient at packaging a (fused) payload into a PVC Needle Complex. In one embodiment, the PVC effector is encoded by PAU_02806 (e.g. has an amino acid sequence of SEQ ID NO: 30). In one embodiment, the PVC effector is encoded by PAU_03332 (e.g. has an amino acid sequence of SEQ ID NO: 32).

In one embodiment, the PVC effector comprises (or consists essentially of) an amino acid sequence of one or more selected from SEQ ID NO: 1 - SEQ ID NO: 46 (for example SEQ ID NO: 22 - SEQ ID NO: 46), or a combination thereof. For example, the PVC effector may comprise (or consist essentially of) a sequence selected from SEQ ID NO: 4, SEQ ID NO: 22, SEQ ID NO: 25, SEQ ID NO: 30, SEQ ID NO: 32 and SEQ ID NO: 46.

In one embodiment, the PVC effector comprises (or consists essentially of) an amino acid sequence of SEQ ID NO.: 4. In one embodiment, the PVC effector comprises (or consists essentially of) an amino acid sequence of SEQ ID NO. 22. In one embodiment, the PVC effector comprises (or consists essentially of) an amino acid sequence of SEQ ID NO. 25. In one embodiment, the PVC effector comprises (or consists essentially of) an amino acid sequence of SEQ ID NO: 30. In one embodiment, the PVC effector comprises (or consists essentially of) an amino acid sequence of SEQ ID NO: 32. In one embodiment, the PVC effector comprises (or consists essentially of) an amino acid sequence of SEQ ID NO. 46.

The term “packaging” (used synonymously with the terms “trans-packaging” and “loading”) means the directing of a payload, by a leader sequence of the invention (to which the payload is linked/ fused), into the interior, or end (tip), of an assembled PVC Needle Complex, such that the PVC Needle Complex is subsequently configured for delivering (e.g. injecting) the payload into a target cell. Thus, the payload may be packaged within a PVC Needle Complex, or may be packaged at the end (or tip) of the PVC Needle Complex (e.g. at least a portion of the payload may be external to the PVC Needle Complex).

The term “payload” (used synonymously with the term “warhead” herein) means a molecule which is packaged into the interior, or end (tip), of an assembled PVC Needle Complex, and subsequently delivered (e.g. injected) into a (target) cell. In wild-type *Photorhabdus*, the payload is a PVC effector (more particularly, the effector portion of said PVC effector), encoded (as described above) by a gene that is downstream to (3’ to) the structural genes of a PVC operon. For example, see model PVC operon of Figure 1(D), having effector genes PAU_03337 (listed as PVCpnf 17), encoding an adenylate cyclase effector (e.g. SEQ ID NO.: 33); and PAU_03332 (listed as PVCpnf 21), encoding a Pnf effector (e.g. SEQ ID NO.: 32).

A leader sequence and a payload of the present invention form an "effector fusion" (or simply "fusion") that is "distinct from a (e.g. wild-type) PVC effector" (e.g. a polypeptide encoded by one of the genes outlined in Table 1). For example, the effector fusion may be a chimaera, formed of a leader sequence from a first PVC effector fused to (an/the effector portion of) a second (different) PVC effector (preferably amino acids 51 to the C-terminal amino acid of said second PVC effector), wherein said first PVC effector and said second PVC effector are different. The effector fusion may be a chimaera, comprising (or consisting essentially of) a leader sequence described herein fused to a non-PVC effector polypeptide. The effector fusion may be a chimaera, comprising (or consisting essentially of) a leader sequence described herein fused to a non-*Photorhabdus* polypeptide. The effector fusion may be a leader sequence-nucleic acid fusion (preferably conjugate), comprising a leader sequence described herein fused to a nucleic acid.

An effector fusion is not limited to a fusion complex comprising a leader sequence fused to a toxic payload (e.g. the leader could be fused to a therapeutic payload). Thus, the term "effector" as used in the context of "effector fusion" means the payload which is packaged into the PVC Needle Complex (which could provide a variety of effects, including toxigenic and/or therapeutic effects). Thus, the term "effector fusion" may be used interchangeably with the term "fusion" herein.

The term "effector fusion" may be used synonymously with the term "leader sequence-payload fusion", and/or "leader sequence-payload complex".

Alternatively or additionally, the payload may be distinct from a PVC effector protein (e.g. distinct from amino acids 51 to the C-terminal amino acid of a PVC effector). For example, the payload may be a polypeptide or nucleic acid that is not found in a wild-type *Photorhabdus* bacterium.

Analysis of the size (e.g. polypeptide length) and structure of the various natural PVC effector payloads encoded by *Photorhabdus*, shows that there exists a wide variety of different PVC effector lengths and structures, demonstrating that the applicability of the PVC Needle Complex delivery system of the present invention is not limited by the size or properties of the payload of interest. To summarise, there is no requirement for particular secondary structure, biophysical property, or length of cargoes, confirming that that the PVC Needle Complex can be utilised as a versatile multifunctional delivery vehicle.

The payload may be one or more selected from a polypeptide (e.g. a polypeptide payload), a nucleic acid (e.g. a nucleic acid payload), or a combination thereof. In a preferable embodiment, the payload is a polypeptide.

Examples of polypeptide payloads include an antibody (e.g. an anti-MDM antibody), a nanobody, a peptide vaccine (e.g. a tyrosinase-related protein 2 (TRP2) peptide vaccine), a nuclear factor-κB inhibitor, a T3SS payload (e.g. a T3SS payload which inhibits the NF-kB and/or MAPK pathways), an anti-apoptotic peptide (e.g. BH4), nicotinamide adenine dinucleotide quinone internal oxidoreductase (Ndi1), a PHOX complex subunit, a myotubularin, a nucleic acid (preferably DNA)-modifying enzyme, or a combination thereof. Examples of suitable nucleic acid-modifying enzymes include a recombinase (e.g. Cre

recombinase), a transposase, a Cas enzyme (e.g. Cas9), and/or a Mad7 (preferably Mad7, more preferably Cre recombinase). The payload may be, for example, tBid (SEQ ID NO.: 109) and/or BaxBH3 peptide (aa59–73) (SEQ ID NO.: 111).

Any polypeptide having enzymatic activity may be a payload.

A nucleic acid payload may be conjugated/ crosslinked to a leader sequence of the invention. For example, copper-free click chemistry (e.g. strain-promoted alkyne azide cycloaddition (SPAAC)) may be used to crosslink a nucleic acid to a leader sequence. Examples of nucleic acid payloads include a primer, an mRNA, a nucleic acid analogue, an aptamer, a small interfering RNA (siRNA), a microRNA therapeutic inhibitor (antimiR), a microRNA therapeutic mimic (promiR), a long non-coding RNA modulator, a single guide RNA (sgRNA), or a combination thereof.

The leader sequence may be fused directly or indirectly (e.g. by means of a spacer) to the payload. The leader sequence may be fused covalently or non-covalently to the payload. In a preferable embodiment, the leader sequence is covalently fused to the payload. For example, the fusion/ effector fusion may be a (recombinant) fusion protein comprising (or consisting essentially of) a PVC effector leader sequence fused to a (polypeptide) payload.

Another aspect of the invention provides an isolated nucleic acid comprising a nucleotide sequence which encodes a PVC effector leader sequence of the invention. Another aspect of the invention provides an isolated nucleic acid comprising a nucleotide sequence which encodes an effector fusion (e.g. fusion) of the invention, and optionally a nucleotide sequence which encodes a PVC Needle Complex.

Another aspect of the invention provides an expression vector comprising: a nucleic acid (preferably an isolated nucleic acid) comprising a nucleotide sequence which encodes a PVC effector leader sequence of the invention. Another aspect of the invention provides an expression vector comprising: a nucleic acid (preferably an isolated nucleic acid) comprising a nucleotide sequence which encodes an effector fusion (e.g. fusion) of the invention, and optionally a nucleotide sequence which encodes a PVC Needle Complex.

Another aspect of the invention provides a host cell comprising an isolated nucleic acid, the isolated nucleic acid comprising a nucleotide sequence which encodes a PVC effector leader sequence of the invention. Another aspect of the invention provides a host cell comprising an isolated nucleic acid, the isolated nucleic acid comprising a nucleotide sequence which encodes an effector fusion (e.g. fusion) of the invention, and optionally a nucleotide sequence which encodes a PVC Needle Complex.

The term “nucleic acid” may be used synonymously with the term “polynucleotide”.

Another aspect of the invention provides a host cell comprising an expression vector, the expression vector comprising a nucleotide sequence which encodes a PVC effector leader sequence of the invention. Another aspect of the invention provides a host cell comprising an expression vector, the expression vector comprising a nucleotide sequence which encodes

an effector fusion (e.g. fusion) of the invention, and optionally a nucleotide sequence which encodes a PVC Needle Complex.

Said host cell may be a mammalian cell, an insect cell, a yeast cell, a bacterial cell (e.g. *E. coli*), or a plant cell. In a preferable embodiment, the host cell is a bacterial cell (preferably *E. coli*).

In one embodiment, the host cell is a *Photorhabdus* cell, optionally wherein the *Photorhabdus* cell comprises a PVC operon operably linked to an inducible promoter (e.g. see Example 3). The PVC operon may be endogenous to the *Photorhabdus* cell (e.g. the PVC operon may be PVCu4). Suitably, the *Photorhabdus* cell may be obtainable from the ATCC under accession no. ATCC 29999.

The sequences (e.g. leader sequence and/or nucleic acid sequence) of the present invention include sequences that have been removed from their naturally occurring environment, recombinant or cloned (e.g. DNA) isolates, and chemically synthesized analogues or analogues biologically synthesized by heterologous systems.

The leader sequence(s) and/or polynucleotide(s) of the present invention may be prepared by any means known in the art. For example, large amounts of the leader sequence(s) and/or polynucleotide(s) may be produced by replication and/or expression in a suitable host cell. The natural or synthetic DNA fragments coding for a desired fragment will typically be incorporated into recombinant nucleic acid constructs, typically DNA constructs, capable of introduction into and replication in a prokaryotic or eukaryotic cell. Usually the DNA constructs will be suitable for autonomous replication in a unicellular host, such as yeast or bacteria, but may also be intended for introduction to and integration within the genome of a cultured bacterial, insect, mammalian, plant or other eukaryotic cell lines.

The leader sequence(s) and/or polynucleotide(s) of the present invention may also be produced by chemical synthesis, e.g. a polynucleotide by the phosphoramidite method or the tri-ester method, and may be performed on commercial automated oligonucleotide synthesizers. A double-stranded (e.g. DNA) fragment may be obtained from the single stranded product of chemical synthesis either by synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

When applied to a leader sequence or nucleic acid sequence, the term “isolated” in the context of the present invention denotes that the leader sequence and/or polynucleotide sequence has been removed from its natural genetic milieu and is thus free of other extraneous or unwanted coding sequences (but may include naturally occurring 5' and 3' untranslated regions such as promoters and terminators), and is in a form suitable for use within genetically engineered protein production systems. Such isolated molecules are those that are separated from their natural environment.

SEQUENCE HOMOLOGY

Any of a variety of sequence alignment methods can be used to determine percent identity, including, without limitation, global methods, local methods and hybrid methods, such as, e.g., segment approach methods. Protocols to determine percent identity are routine procedures within the scope of one skilled in the art. Global methods align sequences from the beginning to the end of the molecule and determine the best alignment by adding up scores of individual residue pairs and by imposing gap penalties. Non-limiting methods include, e.g., CLUSTAL W, see, e.g., Julie D. Thompson et al., CLUSTAL W: Improving the Sensitivity of Progressive Multiple Sequence Alignment Through Sequence Weighting, Position- Specific Gap Penalties and Weight Matrix Choice, 22(22) Nucleic Acids Research 4673-4680 (1994); and iterative refinement, see, e.g., Osamu Gotoh, Significant Improvement in Accuracy of Multiple Protein. Sequence Alignments by Iterative Refinement as Assessed by Reference to Structural Alignments, 264(4) J. Mol. Biol. 823-838 (1996). Local methods align sequences by identifying one or more conserved motifs shared by all of the input sequences. Non-limiting methods include, e.g., Match-box, see, e.g., Eric Depiereux and Ernest Feytmans, Match-Box: A Fundamentally New Algorithm for the Simultaneous Alignment of Several Protein Sequences, 8(5) CABIOS 501 -509 (1992); Gibbs sampling, see, e.g., C. E. Lawrence et al., Detecting Subtle Sequence Signals: A Gibbs Sampling Strategy for Multiple Alignment, 262(5131) Science 208-214 (1993); Align-M, see, e.g., Ivo Van Walle et al., Align-M - A New Algorithm for Multiple Alignment of Highly Divergent Sequences, 20(9) Bioinformatics:1428-1435 (2004).

Thus, percent sequence identity is determined by conventional methods. See, for example, Altschul et al., Bull. Math. Bio. 48: 603-16, 1986 and Henikoff and Henikoff, Proc. Natl. Acad. Sci. USA 89:10915-19, 1992. Briefly, two amino acid sequences are aligned to optimize the alignment scores using a gap opening penalty of 10, a gap extension penalty of 1, and the "blosum 62" scoring matrix of Henikoff and Henikoff (ibid.) as shown below (amino acids are indicated by the standard one-letter codes).

The "percent sequence identity" between two or more nucleic acid or amino acid sequences is a function of the number of identical positions shared by the sequences. Thus, % identity may be calculated as the number of identical nucleotides / amino acids divided by the total number of nucleotides / amino acids, multiplied by 100. Calculations of % sequence identity may also take into account the number of gaps, and the length of each gap that needs to be introduced to optimize alignment of two or more sequences. Sequence comparisons and the determination of percent identity between two or more sequences can be carried out using specific mathematical algorithms, such as BLAST, which will be familiar to a skilled person.

ALIGNMENT SCORES FOR DETERMINING SEQUENCE IDENTITY

	A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
A	4																			
R	-1	5																		
N	-2	0	6																	
D	-2	-2	1	6																
C	0	-3	-3	-3	9															
Q	-1	1	0	0	-3	5														
E	-1	0	0	2	-4	2	5													
G	0	-2	0	-1	-3	-2	-2	6												
H	-2	0	1	-1	-3	0	0	-2	8											
I	-1	-3	-3	-3	-1	-3	-3	-4	-3	4										
L	-1	-2	-3	-4	-1	-2	-3	-4	-3	2	4									
K	-1	2	0	-1	-3	1	1	-2	-1	-3	-2	5								
M	-1	-1	-2	-3	-1	0	-2	-3	-2	1	2	-1	5							
F	-2	-3	-3	-3	-2	-3	-3	-3	-1	0	0	-3	0	6						
P	-1	-2	-2	-1	-3	-1	-1	-2	-2	-3	-3	-1	-2	-4	7					
S	1	-1	1	0	-1	0	0	0	-1	-2	-2	0	-1	-2	-1	4				
T	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-1	-2	-1	1	5			
W	-3	-3	-4	-4	-2	-2	-3	-2	-2	-3	-2	-3	-1	1	-4	-3	-2	11		
Y	-2	-2	-2	-3	-2	-1	-2	-3	2	-1	-1	-2	-1	3	-3	-2	-2	2	7	
V	0	-3	-3	-3	-1	-2	-2	-3	-3	3	1	-2	1	-1	-2	-2	0	-3	-1	4

The percent identity is then calculated as:

$$\frac{\text{Total number of identical matches}}{\text{[length of the longer sequence plus the number of gaps introduced into the longer sequence in order to align the two sequences]}} \times 100$$

Substantially homologous polypeptides are characterized as having one or more amino acid substitutions, deletions or additions. These changes are preferably of a minor nature, that is conservative amino acid substitutions (see below) and other substitutions that do not significantly affect the folding or activity of the polypeptide; small deletions, typically of one to about 30 amino acids; and small amino- or carboxyl-terminal extensions, such as an amino-terminal methionine residue, a small linker peptide of up to about 20-25 residues, or an affinity tag.

CONSERVATIVE AMINO ACID SUBSTITUTIONS

Basic:	arginine, lysine, histidine
Acidic:	glutamic acid, aspartic acid
Polar:	glutamine, asparagine
Hydrophobic:	leucine, isoleucine, valine
Aromatic:	phenylalanine, tryptophan, tyrosine
Small:	glycine, alanine, serine, threonine, methionine

In addition to the 20 standard amino acids, non-standard amino acids (such as 4-hydroxyproline, 6-N-methyl lysine, 2-aminoisobutyric acid, isovaline and α -methyl serine) may be substituted for amino acid residues of the polypeptides of the present invention. A limited number of non-conservative amino acids, amino acids that are not encoded by the genetic code, and unnatural amino acids may be substituted for polypeptide amino acid residues. The polypeptides of the present invention can also comprise non-naturally occurring amino acid residues.

Non-naturally occurring amino acids include, without limitation, trans-3-methylproline, 2,4-methano-proline, cis-4-hydroxyproline, trans-4-hydroxy-proline, N-methylglycine, allo-threonine, methyl-threonine, hydroxy-ethylcysteine, hydroxyethylhomo-cysteine, nitro-glutamine, homoglutamine, pipecolic acid, tert-leucine, norvaline, 2-azaphenylalanine, 3-azaphenyl-alanine, 4-azaphenyl-alanine, and 4-fluorophenylalanine. Several methods are known in the art for incorporating non-naturally occurring amino acid residues into proteins. For example, an in vitro system can be employed wherein nonsense mutations are suppressed using chemically aminoacylated suppressor tRNAs. Methods for synthesizing amino acids and aminoacylating tRNA are known in the art. Transcription and translation of plasmids containing nonsense mutations is carried out in a cell free system comprising an E. coli S30 extract and commercially available enzymes and other reagents. Proteins are purified by chromatography. See, for example, Robertson et al., J. Am. Chem. Soc. 113:2722, 1991; Ellman et al., Methods Enzymol. 202:301, 1991; Chung et al., Science 259:806-9, 1993; and Chung et al., Proc. Natl. Acad. Sci. USA 90:10145-9, 1993). In a second method, translation is carried out in Xenopus oocytes by microinjection of mutated mRNA and chemically aminoacylated suppressor tRNAs (Turcatti et al., J. Biol. Chem. 271:19991-8, 1996). Within a third method, E. coli cells are cultured in the absence of a natural amino acid that is to be replaced (e.g., phenylalanine) and in the presence of the desired non-naturally occurring amino acid(s) (e.g., 2-azaphenylalanine, 3-azaphenylalanine, 4-azaphenylalanine, or 4-fluorophenylalanine). The non-naturally occurring amino acid is incorporated into the polypeptide in place of its natural counterpart. See, Koide et al., Biochem. 33:7470-6, 1994. Naturally occurring amino acid residues can be converted to non-naturally occurring species by in vitro chemical modification. Chemical modification can be combined with site-directed mutagenesis to further expand the range of substitutions (Wynn and Richards, Protein Sci. 2:395-403, 1993).

A limited number of non-conservative amino acids, amino acids that are not encoded by the genetic code, non-naturally occurring amino acids, and unnatural amino acids may be substituted for amino acid residues of polypeptides of the present invention.

Essential amino acids in the polypeptides of the present invention can be identified according to procedures known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, Science 244: 1081-5, 1989). Sites of biological interaction can also be determined by physical analysis of structure, as determined by such techniques as nuclear magnetic resonance, crystallography, electron diffraction or photoaffinity labeling, in conjunction with mutation of putative contact site amino acids. See, for example, de Vos et al., Science 255:306-12, 1992; Smith et al., J. Mol. Biol. 224:899-904, 1992; Wlodaver et al., FEBS Lett. 309:59-64, 1992. The identities of essential amino acids

can also be inferred from analysis of homologies with related components (e.g. the translocation or protease components) of the polypeptides of the present invention.

Multiple amino acid substitutions can be made and tested using known methods of mutagenesis and screening, such as those disclosed by Reidhaar-Olson and Sauer (Science 241:53-7, 1988) or Bowie and Sauer (Proc. Natl. Acad. Sci. USA 86:2152-6, 1989). Briefly, these authors disclose methods for simultaneously randomizing two or more positions in a polypeptide, selecting for functional polypeptide, and then sequencing the mutagenized polypeptides to determine the spectrum of allowable substitutions at each position. Other methods that can be used include phage display (e.g., Lowman et al., Biochem. 30:10832-7, 1991; Ladner et al., U.S. Patent No. 5,223,409; Huse, WIPO Publication WO 92/06204) and region-directed mutagenesis (Derbyshire et al., Gene 46:145, 1986; Ner et al., DNA 7:127, 1988).

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Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Singleton, et al., DICTIONARY OF MICROBIOLOGY AND MOLECULAR BIOLOGY, 20 ED., John Wiley and Sons, New York (1994), and Hale & Marham, THE HARPER COLLINS DICTIONARY OF BIOLOGY, Harper Perennial, NY (1991) provide the skilled person with a general dictionary of many of the terms used in this disclosure.

This disclosure is not limited by the exemplary methods and materials disclosed herein, and any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of this disclosure. Numeric ranges are inclusive of the numbers defining the range. Unless otherwise indicated, any nucleic acid sequences are written left to right in 5' to 3' orientation; amino acid sequences are written left to right in amino to carboxy orientation, respectively.

The headings provided herein are not limitations of the various aspects or embodiments of this disclosure.

Amino acids are referred to herein using the name of the amino acid, the three letter abbreviation or the single letter abbreviation. The term “protein", as used herein, includes proteins, polypeptides, and peptides. As used herein, the term “amino acid sequence” is synonymous with the term “polypeptide” and/or the term “protein”. In some instances, the term “amino acid sequence” is synonymous with the term “peptide”. In some instances, the

term “amino acid sequence” is synonymous with the term “enzyme”. The terms "protein" and "polypeptide" are used interchangeably herein. In the present disclosure and claims, the conventional one-letter and three-letter codes for amino acid residues may be used. The 3-letter code for amino acids as defined in conformity with the IUPACIUB Joint Commission on Biochemical Nomenclature (JCBN). It is also understood that a polypeptide may be coded for by more than one nucleotide sequence due to the degeneracy of the genetic code.

Other definitions of terms may appear throughout the specification. Before the exemplary embodiments are described in more detail, it is to be understood that this disclosure is not limited to particular embodiments described, and as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present disclosure will be defined only by the appended claims.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within this disclosure. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within this disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in this disclosure.

It must be noted that as used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “an effector” includes a plurality of such effectors and reference to “the effector” includes reference to one or more effectors and equivalents thereof known to those skilled in the art, and so forth.

The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that such publications constitute prior art to the claims appended hereto.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of the invention will now be described, by way of example only, with reference to the following Figures and Examples.

Figure 1 shows (A) a schematic representation of one PVC operon layout (gene clusters present in varying regions of the originating genome) encoding a PVC Needle Complex. (B) A schematic representation of Class I, II and III PVC operon layouts. Homologous subunit types amongst the classes are show as having similar shading (in grey scale). (C) An illustration of an assembled PVC Needle Complex. The numbering shown is used to correlate a gene cluster in (A) with the position of the encoded proteins in the structure in (C) (e.g. the cap ‘16’ cluster in A is shown as ‘16’ in the left-most cap region of (B)). (D) A map of

the model Class I *Pa*ATCC^{43949}PVC*pnf* operon (e.g. encoded by SEQ ID NO.: 93), showing two effector genes in the payload region (Rhs-like adenylate cyclase, and PAU_03332).

Figure 2 shows an overview of a cloning procedure for preparation of PVC Needle Complex-expressing plasmids, based on overlapping PCR. PCR fragments (having overlapping regions) are provided from template gDNA of *P. asymbiotica*^{ATCC43949} (available from the ATCC under accession no. ATCC 43949) with relevant primers targeting the PVC operon.

Figure 3 shows a transmission electron micrograph of an (*in vitro*) sample of PVC Needle Complexes (e.g. prepared from cells having the expression vector described above). The PVC Needle Complexes assemble in a distinct 'nanosyringe' structure, consistent with its role as a contractile structure. A 3D rendered model of a PVC Needle Complex as derived from high resolution single particle cryo-EM tomography structure is shown in (B).

Figure 4 shows (A) a transmission electron micrograph of a PVC Needle Complex comprising a Pnf payload following immuno-gold staining with an anti-Pnf (immunogold) antibody, confirming the Pnf-payload toxin is associated with the PVC Needle Complex (referred to as PVC*pnf*). PVC*pnf* Needle Complexes were prepared from supernatants of an *E. coli* cosmid clone, which encodes the PVC*pnf* operon. Anti-peptide antibodies against the Pnf (TGQKPGNNEWKTGR, SEQ ID NO: 96) epitope were used to localise the payload toxin protein. The Pnf toxin could only be detected at the ends of broken or contracted needle complex, providing evidence that the toxins are contained within the complex (arrows). (B) Western blot analysis confirms that the Pnf protein (toxin) can only be detected using the anti-peptide antibody if the PVC Needle Complex is either chemically or physically disrupted. These preparations were taken from *Pa*^{ATCC43949} supernatants. The inability to detect Pnf in clarified supernatants confirms all the protein is associated with the PVC Needle Complex enrichment preparations. Lanes 1+5; sonicated samples, 2+6; 1M NaCl treatments, 3+7; 1% SDS treatments 4+8; 1M Urea treatments. Note the PVC Needle Complex appears stable in 1M NaCl.

Figure 5 shows cryo-SEM image of *ex vivo* hemocytes (insect macrophage/neutrophil equivalents) from 5th instar *Manduca sexta* that had been injected with a native (A) or heat inactivated (B) enriched preparation of *Pa*^{ATCC43949} PVC*pnf* Needle Complexes (nanosyringes) heterologously produced by an *E. coli* cosmid clone. Note the abundant linear structures corresponding to PVC Needle Complexes (nanosyringe) (small arrows) and membrane ruffling effect (large arrows), consistent with the mode of action of the Pnf payload toxin, which are absent from the control treatment. Scale bar = 50µm. 25kV; magnification 40K (A) and 50K (B).

Figure 6 shows experimental results demonstrating the (toxic) cellular phenotype following contact with a PVC Needle Complex is due to intracellular toxin delivery. (A) A Pnf loaded PVC Needle Complex was injected into insects (*Galleria mellonella* insect larvae), showing potent activity within 15 minutes for the given dose (explained in the examples) - note mortality/morbidity is typically associated with the "melanisation" immune response in these dead/dying insects. (B) A control, denatured (via boiling) Pnf loaded PVC Needle Complex injected into animals showed no activity. (C) Purified Pnf (payload), absent the PVC Needle Complex (i.e. Pnf not packaged into the complex), showed no activity against either animals (left) or a HeLa cell line (right). (D) Pnf (payload) delivered into the cytosol of HeLa cells - via 'BioPorter' liposomal preparations containing the protein, or by intracellular expression following transfection with an appropriate plasmid (E) - showed potent activity/toxicity, as evidenced by multi-nucleation in the cells. (F) - The effect of PVC*pnf*+Pnf on the respiration rate of THP1 derived human macrophages as measured by Resazurin plate reader assay.

Note the heat denatured and empty PVC*pnf* nanosyringes showed no strong adverse effect. These same samples were tested by injection into *Galleria* larvae. The PVC*pnf*+Pnf samples showed over around 50% mortality within minutes (darkened larvae in the bottom two panels) while the heat denatured and empty PVC*pnf* injected insects all remained healthy (no darkened larvae in the top two panels).

Figure 7 shows (*in silico*) predicted secondary structures of a range of the endogenous payload (toxin) associated with various PVC operons, demonstrating the large variety of structure types. (B) The amino acid length of various payloads (toxins) plotted against predicted isoelectric point.

Figure 8 shows confirmation that leader sequences (e.g. having 50 amino acids) of the invention are necessary and sufficient for (trans-)packaging payload proteins/peptides into PVC Needle Complexes (nanosyringes) expressed in *Photorhabdus*. (A) 1-6: Schematic maps of chimeric effector protein expression constructs (trans-expressed in the arabinose-inducible pBAD30 vector), including those expressing Pnf and non-native cre-recombinase and Myc-tags. C-terminal Myc-tag epitopes are shown as black arrows. (B) Western blots using anti-Myc mouse antibody. Samples are from purified PVC(u4) Needle Complexes (nanosyringes) overexpressed from chromosomally engineered *P. luminescens* TT01 which harbour the trans-packaging expression constructs 1-6 shown in (A). A blank pBAD30 plasmid was used as a negative control and showed no signal. Arrows show correct band sizes for expected products.

Figure 9 shows an alignment of the leader sequences, demonstrating the presence of a chemical composition consensus amongst the leader sequences, based on amino acid properties. More particularly, the leader sequences comprise similar charge patterns, of 2x negatively charged regions, each followed by a positively charged region [-ve] [+ve] [-ve] [+ve].

Figure 10 shows (A) western blot analysis of PVC Needle Complexes and payloads from particulate preparations (Cesium Chloride gradient and Monolith FPLC preparations, as described in Materials and Methods). In [1] (pBADPVCpnf, in which PVC16 of the nanosyringe is FLAG-tagged providing PVC16::FLAG detectable with AntiFLAG Ab), a signal from the tagged cap protein of "PVCPnf" (PVC Needle Complex with a Pnf payload) can be seen, confirming the presence of PVC Needle Complexes in the purified fraction. In [2] (pBADPVCpnf + Cre::Myc, detectable with AntiMyc Ab, the Cre having an N-term fusion of the Pnf leader e.g. SEQ ID NO.: 78), a signal from the Myc-tagged payload protein packaged in abundance, in the same sample as (1), confirming presence of Cre payload in purified PVC Needle Complexes (nanosyringes). In [3] (PVCU4 + Cre::Myc, detectable with AntiMyc Ab, the Cre having an N-term fusion of the Pnf leader e.g. SEQ ID NO.: 78), a different PVC Needle Complex chassis ("PVCU4") purification is probed for Myc-tagged Cre revealing a packaged (packaged Myc-tagged Cre) corresponding band. This is highlighted in the blot for clarity. (B) Transmission electron micrograph of a PVC Needle Complex, shows both wild-type (having a Pnf payload) PVC Needle Complexes and PVC Needle Complexes having an atypical (non-native) recombinase (Cre) payload, in any chassis tested, does not affect morphology of the PVC Needle Complexes, ensuring they are not assembled aberrantly. Figure 10 (C) provides additional/ complementary data to that of (A). In more detail, (C) provides further proof via Western blot analysis of (trans-)packaging of the Cre recombinase into purified PVC*pnf* expressed in *E. coli*. The Western blot demonstrates that for a given amount of Anti-FLAG antibody Western signal (a specific probe for the nanosyringe due the incorporation of PVC16::FLAG), a much higher amount of the Cre payload is detected (using

the Anti-Myc tag antibody). The numbers denote 2-fold dilutions. Note, upon dilution, the anti-FLAG signal from the nanosyringe is lost, while the payload remains intense in most lanes. CsCl denotes purification by Caesium Chloride density gradient centrifugation. "Mon" denotes the samples were additionally anion exchanged via "Monolithic" columns. "Post-Elution", "Interphase", "Sub-Interph.", denote the liquid fractions where the signal is detected from the purification process. D - Western blot analysis of Cre trans-packaged into PVC*pnf* in *E. coli*. Payloads are probed for their incorporated 'Myc' tags (C-terminal fusions) after purification of the nanosyringe-payload complex. Western blot analysis of particle preps confirms that all four leaders could efficiently trans-package the exogenous Cre enzyme. E – A phylogenetic tree, demonstrating the exemplified leader sequences are well distributed throughout and are therefore at or close to maximally sequentially diverse (see Example 4.2).

Figure 11 shows western blot analysis of PVC Needle Complexes expressed without (1) and with (2) concomitant expression of (Myc-tagged) Pnf from a separate plasmid, probed simultaneously with an anti-FLAG and anti-Myc antibody. In the lanes marked 1, the PVC Needle Complex (nanosyringe) was expressed and purified without the presence of a 'payload plasmid' (an expression plasmid encoding a payload protein linked to a leader sequence) within *E. coli*. This leads to a band corresponding only to the FLAG tag present on the syringe (PVC Needle Complex) itself. For lanes 2, the same approach was undertaken, but using cultures which also included a (separate) plasmid bearing a tagged payload (Myc-Pnf). Bands can be seen which correspond to the FLAG and Myc tags, confirming presence of the Pnf payload (the four lanes within 1 and 2 are simply different purification fractions from Caesium Chloride gradients).

Figure 12 shows western blot analysis of trans-packing experiments in *P. luminescens* TT01 PVCu4 over-expression strain. Results demonstrate the trans-packaging of a myc-tagged Pvc17 (Plu1651whole::Myc).

Figure 13 shows further western blot analysis of trans-packaging experiments in *P. luminescens* TT01 PVCunit4 over-expression strain (as explained in the Examples). Results demonstrate trans-packing of Myc-tagged Pvc17 (Plu1651::Myc) and a Myc tag alone using the leader of Pnf (PAU_03332 leader), and that the leader is necessary. (A) Lane 1 shows packaging of the leader of fused to a Myc-tag (PAU_03332::Myc); Lane 3 shows a lack of packaging when the leader sequence is absent (Myc only is not packaged); lane 4 shows lack of packaging of HvnA (a natural effector) when the leader sequence is absent; lane 6 shows packaging of Myc-tagged PAU_03332::Plu1649, i.e. a chimaera of the leader from PAU_03332 (i.e. amino acids 1-50 of PAU_03332) and the effector (i.e. amino acids 51-C-terminus) from Plu1649. The high intensity of bands in lanes 1 and 6 demonstrate that the Pnf (PAU_03332) leader is particularly effective at packaging a payload). (B) Lane 1 shows packaging of Plu1651 with a C-terminal Myc tag using an anti-Myc antibody Western blot.

Figure 14 shows further Western blot analysis demonstrating the very high level of trans-packaging of Myc-tagged Pnf (PAU_03332::Myc) using the PAU_02806 (GogB) leader (second lane, not including the ladder lane). The first lane demonstrates use of the Plu1649 leader for packaging the PAU_03332 effector (Myc-tagged Plu1649::PAU_03332). The band appears weak due to the relative intensity of the band in the second lane. The experiment involved filter sterilisation of 50 mL culture, 8 M final concentration of urea added to break down PVCs. Samples collected from 10 mL supernatant.

Figure 15 shows further western blot analysis demonstrating trans-packaging of Plu1651 (pvc17) with a C-terminal Myc tag as described in Figure 13 into PVCunit4 expressed from

Photorhabdus . Raw represents particulate preps from supernatants, Be, Be2 and IP represent different "cuts" from a Caesium chloride gradient purification.

Figure 16 (A) provides a diagrammatic explanation of the mechanism of action of Cre in the mouse organoid experiment (of Example 6), and how the positive control (TAM) facilitates Cre activation. White arrows show the location of cells expressing the tdTom fluorescent reporter gene. B - Demonstration of delivery of active trans-packaged Cre-recombinase into murine bile duct organoids by PVC*pnf* expressed and purified from *E. coli*. White circles show the location of groups of cells expressing the fluorescent reporter gene. The upper images show a direct grey scale conversion of an images obtained via light microscopy. The lower image shows a corresponding image with false-colour enhancement of positive cells, which is provided simply to aid identification of the difference between effected cells and surrounding unaffected ones within the former grey scale conversion.

Figure 17 shows a dot-blot analysis of nanosyringe expression both with a payload (the Cas9-like protein MAD7) and without. Some leaky expression of the IPTG inducible MAD7 is seen before induction (T1) as is common with this expression system. There is no Myc signal from the PVC only sample at any time point as expected, and the MAD7 signal grows throughout the expression over a ~24 hour period. Strong Myc signal is maintained post purification via ultracentrifugation as described elsewhere, indicating that the protein is incorporated into the nanosyringe chassis system. FLAG signal is robust in the MAD7 sample, and occurs as expected post-induction and persists post-purification, as this promoter system has reduced leaky expression. It is concluded that the nanosyringes and MAD7 are compatible with one another in terms of expression, and that MAD7, the largest protein tested to date, can be packaged in to the nanosyringe system.

Figure 18 shows western dot-blot analysis confirming trans-packaging of the pro-apoptotic tBid protein domain and BaxBH3 (both having the leader sequence of SEQ ID NO.: 78 fused to the N-term) peptide into purified PVC*pnf* expressed from *E. coli* (7 & 8). The nanosyringe with its cognate toxin "Pnf" is shown, as purified by 2 different methods (5 & 6) as a positive control. The blots at the bottom of the panel represent the same examples as in 7 & 8 in the panels above. These blots were made from another purification of the same constructs, demonstrating reproducibility of purification. This experiment demonstrated that "tBid protein domain and BaxBH3 peptide" packed samples (nanosyringes) can be successfully prepared, e.g. for used in the apoptosis delivery assays in Example 9.

Figure 19 (A) shows TUNEL-stain microscopic analysis from cells exposed to the packaged nanosyringes for 20 minutes only. First (left) bar = DNase I treated cells (+ control); Second bar = no DNAse I or nanosyringe treatment (- control); Third bar = cells were exposed to nanosyringes packaged with tBid (via leader sequence of SEQ ID NO.: 78 fused to the N-term); fourth (right) bar = cells were exposed to nanosyringes packaged with Bax_BH3 domain (via leader sequence of SEQ ID NO.: 78 fused to the N-term). B - Representative micrographs as described in Example 9, showing TUNEL staining of PBMC's, following treatment with nanosyringes and controls. PBMCs were treated with tBID, Bax loaded nanosyringes, and the positive (DNase I treated cells) and negative (no DNase I treatment) controls for 20 minutes at room temperature before performing TUNEL staining to determine an apoptotic response. In the original (non-grayscale) micrographs: Cells negative for apoptotic response show blue or light brown staining. Blue staining (Methyl green) or light brown staining indicates healthy cells with absence of apoptotic signal. Dark brown staining indicates cells undergoing apoptosis.

EXAMPLES

Materials and Methods

Cloning

Plasmids encoding PVC Needle Complexes were prepared using standard molecular techniques known in the art. Briefly, genomic DNA from *P. asymbiotica*^{ATCC43949} (obtainable from the ATCC under accession no. ATCC 43949) was used in PCR (with appropriate primers) to amplify multiple (e.g. four) overlapping regions of the PVC operon. Overlap/extension PCR was employed to prepare a whole operon, and fused (again using overlapping PCR) into an appropriate expression vector as detailed in Figure 1 (using the primers of SEQ ID NO: 101 – SEQ ID NO: 106).

Briefly: four overlapping PVC fragments (generated with primers of SEQ ID NO: 101 (F1) and SEQ ID NO: 105 (R1); SEQ ID NO: 102 (F2) and SEQ ID NO: 106 (R2); SEQ ID NO: 103 (F3) and SEQ ID NO: 107 (R3); and SEQ ID NO: 104 (F4) and SEQ ID NO: 108 (R4), respectively) were made covering the PVC operon (e.g. of SEQ ID NO: 93). The target cloning vector was cut at the required insertion site. These 5 DNA fragments were then assembled by overlapping PCR (using primers of SEQ ID NO: 101 and of SEQ ID NO: 108), and the resulting fragment was ligated into the cloning vector. Products were transformed into laboratory *E. coli* and recovered with vector marker selection (e.g. due to ampicillin resistance).

The operons are typically operably linked to an inducible promoter (e.g. arabinose inducible, and/or IPTG inducible) as is known in the art. This is generally achieved by cloning into pBAD family plasmids (inducible via arabinose) (Invitrogen, catalog number: V43001) and pVTRa (inducible via IPTG) (Biomedal, S.L.) vectors (although any combination of compatible expression vector systems should suffice).

A PVC Needle Complex can be expressed independently of the payload (toxin), and vice versa. Separate expression vectors (e.g. having differing inducible promoters) may harbour the PVC Needle Complex and the payload, respectively.

Expression (e.g. laboratory scale expression) / Purification of PVC Needle Complexes in *E. coli*

A typical process to purify a PVC Needle Complex from a 1L culture of an *E. coli* expression strain (transformed with an appropriate expression vector/ cosmid) is as follows:

1- An overnight culture of the bacteria (transformed with PVC Needle Complex expression vector) is prepared by picking a colony from a plate and inoculating 100 mL of LB media. The culture is grown at 37°C with shaking.
   a. Typically, the media may be routinely supplemented with 0.2% d-Glucose to aid repression of the genetic constructs for optimal cell health.
   b. The media is also supplemented with the relevant antibiotics for maintenance of the expression (PVC Needle Complex) vector. If a payload vector is also being used, the relevant antibiotic for that vector is also supplied.
2- The next day, a 1L flask is inoculated via dilution in a 1:100 ratio from the overnight culture. The media for the 1L flask is identical to the overnight media but typically does not contain glucose.

3- Cultures are grown to approximately mid-to-late exponential (an OD600nm of ~0.8) at which point the plasmids are induced.
    a. For the PVC Needle Complex (nanosyringe) plasmid, typically 0.2% arabinose is added to induce expression. For the payload plasmid (plasmid encoding for the payload, such as Pnf), IPTG concentrations may typically be optimised on a per-protein basis, and a typical starting figure of 0.1 mM is preferable.
4- The cultures are returned to the incubator post-induction and cultured at 18°C until the following day.
5- Cultures are harvested by centrifugation in appropriate centrifuges/bottles/rotors at 5000xg for 30 mins.
6- Cell pellets are then lysed to release PVC Needle Complexes (nanosyringes).
    a. The following lysis methods may be used:
        (i) Lysozyme incubation overnight. (ii) Sonication with a needle sonicator (with or without first treating with lysozyme. (iii) Cell disruptor/homogenisers.
7- Optionally, DNAse, and protease inhibitors can be added to the lysate.
8- Cell debris is removed by centrifugation at 50,000xg, 4°C, for 20 minutes in a high speed centrifuge.
9- Concentrate the lysate through a 100,000 kDa MWCO centrifugation column to reduce volumes and remove small proteins. Once the volume is down to a manageable volume, centrifuge several times replacing the retentate solution with an appropriate sample buffer such as TM (20 mM Tris-HCl, 8 mM $MgCl_2$, pH 7.4) to dialyse.

A subsequent process for purification via Caesium Chloride density gradient is as follows:

1. Prepare CsCl density solutions as follows:
   (a) 1.7 g/mL CsCl in H_2O; (B) 1.5 g/mL CsCl in H_2O; (C) 1.45 g/mL CsCl in H_2O
2. Gradients (from bottom-to-top of the tube) are then set up in ultracentrifuge tubes like so: (1) (bottom of tube) – 2mL density, 1.7 CsCl; (2) – 3ml density, 1.5 CsCl; (3) – 3mL density, 1.45 CsCl; (4) (top of tube) – sample in TM buffer. Suitably, apply each density carefully to side of tube so as not to blend the boundary with the previous density layer.
3. Balanced tubes are then subjected to ultracentrifugation at 35,000 RPM in an SW40Ti swinging bucket rotor, equivalent to 155,000 xg, for 2 hours, 4°C.
4. The correct gradient fraction will be the region just above a 'blue-ish-white' halo that appears. Fractions are extracted via puncturing the tube with a syringe and needle.
5. PVC Needle Complexes of good purity can be obtained in this manner, and stored in buffer at 4°C. Suitably, dialyse back in to TM buffer to remote the CsCl.

Following, or in place of CsCl gradient purification, PVCs can be extracted via Monolith anion exchange chromatography, as follows (note all steps can be performed manually with a peristaltic pump or syringe apparatus, or via F/HPLC):

1. Unless already done, dialyse the sample extract into the binding mobile phase (typically TM buffer) with a low concentration of salt (20 mM NaCl).
2. Equilibrate the column according to the manufacturer's guidelines, briefly:
    a. At least 5 Column Volumes (CV) of dH_2O;
    b. At least 5 CV of binding buffer (TM, with low salt);
    c. At least 5 CV of elution buffer (TM with high salt, >= 1M NaCl);
    d. At least 10 CV of binding buffer once more.

3. Apply the sample to the column at a low flow rate (1-2mL/min)
4. Wash the column with up to 200 mM NaCl-containing TM buffer.
5. Elute with 1M NaCl-containing TM buffer (alternatively, use a gradient elution if using an FPLC machine).
6. PVC Needle Complexes are present in the elution fractions. If a fraction collector is used, subsequent SDS-PAGE or similar may be needed to identify the correct fraction.

The column (of e.g. step 2) was of the CIMmultus(™) Quaternary Amine anion exchange columns (BIA Separations d.o.o.). For example, the CIMmultus™ QA-1, which is a monolithic column with 1.3 µm channel size and a column volume of 1 mL.

Alternatively, a DEAE (a weak anion exchanger) column may be used.

Alternatively, for use with a *Photorhabdus* expression system, PVC Needle Complexes can be purified from supernatants as well as/instead of cell pellets, with the following additions/modifications:

1. Following cell harvest from the standard protocol above, supernatants are transferred to a pyrex bottle, and can optionally be concentrated via 100,000 MWCO columns if necessary.
    a. DNAse (0.25U/mL) and protease inhibitors can optionally be added.
2. NaCl is added to a final concentration of 0.5M, and 80 g/L of PEG6000 is also added. The solution is mixed at 4°C overnight.
3. The solution is centrifuged to pellet the PEG6000 at 8000xg, 4°C for 30 mins.
4. The pellet is resuspended in a small volume (~5 mL) of TM buffer (or similar) and incubated for 2 hours at room temperature, shaking.
5. Pellet by centrifugation at 13,000 xg for 10 mins, and collect the supernatant to a new tube. Proceed with purification method of choice.

Other methods for purifying PVC Needle Complexes have been described elsewhere, for example in Yang et al (J Bacteriol. 2006 Mar; 188(6): 2254–2261), incorporated herein by reference.

<u>Construction of an arabinose inducible over-expression strains for *P. luminescens* TT01 PVCunit4 (chassis encoded by genes plu1667 – plu1652)</u>

Photorhabdus strains overexpressing a PVC Needle Complex were prepared using chromosomal recombineering to place a PVC (operon) of choice (operon encoding PVCunit4 Needle Complex was used here, as an example) under the control of an arabinose inducible transcription promoter. The recombineered strains are then genetically transformed with effector expression plasmids (e.g. based on the arabinose inducible expression vector pBAD30) to facilitate PVC Needle Complex over-expression, PVC effector expression, PVC effector trans-packaging, and secretion of the whole complex simply through the addition of the arabinose sugar.

<u>Recombinant *Photorhabdus* PVC over-expression strain construction</u>

The promoter region of PVCunit4 was amplified using primers PVCpromF (5'-TATCATATGTCTACAACTCCAGAACAAATTGCTG-3', SEQ ID NO: 97) and PVCpromR (5'-ATCTCTAGAACAGATATTCCAGCCAGC-3', SEQ ID NO: 98) using genomic DNA from *P.*

luminescens strain DJC (aka strain TT01) as a template. A suitable *P. luminescens* strain is obtainable from the ATCC under accession no. ATCC 29999. The PCR product was digested with NdeI and XbaI and introduced by ligation into the suicide vector pCEP (ThermoFisher, catalog number: V04450), using *E. coli* DH5α λ-pir (Biomedal S.L.) as the carrier strain. The resulting plasmid was transferred to the *E. coli* donor strain S17.1 λ-pir (Biomedal S.L.) for conjugation into *Photorhabdus*. Briefly, overnight cultures of the donor strain and a rifampicin resistant (RifR) isolate of *P. luminescens* DJC were diluted in LB supplemented with 10 mM $MgSO_4$ and grown to mid-exponential (OD600 ~0.5). Then, 3 ml of each culture were harvested, washed twice and re-suspended in 100 µl of LB supplemented with 10 mM $MgSO_4$. 80 µl of *P. luminescens* DJC RifR were mixed with 20 µl of the donor bacteria (resulting in a recipient to donor ratio of 4:1) and placed in the centre of an LB agar plate supplemented with 0.1 % pyruvate and 10 mM $MgSO_4$. The plate was incubated overnight at 30°C and the resulting growth was harvested in 1.5 ml LB. Aliquots were plated on plates containing rifampicin (50 µg/ml) and chloramphenicol (25 µg/ml) to select for trans-conjugants and the plates were incubated at 30°C for 3 days. Possible transconjugants were re-streaked and confirmed by PCR using primers ParaINF (5'-GGCGTCACACTTTGCTATG-3', SEQ ID NO: 99) and tPVCpR (5'-TCGGTGGCAGTAAATTGTCC-3', SEQ ID NO: 100).

PVC Needle Complex over-expression and purification from *Photorhabdus*

Overnight cultures of *P. luminescens* DJC PVCunit4::pCEP were diluted in 2x 250 ml LB supplemented with chloramphenicol (25 µg/ml) and incubated at 28 °C, 180 rpm. After 2-3 h, arabinose (0.2 %) was added and the cultures were returned to the incubator for another 26 h. The cells were pelleted by centrifugation (7000 g for 30 min) and the supernatant was collected. DNAse I was added to the supernatant at a concentration of 0.25 U/ml to degrade any extracellular DNA. Following an incubation of 30 min at room temperature, polyethylene glycol 8000 (8 %) and NaCl (0.5 M) were added to precipitate the proteins. The supernatants were incubated overnight at 4°C, stirring. The precipitated proteins were then collected by centrifugation at 8000 g for 30 min at 4°C. The pellets were re-suspended in 8 ml TM buffer (20 mM TrisHCl, 20 mM MgCl2, pH7.4) and incubated at room temperature for 2h with gentle shaking. Any remaining debris was removed by centrifugation at 13000g for 10 min and the supernatant containing PVC Needle Complexes was applied to a CsCl density gradient and centrifuged at 35000 rpm for 2h in a Beckman coulter Optima L-90K or XPN-80K ultracentrifuge. The CsCl density gradient was made by layering TM buffer containing CsCl at ρ = 1.7 (2 ml), 1.5 (3 ml), and 1.45 (3 ml) from the bottom of the tube, respectively. The fraction containing PVC Needle Complexes was collected and Ultracel-100K devices (Amicon) were used to remove the CsCl and exchange the buffer for TMS (20 mM TrisHCl, 8 mM MgSO4, pH7.4). The PVC Needle Complexes were further purified using a CIMmultus™ quarternary amine 2 µm pore anion exchange column (BIAseparations). The column was washed with TMS buffer containing 200 mM NaCl and the PVC Needle Complexes were eluted in TMS containing 1 M NaCl. The NaCl was removed by buffer exchange using an Ultracel-100K device and the sample was applied to a CIMmultus™ DEAE 2 µm pore column (BIA separations) for a final purification. The column was washed in TMS containing 200 mM NaCl and the sample was eluted in TMS containing 500 mM NaCl.

It is possible to perform this with and without lysis (e.g. because the PVC Needle Complexes appear to be secreted from live cell, and can be collected in supernatant) of the cells (to release the PVC Needle Complexes).

Transmission electron microscopy

For transmission electron microscopy (TEM) pioloform-covered 300-mesh copper grids that were coated with a fine layer of carbon were used as substrates for the protein fractions. A preferred aqueous negative stain is 3% methylamine tungstate. The coated grids were exposed to UV light for 16 h immediately prior to use to ensure adequate wetting of the substrate. A 10 µl drop was applied to the TEM grid, and the protein was allowed to settle for 5 min. Liquid was absorbed with filter paper from the edge of the grid and replaced immediately with 10 µl of filtered negative stain. The drop was partially removed with filter paper, and the grids were allowed to air dry thoroughly before they were viewed with a JEOL 1200EX transmission electron microscope (JEOL, Tokyo, Japan) operating at 80 kV.

BioPORTER assay and actin stress fibre analysis.

For BioPORTER assays (Genlantis), 80 µl of purified wild-type and mutant Pnf proteins (500 µg ml−1), or PBS as a negative control, were added to one BioPORTER tube (Genlantis) and re-suspended in 920 µl of DMEM. The samples were added to HeLa cells grown in 6-well plates and incubated for 4h. BioPORTER/protein or PBS mixes were replaced by fresh complete medium and the cells were incubated for 20–48 h. To visualize cell morphology and actin cytoskeleton, cells were fixed for 15 min in 4% PBS-formaldehyde, permeabilized with 0.1% Triton X-100 and stained with Tetramethylrhodamine B isothiocyanate (TRITC)-phalloidin (Sigma) and DAPI dihydrochloride (Sigma). Images were acquired with a LSM510 confocal microscope (Leica).

EXAMPLE 1

Cloning and expression of PVC Needle Complexes

The inventors have successfully excised (cloned) the required expression genes from the host bacterium, *Photorhabdus* (e.g. which are comprised within SEQ ID NO: 93, SEQ ID NO.:94 and/or SEQ ID NO:.95), and have devised a reliable, scalable expression system in laboratory *E. coli* as explained above. It has been demonstrated that trans-expression on separate plasmids enables incorporation of payloads (e.g. Pnf) into the syringes, creating a multi-plasmid (modular) platform.

Following purification from *E. coli*, electron microscopy analysis demonstrated that the purified PVC Needle Complexes retained the correct 'nanosyringe' structure (see Figure 3). Furthermore, PVC Needle Complexes remained correctly associated with the payload (e.g. Pnf) following purification (see Figure 4), demonstrating that the inventors have successfully prepared the PVC Needle Complexes (nanosyringes) having the correct structure for payload delivery to cells.

Furthermore, electron microscopy analysis demonstrated that the purified complexes appropriately localise to the cell surface of cells, and PVC Needle Complexes with a Pnf payload (PVC*pnf*) induces a phenotype (ruffling) consistent with the postulated mechanism of the effector (PVC) – see Figure 5.

EXAMPLE 2

2.1 Demonstrating PVC Needle Complexes exert effect via intracellular delivery of effector

The polypeptide Pnf was identified as a PVC effector as follows. This was identified within the *Photorhabdus asymbiotica* ATCC43949 complete genome – GenBank Accession Number: FM162591.1.

The final gene of the PVC operon (*P. asymbiotica* ATCC43949 PVC*pnf* operon, which has a sequence of SEQ ID NO: 93) was identified, namely *pvc16* (e.g. PAU_03338). The position of the *pvc16* genes of a PVC locus is illustrated in Figures 1(A), (B) and (D). ORFs shortly 3' of *pvc16* (e.g. within about 5kb downstream of *pvc16*) were identified – one such ORF (PAU_03332) being 3535bp downstream of *pvc16*. The predicted function of the polypeptide (having a sequence of SEQ ID NO.: 32) encoded by this putative effector ORF was obtained by a combination of BlastP and HHPRED (https://toolkit.tuebingen.mpg.de/#/tools/hhpred). This ORF could then be assigned as a PVC effector based on direct homology to a known bacterial toxin (e.g. of the CNF1 family from *E. coli*).

A Pnf loaded PVC Needle Complex was then prepared according to Example 1.

The inventors have demonstrated that these packaged (e.g. laden) PVC Needle Complexes exert cellular effects consistent with the provenance of the cargoes they carry. By way of example, cells and whole insect animals exposed to PVC Needle Complexes loaded with the cytoskeleton toxin Pnf undergo cell death in a manner consistent with cytoskeleton toxicity.

Injection experiments (injection into the insect larvae) were performed by injection of 10µl of supernatant, provided following centrifugation (pelleting) of an overnight culture (typically 1L) of a culture of *E. coli* harbouring a cosmid clone encoding the PVC Needle Complex with Pnf (PVCPnf) – e.g. a PVC encoded by SEQ ID NO.: 93, packaged with a PVC effector of SEQ ID NO.: 32.

Demonstrating that the PVC Needle Complexes are responsible for the phenotype due to intracellular delivery (e.g. injection) of the Pnf payload, the toxic effect could only be reconstituted when the same protein (Pnf) is provided with another route to access the cell cytosol (transfection and expression of an expression plasmid, or conductance via liposomal preparations containing the protein) – see Figure 6. Conversely, denatured (via boiling) PVC Needle Complex preparations, toxin proteins overlaid on tissue culture cells or toxin proteins injected into whole animals showed no activity.

2.2. Evidence of delivery of the toxic effector enzyme Pnf into cultured human macrophages

To complement the data outlined above, the inventors conducted additional experimentation providing further evidence of delivery of the toxic effector enzyme *Pnf* into cultured human macrophages.

Concept: The inventors tested PVC*pnf* expressed and purified from *E. coli,* (trans-)packaged with the native Pnf toxin on cultured human THP1 derived macrophages. Unlike the lethal effect of the Pnf toxin in insect models, previous liposome mediated Pnf protein transfection

experiments indicated a subtler phenotype in human Hela cells. In those experiments the cells showed actin stress fibre formation at 24h and multinucleation at 48 h. The inventors therefore tested the effect of the purified PVC*pnf* (the nanosyringe) holding/ packaged with the Pnf PVC effector on macrophage respiration rate using a Resazurin colourimetric assay.

Methods:

Background behind Resazurin assays. The blue compound resazurin was explored for use in assays to determine the activity of PVCs on macrophages (M0). Resazurin is metabolically reduced in cell mitochondria, producing a pink and highly fluorescent compound, resorufin. The effect of PVCs on macrophage metabolism can be determined by introducing resazurin into the culture media. The number of macrophages affected by PVCs can be inferred by comparing the fluorescence measured to that of the cell density optimisation curve (see Czekanska, *Methods in Molecular Biology*, 2011, 740, 27-32, incorporated herein by reference).

Optimisation of use of Resazurin for THP1 derived macrophages. The metabolism of macrophages over 18 h was assessed at different seed densities to determine the optimum cell density for use of this assay with PVCs. A 30 mL culture of THP-1 cells was pelleted at 1000 rpm for 4 min, before resuspension in 2 mL of RPMI media (also containing 10 % FBS (v/v) and 2 mM L-glutamine). Cells were counted using a cell haemocytometer, then diluted in media to a density of $2x10^6$ cells mL^{-1}. THP-1 cells were then activated with phorbol 12-myristate-13-acetate (PMA) immediately before plating. 200 µL of the cells were plated in quadruplicate in a 96-well plate, and a 2-fold serial dilution was performed until reaching a final cell density of $1.5625x10^3$ cell mL^{-1}. 125 µL of the starting cell dilution was also plated in quadruplicate on the same plate, for a 5-fold serial dilution, until reaching a cell density of $0.32x10^3$ cells mL^{-1}. Four blank wells were also prepared, containing RPMI and PMA. The plate was incubated at 37 °C with 5 % CO_2 for 48 h. Media was aspirated from the wells and replaced with fresh RPMI, and the macrophages were incubated for a further 24 h. A resazurin tablet (VWR) was dissolved in RPMI (12.5 mg/mL), and 10 µL added to each well in quick succession (well concentration of 1.25 mg/mL). The fluorescence produced was measured on a plate reader every 30 min for 18 h (excitation: 530-570 nm, emission: 580-620 nm, maintained at 37 °C and 5 % CO_2). The optimum cell density over time was then determined for use with PVCs.

Use of assay for PVC testing. THP-1 cells, diluted to $1.25x10^5$ mL^{-1}, were activated and seeded in a 96-well plate, where wells contained 100 µL of cells at a final well density of $1.25x10^4$ cells mL^{-1}. Blank wells were also prepared in quadruplicate, containing cells without PVC samples, as well as wells containing media and PMA only. The plate was incubated for 48 h at 37 °C with 5 % CO_2. The media was then replaced with fresh RPMI, before addition of 10 µL of each PVC sample. The plate was incubated for a further 24 h, before the addition of 10 µL resazurin (12.5 mg/mL) to each well, and the fluorescence was measured every 30 min for 18 h (excitation: 530-570 nm, emission: 580-620 nm, maintained at 37 °C and 5 % CO_2).

Results: Figure 6F shows that challenge with PVC*pnf*+Pnf did indeed lower the respiration rate of the macrophage, while heat denatured or empty PVC*pnf* nanosyringes had no strong adverse effect. Nevertheless, control cells with no sample addition still showed the best

respiration rates. The effects on macrophage were correlated with insect injection toxicity assays. In this case the two PVC*pnf*+Pnf preparations showed lethality to over half the insect cohort, while the heat denatured and empty PVC*pnf* injected insects all remained healthy.

EXAMPLE 3

Demonstrating that a leader sequence is responsible for payload packaging into PVC Needle Complexes

Surprisingly, the inventors have found that the provision of a 'leader' peptide sequence, preferably on the N-terminus of a payload (toxin) protein, can direct the payload to the PVC complex and allow for (e.g. trigger) the packaging of the payload into the PVC Needle Complex. The inventors have demonstrated that amino acid residues 1-50 of a PVC effector protein is/ comprises a leader sequence.

To demonstrate this, an expression construct (overexpression in chromosomally engineered *P. luminescens* TT01) was prepared, in which the leader sequence (the N-terminal amino acid residues 1-50) was ablated such that the payload expressed by Plu1649 (referred to as "hvnA" in the figure, and having a sequence of SEQ ID NO.: 46) (Myc-tagged for detection purposes) was absent a leader sequence (see Figure 8A – construct 1). Following expression (of both the payload and PVC Needle Complex) and isolation of the PVC Needle Complex (and running the components thereof, which includes any packaged payload, on a gel), no (Myc-tagged) Plu1649 ("hvnA") was detectable within the PVC Needle Complex via western blot analysis, demonstrating that the payload (absent the leader sequence) was not packaged into the complex (see Figure 8B, lane 1), and thus not associated with the isolated complex. Successful packaging was seen, however, for hvnA which did retain the leader sequence, see lane 2 (note that the band appears weak, due to the relative intensity of the band of lane 3).

Surprisingly, hvnA having a leader sequence from a different (non-hvnA) PVC effector (i.e. corresponding to the N-terminal amino acid residues 1-50 from the PAU_03332 effector) (see Figure 8A, construct 3) was correctly packaged into the complex and remained associated with the PVC Needle Complex upon isolation/ purification, as demonstrated by Western blot detection of the Myc-tagged hvnA (see Figure 8B, lane 3). Thus, the inventors have demonstrated the surprising ability of the 'PAU_03332' leader sequence (which is associated with a different payload, Pnf) for packaging of a hvnA payload (i.e. a different payload to that of PAU_03332). This demonstrates the ability to swap the leader sequences of the PVC effector, allowing use of an optimal leader sequence (having optimal packaging activity) for packaging.

EXAMPLE 4

4.1 Demonstrating that a leader sequence directs packaging (into PVC Needle Complexes) of atypical/ exogenous payloads

In an unexpected technical effect of the invention, the inventors have found that fusing a leader sequence described herein to exogenous (non-*Photorhabdus*) polypeptides (preferably at the N-terminus) allows for packaging of said exogenous polypeptides into a PVC Needle Complex, with the exogenous polypeptides remaining associated with the PVC Needle Complex upon isolation/ purification. By way of example, see Figure 8B (lane 4) demonstrating that a non-*Photorhabdus* 'Myc' polypeptide (<10kDa) is packaged into the

PVC Needle Complex when fused to a leader sequence, and lane 6, demonstrating a much larger non-*Photorhabdus* 'Cre-recombinase' polypeptide (>32kDa) can likewise be appropriately packaged into PVC Needle Complex when fused to a leader polypeptide of the invention.

The inventors performed in-depth analysis of the size (e.g. polypeptide length) and structure of the various natural PVC effector payloads encoded by *Photorhabdus* (see Figure 7), which show a wide variety of different lengths and structure, demonstrating that the applicability of the PVC Needle Complex (nanosyringe) delivery system of the present invention is not limited by the size or properties of the payload protein of interest. To summarise, there is no requirement for particular secondary structure, biophysical property, or length of cargoes, confirming that that the PVC Needle Complex (nanosyringe) chassis can be utilised as a versatile multifunctional delivery vehicle.

Furthermore, this packaging of exogenous polypeptides is independent of the chosen PVC Needle Complex chassis e.g. has been accomplished using both a "PVCpnf" chassis (SEQ ID NO.: 93) and a "PVC*U4*" (e.g. *PVCunit4*) chassis (endogenous to the *Photorhabdus* overexpression strain) (*see* Figure 10A). Importantly, the inventors have demonstrated that packaging exogenous payloads in either chassis does not affect morphology of the PVC Needle Complexes, ensuring they are not assembled aberrantly (see Figure 10B).

In data shown herein, payload proteins are supplied in 'trans' on separate genetic constructs. The leader sequences are surprisingly sufficient to target these separately synthesised proteins for packaging into the PVC Needle Complex vehicle (see Figure 11). This applies in *E. coli* when the chassis (PVC) genes themselves are also present on a plasmid, as well as with chassis genes being integrated into the chromosome, as is the case in *Photorhabdus*, the host organism.

Further exemplification of trans-packaging of high levels of the Cre site specific recombinase into the PVC*pnf* nanosyringe expressed in *E. coli* is provided in Figure 10(C). In more detail, the inventors constructed a laboratory *E. coli* expression strain harbouring (i) the arabinose inducible expression plasmid for the *P. asymbiotica* ATCC43949 PVC*pnf* operon e.g. of SEQ ID NO.: 93 (with a C-terminal FLAG tag on Pvc16, e.g. immediately 3' to SEQ ID NO.: 93) and (ii) a second IPTG inducible expression plasmid containing the Cre recombinase with a N-terminal fusion of the natural Pnf effector 50 amino acid leader sequence (e.g. leader of SEQ ID NO.: 78) and a C-terminal Myc-TAG epitope. The PVC operon and effector (Cre + leader sequence) were co-induced for 24 hours and the chimeric nanosyringes purified. Western blot analysis was used to confirm the presence of the FLAG-tagged Pvc16 cap protein (and therefore the nanosyringe chassis) and the trans-packaged Myc-tagged Cre recombinase post purification.

4.2 Trans-packaging using additional leaders demonstrating functionality of a larger, diverse sequence space

Complementing the data outlined in Example 3, Figure 10D demonstrates (trans-) packaging of Cre into PVC*pnf* (in *E. coli*) using the following four additional leader sequences (thus demonstrating the functionality of a larger sequence space):

- Lane 1: the leader of PAU_02096 (leader sequence = SEQ ID NO.: 71), experiment referred to as "NanoSyringe + *Iopt50::cre::Myc* in Figure 10D;
- Lane 2: the leader of PAK_02075 (leader sequence = SEQ ID NO.: 50), experiment referred to as "NanoSyringe + *cnf50::cre::Myc* in Figure 10D;
- Lane 3: the leader of PAU_02009 (leader sequence = SEQ ID NO.: 68), experiment referred to as "NanoSyringe + *cif50::cre::Myc* in Figure 10D; and
- Lane 4: the leader of PAU_02806 (leader sequence = SEQ ID NO.: 76), experiment referred to as "NanoSyringe + *gog50::cre::Myc* in Figure 10D.

These results also demonstrate the utility of leader sequences showing greater sequence diversity for (trans-)packaging a payload. Indeed, to provide further validation, the inventors performed a CLUSTALW sequence comparison of a panel of leader sequences to determine diversity. PVC effectors are identified as proteins encoding recognisable toxin-like domains that are encoded immediately downstream of the *pvc16* structural gene. Each PVC operon can encode just a single effector, or several different effector genes in tandem array. A phylogenetic tree is shown in Figure 10E, with the identities of leader sequences exemplified herein for packaging payload proteins into the nanosyringe complexes being elaborated by either the *P. asymbiotica* ATCC43949 PVC*pnf* operon (solid arrows) or the *P. luminescens* TT01 PVC*unit4* operons (dashed arrows) or both.

As can be seen from the tree of Figure 10E, the exemplified leader sequences are well distributed throughout and are therefore at or close to maximally sequentially diverse.

EXAMPLE 5

Tail Fibre / binding domain modification

PVC Needle Complexes are known to comprise tail fibres (see the 3D rendered PVC structure, left most asterix of the rightmost image) which are believed to allow for cell-type specific targeting of the PVC complexes. The inventors have successfully demonstrated that modification of a tail fibre region to incorporate non-natural amino acids (e.g. a substitution of an amino acid in the wild-type sequence for an alternative amino acid of the 20 standard amino acids) does not affect expression of tail fibres.

EXAMPLE 6

Demonstrating delivery of an active (exogenous) enzyme/ payload into *ex vivo* murine organoids with a leader sequence-packaged PVC Needle Complex

Concept: Obtaining data for the delivery of an exogenous functional enzyme to a mammalian tissue. The inventors have demonstrated the delivery of a trans-packaged bacteriophage derived recombinase protein known as "Cre" into *ex vivo* mouse bile duct organoids. The organoids are derived from a mouse line in which the expression of a chromosomally encoded red fluorescent protein (RFP) reporter is normally prevented by a stop signal flanked by *loxP* recognition sites for the Cre-recombinase. If the recombinase is present, the stop signal is recombined out and the cells then go on to express the reporter protein. The general principle behind this experimental demonstration is summarised in Figure 16A.

Method: The Bile Duct organoid preparation: murine primary bile ducts were isolated and expanded as organoids in matrigel using "BD expansion media" for 12 passages following Huch et al (Regen Med. 2013 Jul;8(4):385-7. PMID: 23826690; DOI:10.2217/rme.13.39) protocol. Cells were then plated in 2D and cultured in BD expansion media. Mouse Genotype: LSL-Tom reporter in Rosa26 locus + Axin2CreRT (inducible upon 4OHT treatment). Cells were cultured in uncoated polystyrene plates at a seeding density: of 10,000 cells/well. Nanosyringes were prepared as 30% volume syringe preparation in PBS + 70% culture media. Total volume of 100 µl per well. The positive control represented 500nM 4OHT (in ethanol) at 1:1000 (v/v) as positive control for the recombination. The negative control represents 1:1000 (v/v) ethanol dilution only. Cells were seeded and grown for 48h, nanosyringes added and then cultured for another 24h before fixing (4% PFA fixation 15min RT) and staining for microscopic examination. Staining: Primary antibody Anti-RFP (1:1000) from Rockland. Secondary Anti-Rabbit 568 (used at 1:500 v/v). Samples were visualized on a laser-confocal microscope.

Result: Figure 16B includes representative micrographs from these experiments demonstrating signal for the RFP protein could be detected in a number of cells when treated with the Cre loaded PVC*pnf* nanosyringe. As these are *ex vivo* organoids, rather than simple cell monolayers, some stochasticity in the number of cells that are dosed is expected, and this is even observed in the positive control, which is a small molecule inducer (rather than a large protein complex). It is anticipated that, as these are organoids, there will be some level of cellular differentiation present which may alter the binding characteristics of the nanosyringes. A further interesting observation from this preliminary run, is that while information on total amounts of nanosyringes applied to the system is not yet available, the inventors demonstrate that the TAM small molecule inducer does not appear to have appreciably greater tissue penetration than the nanosyringes, suggesting their ability to distribute is not majorly hampered by their size.

Additional interpretation: To summarise, the inventors have demonstrated the ability to deliver (e.g. dose) exogenous enzymes to a cellular target. Moreover, this "nanosyringe + Cre" experiment is a promising proof of concept for a biotechnology tool/aide, by demonstrating the ability to provide a DNA change leading to a transformed cell. This experiment therefore demonstrates the use of exogenous payloads (a protein of viruses rather than bacteria), and nucleic acid modifying enzymes in particular. It is evident that the Cre enzyme is delivered in a functional manner and is capable of traversing the cellular interior to the nucleus to affect its DNA modifying changes.

EXAMPLE 7

Trans-packaging of MAD7 site specific recombinase (exogenous payload) into the PVC*pnf* nanosyringe expressed in *E. coli*

Concept: As with the Cre data (of Example 6), and other examples of packaged payloads provided herein, the inventors have demonstrated packaging of the Cas-like enzyme MAD7 into a nanosyringe via a leader sequence. This is the largest exogenous example (MAD7 = 147.9 kDa) of a payload described herein.

Methods: Briefly, the chassis genes and the MAD7 gene (the latter being tagged with a C-terminal Myc tag for detection, and a leader sequence for nanosyringe incorporation described herein), were expressed (upon induction) simultaneously in *E. coli*. Upon harvesting and purification of the nanosyringe complex, payload packaging was probed via dot blot analysis (e,g. for detection of the Myc tag). The purification method described herein (using ultracentrifugation) can be employed to select for (e.g. exceedingly) high molecular weight protein complexes/ biological matter, enabling recovery of the nanosyringes and any cargo (payload) they carry. 'Loose'/ unpackaged payload remains in solution and is not subject to sufficient centrifugal force and as such is lost during purification, unless contained within the much larger nanosyringe 'shell' (that is, when successfully packaged). Successful packaging of MAD7 is demonstrated by Figure 17.

EXAMPLE 8

Trans-packaging of apoptosis inducing payloads into PVC*pnf*, expressed in *E. coli*

Using the *E. coli* PVC*pnf* leader::payload::*Myc* trans-packaging system described in Figure 10C (PVC*pnf* leader = SEQ ID NO.: 78), the inventors demonstrated the ability to trans-package at least two pro-apoptotic human derived protein sequences or peptides (e.g. the sequences of SEQ ID NO.: 109 and SEQ ID NO.: 111). The Pnf effector protein leader sequence (e.g. SEQ ID NO.: 78) was fused to the N-terminus, and a Myc epitope tag was fused to the C-terminus. Western dot blot analysis (similar to that of Example 7) confirmed the presence of these human derived proteins in purified nanosyringes (Figure 18).

EXAMPLE 9

Demonstration of the induction of apoptosis in cultured *ex vivo* human cells by nanosyringe delivery of (trans-)packaged pro-apoptotic human polypeptides

A preliminary test has confirmed the ability to use the PVC*pnf* nanosyringe, produced in *E. coli*, to deliver trans-packaged human protein sequences (e.g. packaged according to Example 8) and induce apoptosis in *ex vivo* circulating PBMC cells from human donors. The assay is a TUNEL-stain microscopic analysis from cells exposed to the packaged nanosyringes for 20 minutes only. Results are shown in Figure 19A, demonstrating (via successful induction of apoptosis) delivery of tBid p15 fragment and BaxBH3 domain.

- tBid p15 fragment (SEQ ID NO: 109) is part of the normal human apoptosis regulation pathway. Cellular effects: a pro-apoptotic member of the Bcl-2 family. The C-terminal part of Bid (tBid) translocates to the mitochondria, where it induces the release of cytochrome c. Bid is normally cleaved by caspase 8 from its latent cytosolic full-length pro-Bid form.
- BaxBH3 (aa59–73) (SEQ ID NO: 111) is a minimal BH3 domain synthetic peptide, comprising critical 15 residues of the defined Bax BH3 domain. Cellular effects: these 15 residues contain sufficient information to bind to, and functionally antagonize, Bcl-xL and to induce specifically Bax/Bak. Appears to abrogate Bak/Bcl-2 interactions – freeing up pro-apoptosis factors.

A more detailed test of the delivery of pro-apoptotic human peptides into *ex vivo* Peripheral Blood Mononuclear Cells (PBMCs) is now described. The aim of this study was to investigate whether the pro-apoptotic peptide loaded PVC nanosyringes could induce

apoptosis in *ex vivo* human Peripheral Blood Mononuclear Cells. The nanosyringes were first assessed for any immediate cell toxicity using Trypan blue dye exclusion assays and then for apoptosis response by using the TUNEL assay.

Trypan Blue Exclusion Test for cell viability: Trypan blue is a Diazo dye commonly used to selectively colour dead tissue or cells, hence, dead cells are shown as a distinctive blue colour under a microscope while live cells or tissues with intact cell membranes remain uncoloured. Since live cells are excluded from staining, this staining method is also described as a Dye Exclusion Method. Trypan blue is commonly used for assessment of tissue or cell viability. A suitable number of cells (2×10^5) were exposed to the nanosyringes and empty nanosyringe for 20 minutes. A suitable volume of cells (30µL) were added to an equal volume of 0.4% Trypan blue and the number of viable (unstained) and dead (stained) cells counted using a hemocytometer. Each compound was tested at 3 concentrations. Blood cells from two independent human donors was tested for each compound at each concentration and each sample was tested in duplicate.

Treatment and preparation of cells for microscopy: The viability of Peripheral Blood Mononuclear Cells (PBMCs) from two independent healthy human donors was determined after 20-minute treatment with the two chimeric nanosyringes (e.g. loaded with the exogenous pro-apoptotic peptides) at 3 test concentrations in 2 independent tests. PBMCs were harvested by centrifugation and resuspended in media at 1×10^6 cells/ml. Cells were fixed in 2.5% formalin and incubated for 20 mins at room temperature. Poly-L-lysine coated slides were prepared by spraying with 70% ethanol and leaving to air dry. Cells were centrifuged for 30 seconds. Supernatant was removed and cells were resuspended in 200µl dH_2O. 5µl of cell suspension was added to each slide/fixation. Two fixations were performed per slide to allow staining to be performed in duplicate. Cell suspension was left to air dry.

Results of PBMC cell viability assay: The Trypan blue viability assays confirmed that the PVC preparations were not immediately toxic in themselves to PBMCs taken from healthy human donors (Table 2). Nanosyringe treatment showed > 60% viability indicating low toxicity at maximum dose concentration (Table 2). The inventors then moved on to test the ability of the chimeric nanosyringes to induce apoptosis.

Blood donor sample 1	**Neat**		**1/10**		**1/100**	
Compounds	Well 1	Well 2	Well 1	Well 2	Well 1	Well 2
TBID	60	70	75	75	80	80
Bax	78	82	80	80	83	87
PBMC Controls	93	97				
Blood donor sample 2	**Neat**		**1/10**		**1/100**	
Compounds	Well 1	Well 2	Well 1	Well 2	Well 1	Well 2
TBID	70	72	81	81	84	84
Bax	80	80	84	88	87	87
PBMC Controls	95	95				

Table 2. Viability of Peripheral Blood Mononuclear Cells (PBMCs) from two independent human blood donors after exposure to each compound for 20 minutes at 3 test concentrations (v/v dilutions). PBMC controls are untreated.

Testing for chimeric nanosyringe induced apoptosis using the TUNEL assay: The TUNEL assay was then used to identify apoptotic nuclei in single cell suspensions fixed on slides. In the assay Terminal deoxynucleotidyl Transferase (TdT) binds to the exposed 3'-OH ends of DNA fragments which are generated in response to apoptotic signal factors. This in turn catalyses the addition of biotin-labelled deoxynucleotides which can be detected using a streptavidin-horseradish peroxide (HRP) conjugate. Diamineobenzidine (DAB) reacts with the HRP-labelled sample to generate an insoluble brown substrate at the site of DNA fragmentation. Methyl green counterstaining enables the visualisation of normal and apoptotic cells.

The induction of apoptosis following exposure of human PMBCs to the nanosyringes was determined. A TUNEL assay kit (Abcam) was used for detection of apoptotic cells. The assay was performed following the manufacturer's instructions. Briefly, slides were covered with 100µL proteinase K solution or 5 minutes, slides were rinsed with 1x TRIS buffer saline (TBS). The treatment of nanosyringes or the DNase I positive kit control was performed for 20 minutes at room temperature. Slides were rinsed with TBS. Slides were then incubated with TdT equilibrium buffer for 30 minutes before the addition of TdT labelling reaction mix. Slides were incubated at 37° for 19 minutes. Slides were then washed with TBS before application of the stop buffer and incubation at room temperature for 5 minutes. Slides were washed again with TBS before addition of the blocking buffer for 10 minutes at room temperature. Detection was performed by application of the conjugate to the samples for 30 minutes. Slides were rinsed with TBS before application of the DAB solution for 15 minutes. Slides were rinsed with dH_2O followed by counterstaining with methyl green. Slides were dehydrated in 100% ethanol followed by xylene and mounted with a glass cover slip. All staining was performed in duplicate. An apoptosis endpoint, indicative of positive staining in the apoptosis detection assay is represented by dark brown (DAB) signal. Lighter shades of brown and/or shades of blue/green to green/brown indicate a non-reactive negative cell for apoptosis.

Analysis was performed by selecting 5 random sections of cells on the slide, positive stained cells (dark drown) and negative stain cells (blue or light brown) were counted and the percentage of cells showing apoptotic bodies was determined.

To generate a positive control, slides were treated with 1µg/µl DNase I (the kit positive control) for 20 minutes at room temperature following the proteinase K treatment step detailed below. The DNase I treatment fragments DNA in normal cells to generate free 3'OH groups identical to those generated during apoptosis. A negative control was generated by substituting DNase I with dH_2O in the reaction mix during the treatment stage.

Results of PMBC apoptosis assays: TUNEL staining using PBMCs was performed following treatment with the intact tBID and Bax loaded nanosyringes, with appropriate positive and negative kit controls. Treatment was performed for 20 mins to determine if the nanosyringes elicited an apoptotic signal. A positive control (DNase I treatment) and negative

control (no DNase I treatment) was included. Results showed both nanosyringes, containing either tBID or Bax, showed strong apoptotic signals (**89%** and **78%** positive, respectively) on the PBMCs. The positive control showed a strong apoptotic signal (**79%**), whereas the negative control showed no apoptotic signal (**100%** negative). Also observed was a significant loss of the numbers of attached cells in the nanosyringe treated samples, presumably indicative of a rapid and comprehensive apoptosis response, and a failure to be retained after washing. Note this effect is even more pronounced than the kit positive control suggesting a more rapid response. Representative micrographs are shown in Figure 19B.

Conclusion: It is concluded that the tBID and Bax loaded nanosyringes are able to rapidly induce extensive apoptosis in human Peripheral Blood Mononuclear Cells. Furthermore, Trypan Blue dye exclusion assays have confirmed that these chimeric nanosyringes do not cause rapid lethal lysis or extensive membrane damage to the cells.

EXAMPLE 10

Exemplification of practical utility of leader sequences and PVC Needle Complexes - Intracellular delivery of atypical (non-*Photorhabdus*) payload

(1) An anti-MDM (p53 inhibitor) antibody is linked to a leader sequence described herein, and expressed together with a PVC Needle Complex for packaging therein. Isolated PVC Needle Complex (comprising the antibody payload) is contacted with a tumour for intracellular delivery of the antibody (said tumour cells being characterised by having high MDM-suppression of p53 activity for MDM inhibition). The tumour is suppressed by the activity of the anti-MDM antibody.

(2) A PVC Needle Complex is used to (intracellularly) deliver anti-tumour peptide vaccine to activate the MHC-I dependent cytotoxic T-cell lymphocyte (CTL) response. A tyrosinase-related protein 2 (TRP2) peptide vaccine is delivered for enhancing cross-presentation to CTLs occurs and antitumor effects against TRP2-expressing tumours. The tumour is suppressed by the activity of the peptide vaccine.

(3) A PVC Needle Complex is used to (intracellularly) deliver a nuclear factor-κB inhibitors (which are used for the control of inflammatory disorders, such as rheumatoid arthritis) to a cell. The cell subsequently demonstrates a reduced expression of pro-inflammatory cytokines.

(4) A PVC Needle Complex is used to (intracellularly) deliver a T3SS payload (which inhibits NF-kB and MAPK pathways). This is completed with an isolated (purified) PVC Needle Complex, without any need for the PVC Needle Complex to remain associated with the bacterial cell from which it derives.

(5) A PVC Needle Complex is used to (intracellularly) deliver, to a cell, anti-apoptotic peptides including BH4, the Bcl-xL-protein, and/or a peptide inhibitor of c-Jun N-terminal kinase (which can protect the heart and brain against ischemic injuries (a restriction in blood supply to tissues, causing a shortage of oxygen and glucose needed for cellular metabolism)). For example, Jun-kinase inhibition via a 20 amino-acid binding motif of the JUN kinase is sufficient. A release of e.g. cytochrome c in the cell is inhibited.

(6) A PVC Needle Complex is used to (intracellularly) deliver nicotinamide adenine dinucleotide quinone internal oxidoreductase (Ndi1), the single-subunit yeast analog of complex I (which provides significant cardioprotective effects) to complex I-deficient mutant cells. The Ndi1 protein is correctly targeted to the matrix side of the inner mitochondrial membranes, and restores the NADH oxidase activity to the complex I-deficient cells.

(7) A PVC Needle Complex is used to deliver one of two of the essential subunits of the PHOX complex (which are used in enzyme replacement therapy to restore production of ROS in chronic granulomatous disease) to a chronic granulomatous disease cell. A restoration in production of ROS is observed.

(8) A PVC Needle Complex is used to (intracellularly) deliver (e.g. intramuscularly) a myotubularin (which is used for improving local and distant muscle performance in X-linked myotubular myopathy patients). Myotubularin- dephosphorylation of phosphatidylinositol 3-phosphate and phosphatidylinositol (3,5)-bi-phosphate is observed.

(9) A PVC Needle Complex is used to (intracellularly) deliver a recombinase “Cre” (which is capable of excising defined genetic cassettes) into a mouse cell line, in which the genome has loxP recombination sites flanking a stop signal upstream of an mCherry gene. The Cre payload excises the recombination sites, and removes the stop signal, allowing for expression of the mCherry gene in the cell.

(10) A PVC Needle Complex is used to (intracellularly) deliver a ~15kDa nanobody (antibody fragment) with affinity for an intracellular component. A nanobody-intracellular complex is detected.

(11) A PVC Needle Complex is used to intracellularly deliver (e.g. into insect cells) an atypical (non-*Photorhabdus)* polypeptide toxin for insect crop pests and animal parasites. Suppression of the pests is observed.

(12) A PVC Needle Complex is used to (intracellularly) deliver a nuclease (e.g. Cas9 and/or Mad7) into a target cell comprising a guide RNA. The nuclease performs site-directed gene inactivation

All publications mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described methods and system of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention. Although the present invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in biochemistry and biotechnology or related fields are intended to be within the scope of the following claims.

SEQUENCES

Where an initial Met amino acid residue or a corresponding initial codon is indicated in any of the following SEQ ID NOs, said residue/codon may be optional.

SEQ ID NO: 1 (PAK_1985)

MMREYSNEDDFIKEKTNLVKSENVEADNYLETEYLTYLAKLIGMTERENHHLNSIKLIDDIIELHNDRKGNKLL
WNDNWQDKIIDRDLQSIFKKIDEMVSEFGGLEAYKDIVGENPYDPTEPVCGYSAQNIFKLMTEGEYAVDPVK
MAKTGKINGNQFAEKLEHLNSSNNYVALINDHRLGHMFLVDIPSTNRERVGYIYQSDLGDGALPALKIADWL
KSRGKESINVNKLKKFLNDEFTMLPDNEQKGLIAEIFDLNKDIDSVKSGKIKKDKAVDIYLREYDINDFISNIEKL
KTKLA

SEQ ID NO: 2 (PAK_1987)

MFQNRIRNEKTTQSGKGKTLDRMTDSLYLEIPNVEAVTLAYQKLTSKYRKFDNKTKLILDSSDEFSQLKSEK
QRKGFSKSGLKNNGVSDRKFIYTKNALKNFAAHAGYEHNGHYEDEFVNFKDNNKNLAKGKLFPGISLIERR
KLSIVKNKEGKWEHKETDEAEAYKVTDIEKFISGVRSMYLQGNTFLHAKTEALIRKHIANNENILPTMAGIAGL
HAEVQALNNLFISGDKGTKKREKWKYIRNMLESSIFTQRLTTGQAGKDFAACHNCSGILSSPVNVITGKVES
AGDNFLSTLSRYKTSQESPI

SEQ ID NO: 3 (PAK_1988)

MEREYSEKQKNPSKLSRKTAISERIAALERSGLSNSNQPVPQFARPYTSNRPVVNINPGRSSIAVATANSTS
PVNIPTPAPASPDKLLPSTSCDTTSSILIVGKYNLELTSQGKIVVFRGDNRTPEQIVAAGGFYPWSKQDVGKI
KKELIDEFIEIGPSAHMMGHVRSPNKNYVSTGMNMDSGGFGEQSNYLYKMEIPGLKPQDMNERTLGEKIRQ
DKRGINYPHFLMSHLTLAESEFVAMIPARSEELTFITPIPLSYITSYRKRGTNTWLPMPLKK

SEQ ID NO: 4 (PAK_2075)

MSNYEYDIVTQHDTYQIKDNEYTVVNGKYWQYEQEGNKNNNKVSISLMKENQNDPVWITSDIKEISLYIIENL
FSYHKFSAELQHTLKNAVKAVFNEYSEIKYSELLHNINNIFNLFFIKIYNTSDIDTAINILTAKIEIYDKLEKINQDK
TDSNNTNVDIWEELGINAEEPLLKIYRQAFSTGDIDDEVYSDALLTFMSDGNLELGDKEKSDYNQRIKDKTDL
FESYKKGIEKVASLITTNNINPGIPITYPETEKSINIGDDLLLAQLAKEEIALKKQNRTEYSQQDIFELQTLQAAK
YHLLILSSLGALLYQIAPNVEKMTKGHGDYRDIIFSQEQAESLFKKHNIQYDTNHVLSQESKHIEMEGCIILTAA
IIYRMRKENATVEQALNYSTLETIKLFENDKKKLNPFNTNNVKPAGYFSFIDFKKRDKFDSQYNFNEQFNVYK
NKYSHYESISFSKLILSSPAAQLTAEEIVNPPEEAFLYSVEQGMGNVAMIKMYQQGNWLVISTIQGGVKAKKYS
RQQVDSNPTLRAMSKPNALFLIERKMETGMGILMPNMMVNTGKRLFPTGYERAKTLSGFAETSRYKNSYN
AFWNDYYGITSGMNVGISFTGSPKFNFYKEENLLSVTATIIQQGLNDIAIKSKQALDITSGWHIAATILIPFYNVI
YKSTTDSEYELTGEDIGSIVFDTANVLLVVATLGMSLTESMAAKVTQTTLRLRQAGLTGRALITAVVRTLPEH
GIITLRQSSGIILGGLIDLIEPLPIRSTLTLTYRGVINAVGAMRNSIKLEKSFADIFGKSTRGLGKLKNEWKVSNL
PLEEIVPHSNGGEIYKGIYSIRPTNPETAVKQNFYIKEAGANYQVKWDDANHTWRVVNPTYPEQFSYWPAV
KLDKNGHWVTHADVSNKFLILEQSKRIDQELEAAHSNINNDNILDAFIHINTAFKDCERYDIDKLSDITDTLTHF
FEKSLKPGDKKAIFSTEIMSIQQAWIREVILPLQNNSSISIEKINAIKTELPYLLRKTFPIESQLPNQLVANKIALAI
EEIPNTRIPKYTSGNISKTVQYTSLLENNHVDIPPVGITITGNDTFINQVTRVLSEIDEIPSGNIVIQELEKQGLNI
QPPTMNDIVREKNGQFYANNSAGSHIAFDPENHLIGTEEKLIDEPWRTREPAIALYHEMLHIYYNRYPTWFT
SIDNKVIDQKVSGGFSLLEESRIVGTKYYVNDKNTLFDFNDSDYLLENNSALLTENRFRAEYAIFKNKSEYVIR
PYSGKGDSQIPLTKTKININESHRNVMGVGSGKPEKMPNESATDYRNRVREWRKANKQPEADIGTGDMRK
TKAEARVKLLKENYPQFEPQKIELGGAFQLWTVPNEPANKLMLSSHGYFFSDSAATQVPAGKTIQFLGPHG
KTLLEAPENPLYSPFDVTLGNSGFTVQPYATIESGNKAGLGSVKIGDKTFTVNDIQNIATDDVENYLLATGVE
ANASNHGKVRNYGIKYYEKMPDEEVKAAIWKNRADETSTHKYDALLVSPEAGNRKKLSDIFALMKTDERMS
KYDEITFVACREELNRINMKSIHDTGLGGGYEPKLEPTVILSRRRREATFTADGAIIYSIIAVNLHHNFITEEIVG
IAPFLFINN

SEQ ID NO: 5 (PAK_2077)

MEHEYNEKEKQRNSAIKLNDAIRNNEENMDMTSPLELNFQNTNRKSRGLRERFSATLQRNLPGHSMLDRE
LTTDGQKNQESRFSPGMIMDRLMHFGVRTRLGKVRNSASKYGGQVTFKFAQTKGTFLDQIMKHKDTSGGV
CESISAHWISAHAKGDSIFNQLYVGGKKGKFHIDTLFSIKQLQMDGYLDDEQSTMTEYWLGTQGMQPNIQR
NDDTDEHSSKVVGETGNRGTKDLLHAILDTGDKGSGYKKISFLGKMAGHTVAAYVDDQKGVTFFDPNFGE
FSFPDKTSFSHWFTDDFWPKSWYSLEIGLGQEFEVFNYAPEAP

SEQ ID NO: 6 (PAK_2892)

MPNKKYSENTHQGKKPLMKSEANNEHDIQNSSLGIGLDLNSMMGNSSTSLSHIQDYSFWKENISEYYKWM
VVVKAHLKQLDWTLKSMDSPESAGTNIAKNTGTTALQTLLNTGGSIAGAAIGGAIGSAIAPGVGTIAGMGIGA
LAGTGLNYLNDTVIEKLNEKLEIAYPYPKTRNMIFDINNYDKNPIIKAIKKKTNKDNLKVTAGSSLTSQLVGKVT
SPIKFPAYKLADLAIALAGLSSDKARHILDFTDSIREVLNESHSDAVAFMRKNYGDNAMGLAGLSSRIK

SEQ ID NO: 7 (PAK_2893)

MEREYSEKEKHKKRPIQLRNSIEQHEEETANNSLGLGLDLNQATNPPKVPKDNYNEENGDLFYGLANQRG
RYIKSVNPNFDPDKINSSPMIIDVYNNNVSNTILNKYPLDKLVKLSGNPQKYANNIKVENSLQQDVASSKRGW
YPLWNDYFKTGNENKKFNIADIYKETRNQYGSDYYHTWHTPTGAAPKLLWKRGSKLGIEMAASNEKTKIHF

VLDGLNIQEVVNKQKGSTPLEQGRGESITASELRYAYRNRERLAGKIHFYENDQETVAPWEKSPELWQNYI
PKNKNQNESSTPQRNNGTLYRLGGPFRKLRASLRKRS

SEQ ID NO: 8 (PAK_2894)

MMEHEYSKEEEKKRQQSKPNNATHDESNLPLELEKHFNARTPATAHSKWFTYENDTEVELTTERIKEIFSN
KQPKIIIAGDGHNKPPFQYAKNIPDVNSSFDAGTLQLYIEATDEQINENNPEYIPKEFMAKPGLFTNKNRRAEI
VGWEDSELSNAMKEMFELSDKSTREKLTPEETSSFYKLHETAIRHFFRPEFNQLRDEFFEILAKAGSNRELD
KIALEMIGFTSGTWRDEYINPTLAEKIAKHAAEKENHTFVVSIGDAHLSENPMQEYLNKRRNGGEFKHQIIFT
RDKRPILPDNMKTGNKNS

SEQ ID NO: 9 (PAK_3525)

MLKYANPQAVPTQRTKNTAKKPSSSSSFDGQLELSNGEWSKHSEMGLKRGGLINSIRRRIARNGNIGRFNE
LIDSEAKKWPSEPVDKNIHMIWIGTRNISEKNIKLSIDTAKKNPDYNTSIIYDSGISGHEGARNFMLEKFEGSN
VNXSLAFPKGIGVMREYAPEAGKATAFPNTPIAVTKNNPIINKTLDLAVGNYQRGEKNVLKLAGPDVFTQALY
QEIPGLNSKVLNAQLDQFELAKRQALGLPLEKPKSFADEKLTSVEKEKINRPYQSMRGLSGHVMNGADHS
WAVDTEVLGH

SEQ ID NO: 10 (PAT_00148)

MMREYSNEDDCTKEKTNLVKSENVEADNYLEMEHLTYLAKLISMTERENHHLNSIKLIDDIIELHNDRKGNKL
LWNDNWQDKIIDRDLQSIFKKIDEMVSEFGGLEAYKDIVGESPYDPTEPVCGYSAQNIFKLMTEGEYAVDPV
KMAKTGKINGNQFAEKLEHLNSSNNYVALINDHRLGHMFLVDIPSTNRERVGYIYQSDLGDGALPALKIADW
LKSRGKESINVNKLKKFLNDEFTMLPENEQKGLIAEIFDLNKDIDSVKSGKIKKDKAVDIYLREYDINDFISNVE
KLKTKLA

SEQ ID NO: 11 (PAT_00149)

MIFKMLNLAVFYLLGNIFHYLICQKFICYFCSVLKSVTMFLTKVAVQIALYLNILPTMAGIAGLHAEVQALNNLFI
SGDRGTEKRENWKYIRNMLESTIFTQRLTAGQAGKDFAACHNCSGILSSPVNVITGKVESAGGNFFINIISI

SEQ ID NO: 12 (PAT_00150)

MEREYSEKPKNLSQLSRKTAISERRAMFERNASSNNEQPVPQFARSYTSNRSVVNINPGRSSIAVVTANST
SPVNISTPAAASPDKLLPSTSCDTTSSTLTVGKYKLELTSQGKVVVFRGDNRTPEQIVAAGGFGEQSNYLYK
MEIPGLKPQDMNERTLGEKIRQDSRGN

SEQ ID NO: 13 (PAT_00152)

MKYDPRLRTWVEDDFDYEKNFKKQTDYINYKDLEKQLKENVDYYALLDENEAIIFLKELGCDIKSFLNDTAFP
VTDVLSNFAGNIKDALGVFKVAKNFKPINIGIFTYIINELKGKGIKAIEYLGKNGERYIKLTDRPGIRKYLNATRY
LINNKKIMEVGIGSVAMEGSIVKGARFGVIYSAAYRSVELMFKSEYDLTNFFVNLSMDMAKIIVATIIAKSTVAA
ATSFVVTAALSTTAIAIGVFIIGALVVWGLMWLDDEFKISETIIRRLKEHKVKTPISTYHSDQIFNAWGRYYRG

SEQ ID NO: 14 (PAT_02308)

MPNKKHSENTHQGRKPLIKSEANNEHDIENSSLGIGLDLNSTIGNNSASLSQIQDYSFWKENISEYYKWMVV
VKAHLKQLDWTLKSMDSSESAGTNIAKNIGTTALQTLLNTGGSIAGGAIGGAIGSAIAPGVGTIAGMGIGALA
GTGLNYLNDTVIEKLNEKLEIAYPYPKTRNMIFDINNYDKNPIIKAIKKKTNKDNLKVTAGSSLTSQLVGKVTSP
IKFPAYKLSDLAISHNRALAGLSSDKARHILDFTDSIREVLNESHSDAVAFMRKNYGDNAMGLSGLSSRIKGE
KLTLATLARTRNKIENRINSINKQTLKLSSKNSNE

SEQ ID NO: 15 (PAT_02309)

MEREYSEKEKHKKRPIQLRNSIEQHEEETANNSLGLGLDLNQATNPPKVPKDNYNEENGDLFYGLATQRGR
YIKSVNPNFDPDKINSSPMIIDVYNNNVSNTILNKYPLDKLVKLSGNPQKYANNIKVENNLQQDVASSKRGWY
PLWNDYFKIGNENKKFNIADIYKETRNQYGSDYYHTWHTPTGAAPKLLWKRGSKLGIEMAASNEKTKIHFVL
DGLNIQEVVNKQKGSTPLEQGRGESITASELRYAYRNRERLAGKIHFYENDQETVAPWEKSPELWQNYIPK
NKNQNESSTPQRNNGALYRLGGPFRKLRASLRKRS

SEQ ID NO: 16 (PAT_02310)

MMEHEYSKEEEKKRQQSKPNNATHDESNLPLELEKHSNARTSATAYSKWFTYENDMEVELTTERVREIFS
NKQPKIIIAGDGHNKPPFQYTKNIPDVNSSFDAGTLQLYIEATDEQINENNPEYIPKEFMAKPGLFTNKNRRA
EIVGWEDSELSNAMKEMFELSDKSTREKLTPEETSSFYKLHETAIRHFFRPEFNQLRDEFFEILAKAGSNRE
LDKIALEMIGFTSGTWRDEYINPTLAEKIAKHAAEKENHTFVVSIGDAHLSENPMQEYLNKRRNGGEFKHQII
FTRDKRPILPDNMKTGKKNS

SEQ ID NO: 17 (PAT_02956)

MSNYEYDIVTQHDTYQIKDNEYTVVNGKYWQYEQEGNKNNNKISISLMKDNQNDPVWITSDIKEISLYIIENL
FSYHKFSAELQHTLKNAVKAVFNEYSEIKYSELLHNINNIFNLFFIKTYNTSDINTAINILTAKIEIYDKLEKINQD
KTDLNNTKVDIWEELGINAEEPLLKIYRQAFSTGDIDDEVYSDALLTFMSDGNLKLGDKEKSDYNQRIKDKTD
LFESYKKGIEKVASLITTNNINPGIPITYPETEKSINIGDDLLLAQLAKEEIALKKQNRTEYSQQDIFELQTLQAA
KYHLLILSSLGALLYQIAPNVEKMTKGHGDYRDIIFSQEQAESLFKKHNIQYDTNHVLSQESKHIEMEGCIILTA
AIIYRMRKENATVEQALNYSTLETIKLFENDKKKLNPFNTNNVKPAGYFSFIDFKKRDKFDSQYNFNEQFNVY
KNKYSHYESISFSKLILSSPAAQLTAEEIVNPPEETFLYSVEQGMGNVAMIKMYQGNWLVVSTIQGGVKARK
YSQQQVDSQPTLRAMSRPNALFLIERKIMIGIGIFMENQIVNTGKRLFPTGYERAKTLSGFAETSRYKNSYNA
FWNDYYGITSGMNVGISFTGSPKFNFYKEENLLSVTATIIQQGLNDIAIKSKQALDITSGWHIAATILIPFYNVIY
KSTTDSEYELTGEDIGSIVFDTANVLLVVATLGMSLTESMAAKVTQTTLRLRQAGLTGRALITAVVRTLPEHGI
ITLRQSSGIILGGLIDLIEPLPIRSTLTLTYRGVISAVGAMRNSIKLEKSFADIFGKSTRGLGKLKHEWKVSNLPL

EEIVPHSNGGEIYKGIYSIRHTNPETAVKQNFYIKEAGANYQVKWDDANHTWRVVNPTYPEQFSYWPAVKL
DKNGHWVTHADISNKFLILEKSKRIDQELEAAHSNINNDNILDAFIHINTAFKDCERYDIDKLSDITDTLTHFFE
KSLKPGDKKAIFSTEIMSIQQAWIREVILPLQNNSSISIEKINAIKTELPYLLRKTFPIESQLPNQLVANKIALAIEE
IPNTRIPKYTSGNISKTVQYTSLLENNHVDIPPVGITITGNDTFINQVTRVLSEIDEIPSGNIVIQELEKQGLNIQP
PTMNDIVREKNGQFYANNSAGSHIAFDPENHLIGTEEKLIDEPWRTREPAIALYHEMLHIYYNRYPTWFTSID
NKVIDQKVSGGFSLLEESRIVGTKYYVNDKDTLFDFNDSDYLLENNSALLTENRFRAEYAIFKNKSEYVIRPY
SGKGDSQIPLTKTKININESHRNVMGVGSGKPEKMPNESATDYRNRVREWRKANKQPEADIGTGDMRKTK
AEARVKLLKENYPQFEPQKIELGGAFQLWTVPNEPANKLMLSSHGYFFSDSAATQVPAGKTIQFLGPHGKT
LLEAPENPLNSPFDVTLGNSGFTVQPYATIESGNKAGLGSVKIGDKTFTVNDIQNIATDDVENYLLATGVEAN
ASNHGKVRNYGIKYYEKMPDEEVKAAIWKNRADETSTHKYDALLVSPEAGNRKKLSDIFALMKTDERMSKY
DEITFVACREELNRINMKSIHDTGLGGGYEPKLEPTVILSRRRREATFTADGAIIYSIIAVNLHHNFITEEIVGIA
PFLFIDN

SEQ ID NO: 18 (PAT_02957)

MEHEYNEKEKQRNSAIKLNDAIRNNEENMDMTSPLELNSQNTNRKSRGLRERFSATLQRNLPGHSMLDRE
LTTDGQKNQESRFSPGMIMDRLMHFGVRTRLGKVRNSASKYGGQVTFKFAQTKGTFLDQIMKHKDTSGGV
CESISAHWISAHAKGDSIFNQLYVGGQKGKFHIDTLFSIKQLQMDGYLDDEQSTMTEYWLGTQGMQPNIQR
NDDTDEHSSKVVGETGTKGTKDLLHAILDTGDKGSGYKKISFLGKMAGHTVAAYVDDQKGVTFFDPNFGEF
SFPDKTSFSHWFTDDFWPKSWYSLEIGLGQEFEVFNYAPKEP

SEQ ID NO: 19 (PAT_03171)

MFKYDTSEKMAKFGKGKTSDGMLLDTLYLEIPDEKAVMSAYKSQILDELRNFSEKTHSFFSGKKPLYSKKYL
ANLAAHAGYVHVTDYNSIGNYKDGFVNFKDNSRNLAEGKLFPGIRLIKRPKLSIVRDKETERWKKQESDEAD
AYEITDIESFISGVRDMYSRANVDLHPVIESLIRNHIVNNDHVLPTMAGIAGLHAEVQALNNLLILADGRAGKIV
GGRKIEEYMQDMLKSFIFTQRLTTKQAGNDFAACHNCSGILSVPANVITGKVASAGSNFSLILSRYKNSQES
PI

SEQ ID NO: 20 (PAT_03172)

MLKHANPQTVSTQRTKSTAKKPSSSSSFDRQFELSNSENQPGEGNKDWTIKGWRQRFADRSLNKGHISPL
MNKGLLVGSEEALINVPVVAHRYDSSHQLTDAGPLKADSHSNNLDPFYGVVTGFRGDQVTSSESGSGSIG
GHWGKNTLDSNITGINVVNGASGTVGIRIALKDIQHGAPVIVTSGALSGCTMVYAVKNGYFFAYHTGQKPGD
KEWKTGRQGVVATYRSHQALSPDSEPMAVGEQNNDLVNIFASYDQGIITYMGKPGVIIDNTAENVGVFNYD
EVKLEKPDIRAGYSYALLAKDDKGKVNVKVLSEDVIVPLGNKGKTIKAINSLKKRLL

SEQ ID NO: 21 (PAT_03177)

MPRYANYQINPKQNTKNSHGKSSSSNFSSGYFSSSNNSLDDSLIRQQVKREFIWEGHMKEIEEASRLGNFA
VSFRAAGGPTLRALGKGAAAKGHDILEKTIKPGSINKAYPKDEASNVIKKVQEAGIEGYVGHWDKKTGRLLGI
YMSSGHGLSDEQVNGKIYPIDLNNLEASLSALKTKENWAALPFTGDYDMHDMISFTGQPHSVPSNSSEERK
IIDRINRLVARSDPNRPFGDIEHNVIRHGAQVSYPAFAMDKEKEEIKKHGGIVKAVAEPGEFPVAIVSKGKWTI
ANNIDELNQFYNSIGAKMKVSWKPGAENPGFVSNPQRPGMARFSRKR

SEQ ID NO: 22 (PAU_02009)

MMREYSKEDDCVKEKTNLAESENVEADNYLEMDCLNYLAKLNGMPERKDHSLNSTKLIDDIIKLHNDRKGN
KLLWNDNWQDKIIDRDLESIFKKIDEMVSEFGGIEIYKDIVGENPYDPTEPVCGYSAQNIFKLMTEGEHAVDP
VKMAQTGKINGNEFAEKLEQLNSSNNYVALINDHRLGHMFLVDIPSTNREKVGYIYQSDLGDGALPALKIAD
WLKSRGKESINVNKLKKFLSNEFTMLSESEQKELIAEIFDINKDIANVKLGKIKKDKAVDVYLREYDLNDFISNI
EKLKTKLV

SEQ ID NO: 23 (PAU_02010)

MPIIGHKEDLIRTERSSVDLTRSSNNRQTDNLELNIPQHKRDNKDIEHAVIYGFSQHRGPEMQKAFADNKNP
VTIDEYNAGLGIMGELSLSDYFRISQDLKENRLPELNEKNIQNHSLKYFDAMGVNMKSADPNVKEEAKEQQ
RAYTRSWGFYMMENKEKLDIQSKINNLIPKKKSFFSKSPGEDEYKKLDEFILKNSNGSNLTIPKQRKILMKFA
SAKNAVDVTKNLSGEEQTWLKDIIATAFFRQTSKLGMSWFIEQLASPDFRFVIVGFNGEELTTDQIRSNKPW
KHGNRRKEGASEYAEPITFSEIRHAHRKGYDSKINFIKK

SEQ ID NO: 24 (PAU_02095)

MISTFDPAICAGTPTVTVLDNRNLTVREIVFHRAKAGGDTDTLITRHQYDLRGNLTQSLDPRLYDLMQKDNT
VQPNFYWQHDLLGRVLHTVSIDAGGTVTLSDIEDRPALNVNAMGVVKTWQYEANSLPGRLLSVSEQSANE
AVPRVIEHFIWAGNSQAEKDLNLAGQYMRHYDTAGLDQLNSLSLTGAHLSQSLQLLKDDQMPDWAGDNES
VWQNKLKNEVHTTQSTTDATGAPLTQTDAKENMQRLAYNVTGQLKSSWLTLNGQLEQIIVKSLAYSESGQK
IREEHGNGVVTKYSYEPDTQRLINITTQRSKGHVFSEKLLQDLLYEYDPVGNIVSILNRAEATHFWRNQKVSP
RNTYTYDSLYQLIQSTGREMADIGQQNNKMPTPLVPLSSDDKVYTTYTRTYSYDRGNNLTKIQHRAPASHNI
YTTEITVSNRSNRAVLSHNGLTPREVDAQFDASGHQISLPTGQNLSWNQRGELQQATTINRDNSATDREW
YRYNAGSARILKVSEQQTGNSTQQQQVTYLPGLELRTTKSGTNTTEDLQVITMVETERTQVRILHWSAGKP
NDIANNQVRYSYDNLIESNVMELDTKGKIISQEEYYPYGGTAIWTARNQIEASYKTVRYSGKERDKTGLYYY
RHRYYQPWLGRWLSADPAGTVDGLNLYRMVKNNPIRYQDESGTNANDKAQAIFKEGKKIAINQLKIASNFL
KDSKNSENALEIYRIFFGGHQDIEQLPQWKKRIDSVIYGLDKLKTTKHVHYQQDKSGSSSTVADLNVDEYKK
WSEGNKSIYVNVYADALKRVYEDPLLGREHVAHIAIHELSHGVLRTQDHKYIGVLSSPGSHDLTDLLSILMPP
ANEQDRTEKQRRATGARKALENADSFTLSARYLYYTAQDPNFLSSLRKAHRDFNNKKTDRLIIRPPERR

SEQ ID NO: 25 (PAU_02096)

MEREYNKKEKQKKSAIKLDDAVGNNEENMDMTSPLELNSQYTNRKRPGLRERFSATLQRNLPGHSMLDRE
LTTDGQKNQESRFSPGMIMDRIMHLGVRTRLGKVRNSASKYGGQVTFKFAQTKGTFLDQIMKHKDTSGGV
CESISAHWISAHAKGESIFDQLYVGGQKGKFHIDTLFSIKQLQMDGYLDDEQSTMTEYWLGTQGIQPNRQK
NDNMNEHSSKIVGETGTRGTKDLLRAILDTGDKGSGYKKISFLGKMAGHTVAAYVDDQKGVTFFDPNFGEF
NFPDKVSFSHWFTDDFWPKSWYSLEIGLGQEFEVFNYEPKEP

SEQ ID NO: 26 (PAU_02097)

MVYEYAKTNDRKRKLSTQSDNYEEKSFSPVLDLSRNNQNTPNMEDEYETPQNFINRTGREKLFRAIRMVAS
NKRDPITKDQVSVPPDGNLFTELKDKHLDRAAEYKKLKTWPTHASIIATSPSANTPIAQHVSGDDALSPYIST
GDKPGAVQNTVRNWNGIGPASERRLRPEKTWSPIIEIDVNKLPDTTKIFDLNKPNNTFFSTTNSDIAQNAFAD
KEVLISPEIPGLAITRVINDPEEIKQIANLNPSQSLIEKKNTIPEEKIIFEEKKSVPIHDSDADIPSSSFVFPKRKKP
RNIRSRTDS

SEQ ID NO: 27 (PAU_02098)

MVFEHDKTVERKRKPSIQLGNDKEKSSEQALELPQSKQNNPLLHDLITSNNLRKEAAVFAKQIGPSYQGILD
GLEHLHNLSGNEQLTAGFELHRRITRYLEEHPDSKRNAALRRTQTQLGDLMFTGTLQEVRHPLLEMAETRP
AMASQIYQIARDEAKGNTPGLTDLMVRWVKEDPYLAAKSGYQGKIPNDLPFEPKFHVELGDQFGEFKTWLD
TAQNQGLLTHTRLDEQNKQVHLGYSYNELLDMTGGVESVKMAVYFLKEAAKQAEPGSAKSQEAILLNRFA
NPAYLTQLEQGRLAQMEAIYHSSHNTDVAAWDQQFSPDALTQFNHQLDNSVDLNSQLSFLLKDRQGLLIGE
SHGSDLNGLRFVEEQMDALKAHGVTVIGLEHLRSDLAQPLIDKFLTSENEPMPAELAAMLKTKHLSVNLFEQ
ARSKQMKIIALDNNSTTRPAEGEHSLMYRAGAANNVAVERLQQLPAEEKFVAIYGNAHLQSHEGIDHFLPGI
THRLGLPALKVDENNRFTAQADNINQRKCYDDVVEVSRIQLTS

SEQ ID NO: 28 (PAU_02230)

MKGIEGVIMLSHDILPEKLLVSEKKHENVGSYFSDDIGEQSEQTEVSHFNLSLDDAFDIYADISIENQQELKNK
DNNTNIWSSLGRGDDDHNLKKIINDAFKEKLPQLMEYRRKGYNVIGLDKEGIKKLEGMLKAVPPEIQQPTMK
NLYSAAQELLNTLKQHPLLPENQDMIQQSNLVIRNLSDALEAINAVSKVNQVEWWEEVHKTNKAQSDRLIAA
TLEELFFKVKDKRLPGSNDDYCQQEREETERKIKDLLLYDGYQLTAEHFKFGRLRKSLLAESRVTRLKLAEY
LEKKSVGILTAARDAKMYAMKILLAQTRNNGFNAKDLINAGQVNDRLLSFQQYARHIRAVDGEIDGIILSNPLV
VACIKETNDEPAHIKIARAILPVSEELGTVSKVLRETKEKVQPSKPKEELNHPHQDWWNRGDELWKYIKKTS
WNIKETSVHVTQMVGYEASKTASRAKHKLKESSYSESINGAVKGTALLLLDEIQQAENRIRQIPQFAWDVQE
AVEQHSSVIQRTAYPDELPELSELLNEQLKHEEARWQAVKKQSRDKLQELIAPITRLAQEKWAQDLYFQLG
EELRKERQDRWKDIQQFDEIMAEAVGQFAEMARELDSEAVRLAEHGHSGGKELQEKVAKWLRDLSKLKGK
VKAGVAKITGTSLDNFSRSGMLARGMSEWAEDLKQSYLQETLQEGSAVAAELFERTLMEVVEENRTHFAK
ESDPEAERFLKRLALALKHAAENTTVYPPTPEEILAGSRSLPEDIRHWAEKKVVSGAISAAFRGGFKLVTGTF
SLPVRVVIRGAKTGGTLYRGVRAINRSVRLGQGPATQVKSKFINQELSKTAFRLTLSLSPLVAWGMAASITA
GRLYNEKDYPEKIIKNIVIDLPEELLWIGGYAGINAAIRAHAEKAIQQAIQHALDEQADKLALRINKEIAGKSADV
NVEIIPQETSVSPAETAQSTPEPLSDFASTSQLTMPELIDIQDNNSAQQPKVRRKRDVSVESEISIDNLNIINA
NTREDKVNSEIKSELRSELKRFENSDANSPMSDVERAIFIDLFLYKNKYEVSESQQDYKNTWLKFRRELESQ
ENKEIKEYLRFRSIIEAYEIYDKKRLDDDTIPEAGTIIKEVIDFFQKLKKENPITFMKLAEAMVKFQYYYEEEDEN
EDRYFKMAEIYYFLNKTENEKKSKTFHLDIIDKYPNENNRLLDEFFLNKNNNNPDLDEIIYKLQSMQEKYRES
YEMLSKVENIHQVLSDDSKNEENIFLDNRIIAAQVFDGSINISLQDKKKWLNRYDQIRNEEGSDGWKLMHIES
ILINLRRINTAINLTAMKSESALLLIDKLLNFQKKARENILHISETPHEDFTSYSQFKTRKELGNDDSKYYAQFD
NYKDNHDAEKEAKEILSQVVARASLSFSELFDKVESIKLFSFVYKNRDGGAPLAAPGRTVVIKFPGKDTGGL
VISNLFLRNHVKRISTKEMEDLKPLTEGMYTRATQHRSLGSYYHIGSQSEHTNALEILSGMNKEELKTHLKK
QGIWFGEPALFSNEYPKQENTGHLENTTLKNAIIGVSTIQNNAAANYLRSTMYESTGWEKLGDRFIPFYEIGR
RKHYDREYEINSEQLTLDIITSIAIAYPAARGIVATIRSSAIPSILKSGLRGSALFKSLSLELGKMGFNASKVFGG
AVYELIEPYPINSHLNRHNVFNKVKDTAWEFHTDVGLKGGGLKDFIDRFTKEPKEITISGYKFKRIKYNQENF
DTMQRMALDYAYNPDSKGKIAQAQQAYKTGKEDYNAPQYDNFNGLSLDKKIERYISPDTDATTKGVLAGK
MNESIKDINAFQTAKDAQSWKKSANKANKVVLTPQNLYLKGKPSECLPESVLMGWALQSSQDAKLSKMLM
GIYSSNDITSNPLYKSLKELHANGNASKFNASATSISNINVSNLATSETKLFPTEISSVRVDAPKHTMLISKIKN
RENKIKYVFYDPNYGMAYFDKHSDMAAFFQKKMQQYDFPDDSVSFHPLDYSNVSDIKISGRNLNEIIDGEIP
LLYKQEGVQLEGITPRDGIYRVPPKNTLGVQETKHYIIVNNDIYQVEWDQTNNTWRVFDPSNTNRSRPTVPV
KQDTNGEWFKHSETGLKGGGPIDDIRKYIARKSAIKIFNQSINYSATKWPPEPIDKNIHMIWIGTKNISEKNIKL
SIDTAKKNPDYNTSIIYDSGISGHEGAKKFMLEKFQDSNVNIIDFRKKSYFSQLKQEPSFAYYEQVIAENKYAQ
ASDILRLLVLKYEGGIYKDIDDIQVKGFGSLTFPKGIGVMREYAPEAGKATAFPNTPIAVTKNNPIINKTLDLAV
SNYQRGEKNVLKLAGPDVFTQALYQEIPGLDSKVLNAQLYQLELAKRQALGVPLEKPKNFADEQLTSAEKE
KINRPYQSIRGLSGYVENGADHSWAVDTNIPSTSTQTSTIVTPLAPKTEMLPPVPSSSTKSSTSAPVLQEKIS
YNLATDIDATDYLNQLKQKTNINNKISSPAGQCESLMKPVSDFMRENGFTDIRYRGMFIWNNATEQIPMNHF
VVVGKKVGKDYVFDVSAHQFENKGMPDLNGPLILAAEDWAKKYRGATTRKLIYYSDFKNASTATNTYNALP
RELVLESMEGKTFITSPNWYQTFKRTHNIHPEVTVSDPATFSLNYSVNPTAENLSPPPPPPIPSHGQVPKTV
TPPPPPMRSPLSLSQPLERLPANKTKPIGFNPGENKASFSKLEEAGKHYYKDDKSRQAAPVNTMSDFDNRY
LSHTTEAPAPSNVAHLAPGNIYNTKVTAKGAEKPAYDIYISKDGESLITSSSYKVDDITTDSKFGKPLPYSEIM

FNSLKKSGVDPKNLKRSVQASIENKVTQDVISAIGTRIQRGQVIRVSPTENPDAFYTLLGTDNCKATLHMLNQ
HAEEFGHKVVTSIEFKGTGYLVMNIGTSTQTSTIVTPPPMPGTSQLVQ

SEQ ID NO: 29 (PAU_02805)

MPNKKYSENTHQGKKPLIKSEANNEHAIDNSPLGIGLDLNSILGNNSASLSQIHDYSFWKENISEYYKWMVV
VKAHLKQLDWTLKSMDSPESAGANIAKNIGTTTLQTLLNTGGSIAGGAIGGAIGSAIAPGVGTIAGMGIGALA
GTGLNYLNDTAIEKLNEKLEIAYPYPKTRNMIFDINNYDKNPLIKAIKKKTKKDNLKVMAGSSLTSQLLGRITPI
KIPAYKLADLAVSHHRALAGLSSDKARHILDFTNSIREVLNESHSDAVAFMRKNYGDNAMGLSGLSSKIKGD
KLTLDTLARTRNKIENRINSINKQTLKLSSKNSNE

SEQ ID NO: 30 (PAU_02806)

MEREYSEKEKHKKHPIQLRDAIEQHAEETANNSLGLGLDLHQAINTPKVPKDNYNEENGDLFYGLAAQRGR
YIKSVNPNFDPDKTNSSPMVIDVYNNHVSNTILNKYPLDKLGKLYGNPQKYAKDIKVTNSLQQDVAASKRGW
YPLWNDYFKAGNENKKFNIADIYKETRNQYGSDYYHTWHEPTGAAPKLLWKRGSKLGIAMAASNEKTKIHF
VLDGLNIQEVVNKQKGSTPLEQGRGESITASELRYAYRNRERLAGKIHFYENDQETIAPWEKSPELWQNYIP
KNKSQNESSTPQRNNGALYRLGGPFRKLRASLRKRS

SEQ ID NO: 31 (PAU_02807)

MVHEYSINDRQKRHSFSSANPIDPEVTNRENSRHRFPKDNYNKGHGDLFYGLAPERGKYIKEANPKFDPNN
PENAAMIIDVYNDEISRVILNNNANKISTNRLLNFIYNFRKNRLENLMKNPEKYAKDIKVKDNLRENISPKKIEK
YPLWNDYFEAGIRNKKFNIAEIFKETASQYNSDYYHAWHIGGNSAPRLLWKRGSKLGIEIAASNQRTKIHFIL
DGLKIEDVVNKTKGPAPLKAGPGESITASELRYAYRNRARLAGRIHFYENGKETIAPWDKDPELWQKYTPKN
RSGMEL

SEQ ID NO: 32 (PAU_03332)

MLKYANPQTVATQRTKNTAKKPPSSTSFDGHLELSNGENQPYEGHKIRKIKGLRQHLADRSLNKGHISPLM
NKGLLVGSKDVSIDIPVIAHRYDSSHQLTDAEPLKADSHSNHLDPFYGVIAGFRGDQVTSSESGSGSIGVHW
GKNTLDSNIMGVNVVNGASGTVGIRIALKDIQHGSPVIVTSGALSGCTMVYSVKNGYFFAYHTGQKPGNNE
WKTGRQGVVATYLSHQALSPDSEPMTVGEQNNDLVNIFANYDQSVITYMGKPGVLIDKMAENVGVFNYDEI
KPEKPAIRAGYSYALLAKDDKGKVNVKVLSEDVIVSSGKQGNTVKAINSLKKRLL

SEQ ID NO: 33 (PAU_03337)

MPRYANYQINPKQNIKNSHGKSSSSDFSSGYLSFSNNSLDDPFIRQQVKREFIWEGHMKEIEEASRLGNFA
VSFRAAGGPTLRALGKGAAAKGHDILEKTIKPGSINKAYPKDEASDVIKKVQEAGIEGYVGHWDKKTGRLLGI
YMSSGHGLSDEQVNGKIYPIDLNNLEASLSALKAKENWAALPFTGDYDMHDMISFTGQPHSVPSNSSEERK
IIDRINRLVARSDSNRPFGDIEHNVIRHGAQVSYPAFAMDKEKEEIKKHGGIVKAVAEPGEFPVAIVSKGKWTI
ANNIDELNQFYNSIGAKMKVSWKPGAENPGFVSNPQRPGMARFSRKR

SEQ ID NO: 34 (Plu1651)

MPNKKYSENTHQGKNPLMKSGANNEHDLQDSPLGIGLDLNSMLVNSSTSLSQIQDYSFWKENISEYYKWM
VVVESHLKQLDWTLKSMDSPESAGTNVAKNMGVTALQSLLNTGSSIAGGAIGGAIGSAIAPGVGTIAGAGIG
ALAGTGLNYLNDTAMSKLSKKLEIAHPYPKTRNMILDINNYDKNPIIKAIKKNVNKDNLKVTAGSSLTSKLVGT
VTSPIKFPAYKFAELAVSHHRALEGLSDDKARHILDFTNSIREVLKESHSDAVAFMRKNYGDNAMGLSGFSS
KIKREKLTLNTLAKTKNEIENRINSINKQTLKVSSRSRNE

SEQ ID NO: 35 (Plu1671)

MLSTEKHNKDTKHPRNREKKFSIQPENSTQDDEDIKNNSLGVGLDLDQMIRNTSSTLTNAPQKPEDGYYYHI
SRGNNLQSFLQNGFKPQGSPGPTLSEEDFSRRKIGIIKLIYSIIATTINKNRKAKKISKDNFLMPQEFWHEFKN
FYQNIPTQTNIDDQLLKKSITESIDKLDQNKFMEKHSDRKQTIINNEREAILQQDERINEIISSRAKMIQQREAE
NTEGYIYLAPHKNTLLEYMKHLQEEKNLFLILAVKEDIFTEKGLEQDPQEPHGAVRYKGALSTEELNFVNQE
GQICAIPASIGEMDYGDFILNQQQVIDFCKK

SEQ ID NO: 36 (Plu1672)

MPINDLKKKFEISPQAAQAIGAPARSNSSKQAEHQTEHLELDTSKNRRDRKDLNAQATPNQQHTKKLETEV
NNGGNKSKAQAHTPDLVMKKESSVTPNTRKSPNEKIKAEDIFHRYKDRFSPSDRELPFEIMNEITNNGIAFS
SEKAPESHLDKVKDKKFTLRHYTSGNGQEKPTFNEIGSNFNLVNEGIKTLKRTQGSNTNEDDWNRLGNTAF
TFFLLAIDGEVSDRKFLSNTTHFAEIDIENPAELKELGLDETEFFASPDLLHEKNLSQAPAVKGKLSDLKSLLL
KQSGIKPVQLQSLGAKGILERIDSKFNGSLEIKIPGNVKVKEWKKVEK

SEQ ID NO: 37 (Plu1690)

MPNSKYSEKVNHSANGAEKCSIHSNQYNINNCTLGLGLDLNKKLRTGNERNIEGAQPFIPFPSKQKQYSTSP
IAMADILNESALTSQPIITDLINPQKIKMSDGVKNILNNKEGGGDLVFKALQIKPSDETLPFNALKIVDTYQEEM
PNKDMSISAYWAPQGGYVDIPAQPDISRHPQYVFTPNFSGCSFVVDKMNEDTLRVRHVQGGQEDVEYNN
QNIDHGMGMITAMEFRDYGYHEADDKVIENTYGFAFLKFNQEKKQWQLHYQKIAAAPNIINIKTKSSWLPFS
KPSIEADTFTFKNMKVPGYSRKNINNN

SEQ ID NO: 38 (Plu1691)

MPKLTELLSRFENPIQNQPNHISKKNPISNSKVLNNSEEKTAPLELKHDDSKIKSQVSIPNLVKKNEKPAASNT
PNNSHEKVKAEDIFNRFKSKFDPYDRELPFDIMNKITNNEIKFSSEKSKDDYLAKVKDKKFTLRHYTAGTGQE
KPTFDEISSNFNLVNKGIKTLNRTQGSNTNEDDWNRLGNTAFTFYLLAIDGEVSNRKFLSNTTHFAEINIEDS
EELKELGLDQAEFFASPDLLHEKNLSQAPAVKGKLSDLKSLLLKRSGISSVQLGRLDAKAILKSIDNEFGNSL
EIKIPGNVKVNKWNKI

SEQ ID NO: 39 (Plu1712)

MPRYSNSQRTPTQSTKNTRRTSPSSNSSTEHLSLSNAPTNDSSVRQEVKEKFIWEGHWEGHMEAIEKASIL
GNFAVSFRAAGKPTLEALGKGAAAKGHDILEKTIKPGSIEKAYPENEASDVIKKVREAGIEGYVGHWNKETG
RLEGIYMSSGHGLPNGQVNGKIYPIDLNNLEASLAPLKEKKNWAALPFTGDYDMHDMISFTTQPHSVPSNS
SEEKKIIDRINEYIAKSDSNRPFEDIEHNVIRHGPQVSYPAFAMDKEKKEIKERGGIVKAVAEPGEFPVAIVSK
GKWTIANNINELEQFYNSIGAKMKASWKPGAGNPGFVSNPQKPGMARFSRKK

SEQ ID NO: 40 (Plu1713)

MFSTYSSKNDNQTINKINTEEKHENTETDNHLEINLEHTGKSKPDIEPKDVTTGTINAGTLLYKTTAIPEFLDN
AKSLGLAEYEKRHKDIQDYLNLGKAEDAEKLKNKSQWAGQYFALEKSYDEYANEAPDSYNNLLKNAGKDLL
ENTEEVKVFLYTFKVTKDIKVLKPHNNSNSYYVGDTEGWEKAKEIMNDVQSQSEKNDNPFPELKNLEDKNF
LLEELGEKGYAWMGPLHAKEGAEKGTEFSYELAISPNLLRQHLTLESEELLGTYKNRYGYWDKK

SEQ ID NO: 41 (Plu1714)

MKKTDEKYGQYEYKDEDITSYPIAWTNPDNGKIYIGINSPEYSHLNNKGESELNLAKIISTIIHESLHASSHQH
KGLQSQTDTGADNLNYDEYVTDYFAREVYKQILPDKDYVANCFTKGLGGENKIWGGNIVEFMIQ

SEQ ID NO: 42 (Plu2400)

MVYEYDKTIERRRNPSIQLNNNEKSSEQALELSQNNPLLHDLITSNNLRKEAAVFAKRIGPSYQEILDELEHL
HHLSGNEQLAAGFELHRRITHYLEEHPDSKRNTALRRTQTQFGDLMFTGTLQKIRHSLLEMAETRPEMASHI
YQIAREEVKGNTPGLTDLMVRWVKEDPYLAAKTGYQGKIPNDLPFEPKFHVELGAQFDDFKKWLDTAQSK
ELLTHTRLDEQNKQVHLGYSYNELLDMTGVESVQMAVYFLKEAAKQAEPGSTKSQEDILLHRFANPTYLAQ
LEHSRLAQIEAIYHSSHDTDVTAWDQQFASDALTQFNHQLNNTVDLNSQLSLLLKDRQGLLIGESHGSDLNG
LRFVEEQMEVLKAHGVTVIGLEHLRSDLAQPLIDKFLASGNEPMPAELAALLKTKHLSANLFEQARSKQMKII
ALDNNSTTRPTVEGTQHGLMYRAGAANNVAVERLRQLPAGEKFVAIYGNAHLQSHEGIDHFLPGITHRLGL
PALKVDENNRFTAQVDNINQRKRYDDVVELPRIQLTS

SEQ ID NO: 43 (Plu2401)

MEHEYSEKEKPQKCPIQLRDSIEHDKEDINTTTPLELNSQYTNRKRAGLRERFSTTLQRNLPGHSMLDRELT
TDGMKNQESRFSPAMIMDRMMHFGVRTRLGKVRNSASKHGGQVTFKFAQTKGTFLDQIMKHKDTSGGVC
ESISAHWISAHAKGESIFDQLYVGGQKGKFHIDSLVSIKQLQMDSYLDDEQSTMTEYWLGTQGIQPIMQKND
VDEHSSKVVGQTGNKGTTDLLRAILDTGDKGSGYKKISFLGKMAGHTVAAYVDDQKGVIFFDPNFGEFSFP
SITSFSRWFTDDFWPKSWYNLEIGLGQQFEVFNYELKKS

SEQ ID NO: 44 (Plu2514)

MYDSKKKNSEPTTKKKFERSNYSQWDDSINHYEDMNRARIKNRNDILTTVDYFGEKKKTMHTFEYQSDIKH
DTNFNNKNKSLFESFAASFVLQNPSFFSGVIDKLSKKLFNIISKIDERNNFQKKLYDFIEKDTSPEGQFGRFTL
GKNEILNVLQVKSDTPQLFVKKMLLIKSLGAFIIDFSSKDIGNYDFIFDGKGREVNDIIEKNRPTNLFKVRGRTN
IKSSQHRSDIGILDTPTFDSLTEEQKSFLTIPELTKRRPLFRTFTHELDAEDKRVVESVFVNRTFDCDSPLIGS
VSGSTSCVLVAADILFPDMTMVERKKLAIATFAFLVGGGYHSATEVFDVAYPGLDLNKEIEELIENNPIQENA
GVATLRQLIGNSGF

SEQ ID NO: 45 (Plu2515)

MPISNLAKESEVRAVKDIPCKNIETDNHLEIGLSSGLSRSKDTSKFKKNSINTIKLIDDIIALHNDPKGNKLLWN
DNWQDKIINRDLANIFEKIDESVSELGGLEMYQEMVGVNPYDPTEPVCGLSAQNIFKLMTEGEHAVDPVEM
AQTGKIDGNEFAESVDQLSSAKNYVALVNDRRLGHMFLIDIPSNDQETVGYIYQSDLGQGALPPLKIADWLN
SRGKDAVSLNKLKKLLSREFNLLSDDEKRALISETLDIHKDVSNVELDRIKRDRGVDIYLTEYDVNNFYENIET
LKSKLSNYDKKLSKPK

SEQ ID NO: 46 (Plu1649)

MLANVLPNLASFLKYEKETPLFFIEDGFNFQNLNPGRVPLIKTPEQRKAGDTQSPAFLCSGVILRGTIHSNDY
KFWQPSPSSIKSGGVSFSYLRKDAKFKRLAYGYKNGFIIFPEHIAPEDRVDFSVLCAFPIDGYTNERANQGC
GENITKAKDKGKSCQEQNVTNSDDWIKNYRKVNSQDFFQCGFNVTKDVNNPAIAFYQMLESIKKLPRTPNT
PPKQNEIRISTWEESDPNKLPIEALFYSENSGLADAQKDQRDYKNATGKFLPIVKMLLPRTLNEDALFKFNIK
DQVINP

Leader Sequences (e.g. with SEQ ID NO: 47 – 92 corresponding to amino acids 1-50 of SEQ ID NO: 1 – SEQ ID NO: 46, respectively)

Sequence ID	Amino acid sequence	Sequence ID	Amino acid sequence
SEQ ID NO: 47	MMREYSNEDDFIKEKTNLVKSENVE ADNYLETEYLTYLAKLIGMTERENH	SEQ ID NO: 70	MISTFDPAICAGTPTVTVLDNRNLTVREIVF HRAKAGGDTDTLITRHQYD
SEQ ID NO: 48	MFQNRIRNEKTTQSGKGKTLDRMTD SLYLEIPNVEAVTLAYQKLTSKYRK	SEQ ID NO: 71	MEREYNKKEKQKKSAIKLDDAVGNNEEN MDMTSPLELNSQYTNRKRPGLR
SEQ ID NO: 49	MEREYSEKQKNPSKLSRKTAISERIA ALERSGLSNSNQPVPQFARPYTSN	SEQ ID NO: 72	MVYEYAKTNDRKRKLSTQSDNYEEKSFS PVLDLSRNNQNTPNMEDEYETP

SEQ ID NO: 50	MSNYEYDIVTQHDTYQIKDNEYTVVN GKYWQYEQEGNKNNNKVSISLMKE	SEQ ID NO: 73	MVFEHDKTVERKRKPSIQLGNDKEKSSEQ ALELPQSKQNNPLLHDLITSN
SEQ ID NO: 51	MEHEYNEKEKQRNSAIKLNDAIRNNE ENMDMTSPLELNFQNTNRKSRGLR	SEQ ID NO: 74	MKGIEGVIMLSHDILPEKLLVSEKKHENVG SYFSDDIGEQSEQTEVSHFN
SEQ ID NO: 52	MPNKKYSENTHQGKKPLMKSEANN EHDIQNSSLGIGLDLNSMMGNSSTSL	SEQ ID NO: 75	MPNKKYSENTHQGKKPLIKSEANNEHAID NSPLGIGLDLNSILGNNSASL
SEQ ID NO: 53	MEREYSEKEKHKKRPIQLRNSIEQHE EETANNSLGLGLDLNQATNPPKVP	SEQ ID NO: 76	MEREYSEKEKHKKHPIQLRDAIEQHAEET ANNSLGLGLDLHQAINTPKVP
SEQ ID NO: 54	MMEHEYSKEEEKKRQQSKPNNATH DESNLPLELEKHFNARTPATAHSKW F	SEQ ID NO: 77	MVHEYSINDRQKRHSFSSANPIDPEVTNR ENSRHRFPKDNYNKGHGDLFY
SEQ ID NO: 55	MLKYANPQAVPTQRTKNTAKKPSSS SSFDGQLELSNGEWSKHSEMGLKR G	SEQ ID NO: 78	MLKYANPQTVATQRTKNTAKKPPSSTSFD GHLELSNGENQPYEGHKIRKI
SEQ ID NO: 56	MMREYSNEDDCTKEKTNLVKSENVE ADNYLEMEHLTYLAKLISMTERENH	SEQ ID NO: 79	MPRYANYQINPKQNIKNSHGKSSSSDFSS GYLSFSNNSLDDPFIRQQVKR
SEQ ID NO: 57	MIFKMLNLAVFYLLGNIFHYLICQKFIC YFCSVLKSVTMFLTKVAVQIAL	SEQ ID NO: 80	MPNKKYSENTHQGKNPLMKSGANNEHDL QDSPLGIGLDLNSMLVNSSTSL
SEQ ID NO: 58	MEREYSEKPKNLSQLSRKTAISERRA MFERNASSNNEQPVPQFARSYTSN	SEQ ID NO: 81	MLSTEKHNKDTKHPRNREKKFSIQPENST QDDEDIKNNSLGVGLDLDQMI
SEQ ID NO: 59	MKYDPRLRTWVEDDFDYEKNFKKQ TDYINYKDLEKQLKENVDYYALLDEN	SEQ ID NO: 82	MPINDLKKKFEISPQAAQAIGAPARSNSSK QAEHQTEHLELDTSKNRRDR
SEQ ID NO: 60	MPNKKHSENTHQGRKPLIKSEANNE HDIENSSLGIGLDLNSTIGNNSASL	SEQ ID NO: 83	MPNSKYSEKVNHSANGAEKCSIHSNQYNI NNCTLGLGLDLNKKLRTGNER
SEQ ID NO: 61	MEREYSEKEKHKKRPIQLRNSIEQHE EETANNSLGLGLDLNQATNPPKVP	SEQ ID NO: 84	MPKLTELLSRFENPIQNQPNHISKKNPISN SKVLNNSEEKTAPLELKHDD
SEQ ID NO: 62	MMEHEYSKEEEKKRQQSKPNNATH DESNLPLELEKHSNARTSATAYSKW F	SEQ ID NO: 85	MPRYSNSQRTPTQSTKNTRRTSPSSNSS TEHLSLSNAPTNDSSVRQEVKE
SEQ ID NO: 63	MSNYEYDIVTQHDTYQIKDNEYTVVN GKYWQYEQEGNKNNNKISISLMKD	SEQ ID NO: 86	MFSTYSSKNDNQTINKINTEEKHENTETD NHLEINLEHTGKSKPDIEPKD
SEQ ID NO: 64	MEHEYNEKEKQRNSAIKLNDAIRNNE ENMDMTSPLELNSQNTNRKSRGLR	SEQ ID NO: 87	MKKTDEKYGQYEYKDEDITSYPIAWTNPD NGKIYIGINSPEYSHLNNKGE
SEQ ID NO: 65	MFKYDTSEKMAKFGKGKTSDGMLLD TLYLEIPDEKAVMSAYKSQILDELR	SEQ ID NO: 88	MVYEYDKTIERRRNPSIQLNNNEKSSEQA LELSQNNPLLHDLITSNNLRK
SEQ ID NO: 66	MLKHANPQTVSTQRTKSTAKKPSSS SSFDRQFELSNSENQPGEGNKDWTI	SEQ ID NO: 89	MEHEYSEKEKPQKCPIQLRDSIEHDKEDIN TTTPLELNSQYTNRKRAGLR
SEQ ID NO: 67	MPRYANYQINPKQNTKNSHGKSSSS NFSSGYFSSSNNSLDDSLIRQQVKR	SEQ ID NO: 90	MYDSKKKNSEPTTKKKFERSNYSQWDDS INHYEDMNRARIKNRNDILTTV
SEQ ID NO: 68	MREYSKEDDCVKEKTNLAESENVEA DNYLEMDCLNYLAKLNGMPERKDHS	SEQ ID NO: 91	MPISNLAKESEVRAVKDIPCKNIETDNHLEI GLSSGLSRSKDTSKFKKNS
SEQ ID NO: 69	MPIIGHKEDLIRTERSSVDLTRSSNN RQTDNLELNIPQHKRDNKDIEHAV	SEQ ID NO: 92	MLANVLPNLASFLKYEKETPLFFIEDGFNF QNLNPGRVPLIKTPEQRKAG

SEQ ID NO: 93 (*Photorhabdus asymbiotica* strain ATCC43949 PVCPnf operon, *pvc1 – pvc16; e.g.* corresponding to genes PAU 03353 to PAU 03338 of the sequence of GenBank accession no. FM162591.1)

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SEQ ID NO: 94 (*Photorhabdus asymbiotica* strain ATCC43949 PVClopT operon, *pvc1 – pvc16*; e.g. corresponding to genes PAU_02112 to PAU_02099 of the sequence of GenBank accession no. FM162591.1)

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SEQ ID NO: 95 (*Photorhabdus asymbiotica* strain ATCC43949 PVCPaTox operon, *pvc1 – pvc16*)

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SEQ ID NO: 96 (Pnf epitope)
TGQKPGNNEWKTGR

SEQ ID NO: 97 (PVCpromF)
TATCATATGTCTACAACTCCAGAACAAATTGCTG

SEQ ID NO: 98 (PVCpromR)
ATCTCTAGAACAGATATTCCAGCCAGC

SEQ ID NO: 99 (ParaINF)
GGCGTCACACTTTGCTATG

SEQ ID NO: 100 (ParaINF)
TCGGTGGCAGTAAATTGTCC

SEQ ID NO: 101 (F1 primer)
ATGTCTACAAGTACATCTCAAATTGCG

SEQ ID NO: 102 (F2 primer)
GACTCCCTTGAGGGTACGG

SEQ ID NO: 103 (F3 primer)
TTCTGATGAGAGTGATGGTAC

SEQ ID NO: 104 (F4 primer)
TGAATAAAGAATTCAGTCAATATC

SEQ ID NO: 105 (R1 primer)
TAGTGGCTGATGAAAGTCTG

SEQ ID NO: 106 (R2 primer)
GGAAGCCAAAGATAATGAAGTG

SEQ ID NO: 107 (R3 primer)
CATTTCTTCCCTATGGTTG

SEQ ID NO: 108 (R4 primer)
TTAAATTCCTACAAGATTATCTTT

SEQ ID NO: 109 (tBid amino acid sequence)
RSSHSRLGRIEADSESQEDIIRNIARHLAQVGDSMDRSIPPGLVNGLALQLRNTSRSEEDRNRDLATAL
EQLLQAYPRDMEKEKTMLVLALLLAKKVASHTPSLLRDVFHTTVNFINQNLRTYVRSLARNGMD

SEQ ID NO: 110 (*E. coli* Sequence Optimised tBid bases)
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TTCACACCACTGTTAATTTCATCAATCAGAACCTGCGTACTTATGTGAGATCTTTGGCGAGAAATG
GTATGGAT

SEQ ID NO: 111 (BaxBH3 peptide (aa59–73))
LSESLKRIGDELDSN

SEQ ID NO: 112 (*E. coli* Sequence Optimised BaxBH3 bases)
CTGTCGGAGAGTTTGAAGCGTATAGGTGACGAGCTGGACAGCAAT

CLAIMS

1. Use of a *Photorhabdus* Virulence Cassettes (PVC) effector leader sequence, for packaging a payload into a PVC Needle Complex;
wherein the payload is one or more selected from a polypeptide, a nucleic acid, or a combination thereof; and
wherein the leader sequence and the payload form an effector fusion that is distinct from a wild-type PVC effector protein.

2. The use according to claim 1, wherein the leader sequence comprises amino acid residues 1-50 of a PVC effector.

3. The use according to claim 1 or claim 2, wherein the leader sequence comprises an amino acid sequence having at least 60% sequence identity to one or more sequence selected sequence from SEQ ID NO.: 47 - SEQ ID NO.: 92.

4. The use according to any one of the preceding claims, wherein the PVC effector comprises an amino acid sequence of one or more sequence selected from SEQ ID NO.: 1 - SEQ ID NO.: 46.

5. The use according to any one of the preceding claims, wherein the PVC effector comprises a sequence selected from SEQ ID NO: 4, SEQ ID NO: 22, SEQ ID NO: 25, SEQ ID NO: 30, SEQ ID NO: 32 and SEQ ID NO: 46.

6. The use according to any one of the preceding claims, wherein the leader sequence is covalently fused to the payload, preferably at an N-terminus of the payload.

7. A method for manufacturing a PVC Needle Complex comprising a payload, the method comprising:
   a. contacting a PVC Needle Complex with an effector fusion comprising a PVC effector leader sequence fused to a payload;
   b. wherein said payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof; and
   c. wherein the effector fusion is distinct from a wild-type PVC effector protein.

8. The method according to claim 7, wherein said contacting occurs within a cell, in a cell lysate, or in a purified cell lysate.

9. An *in vitro* and/or *ex vivo* method for delivering a payload into a cell, the method comprising:
   a. contacting a cell with a PVC Needle Complex comprising an effector fusion;
   b. wherein the effector fusion comprises a PVC effector leader sequence fused to a payload;
   c. wherein said payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof; and
   d. wherein the effector fusion is distinct from a wild-type PVC effector protein.

10. A method for suppressing a pest, the method comprising:
    a. contacting a pest, or a target area comprising a pest, with a PVC Needle Complex comprising an effector fusion;
    b. wherein the effector fusion comprises a PVC effector leader sequence fused to a payload;
    c. wherein said payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof; and
    d. wherein the effector fusion is distinct from a wild-type PVC effector protein.

11. A PVC Needle Complex, for use in a method of treatment;
    a. wherein the PVC Needle Complex comprises an effector fusion which comprises a PVC effector leader sequence fused to a payload;
    b. wherein said payload is one or more selected from a polypeptide, a nucleic acid, or a combination thereof; and
    c. wherein the effector fusion is distinct from a wild-type PVC effector protein.

12. A PVC Needle Complex comprising an effector fusion;
    a. wherein said effector fusion comprises a PVC effector leader sequence fused to a payload;
    b. wherein said payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof; and
    c. wherein the effector fusion is distinct from a wild-type PVC effector protein.

13. An effector fusion, comprising a PVC effector leader sequence fused to a payload;
    a. wherein said payload is one or more selected from a polypeptide, a nucleic acid or a combination thereof; and
    b. wherein the effector fusion is distinct from a wild-type PVC effector protein.

14. An isolated PVC effector leader sequence.

15. The method, PVC Needle Complex for use, PVC Needle Complex, effector fusion, or isolated PVC effector leader sequence according to any one of claims 7-14, wherein the leader sequence comprises amino acid residues 1-50 of a PVC effector.

16. The method, PVC Needle Complex for use, PVC Needle Complex, effector fusion or isolated PVC effector leader sequence according to any one of claims 7-15, wherein the leader sequence comprises an amino acid sequence having at least 60% sequence identity to one or more sequence selected from SEQ ID NO.: 47 - SEQ ID NO.: 92.

17. The method, PVC Needle Complex for use, PVC Needle Complex, effector fusion or isolated PVC effector leader sequence according any one of claims 7-16, wherein the PVC effector comprises an amino acid sequence of one or more sequence selected from SEQ ID NO.: 1 - SEQ ID NO.: 46.

18. The method, PVC Needle Complex for use, PVC Needle Complex, effector fusion or isolated PVC effector leader sequence according any one of claims 7-17, wherein the

PVC effector comprises a sequence selected from SEQ ID NO: 4, SEQ ID NO: 22, SEQ ID NO: 25, SEQ ID NO: 30, SEQ ID NO: 32 and SEQ ID NO: 46.

19. The method, PVC Needle Complex for use, PVC Needle Complex, effector fusion or isolated PVC effector leader sequence according to any one of claims 7-18, wherein the leader sequence is covalently fused to a payload.

20. An isolated nucleic acid comprising a nucleotide sequence which encodes the isolated PVC effector leader sequence of any one of claims 14-19.

21. An expression vector comprising an isolated nucleic acid molecule of claim 20.

22. A host cell comprising an isolated nucleic acid molecule of claim 20, or an expression vector of claim 21.

23. The host cell of claim 22, wherein said host cell is one or more a selected from a mammalian cell, an insect cell, a yeast cell, a bacterial cell, and/or a plant cell;
preferably wherein said bacterial cell is an *E. coli* cell.

24. The host cell of claim 22, wherein said host cell is a *Photorhabdus* cell.

25. The host cell of claim 24, wherein said *Photorhabdus* cell comprises a *Photorhabdus* PVC operon operably linked to an inducible promoter.

FIGURE 1

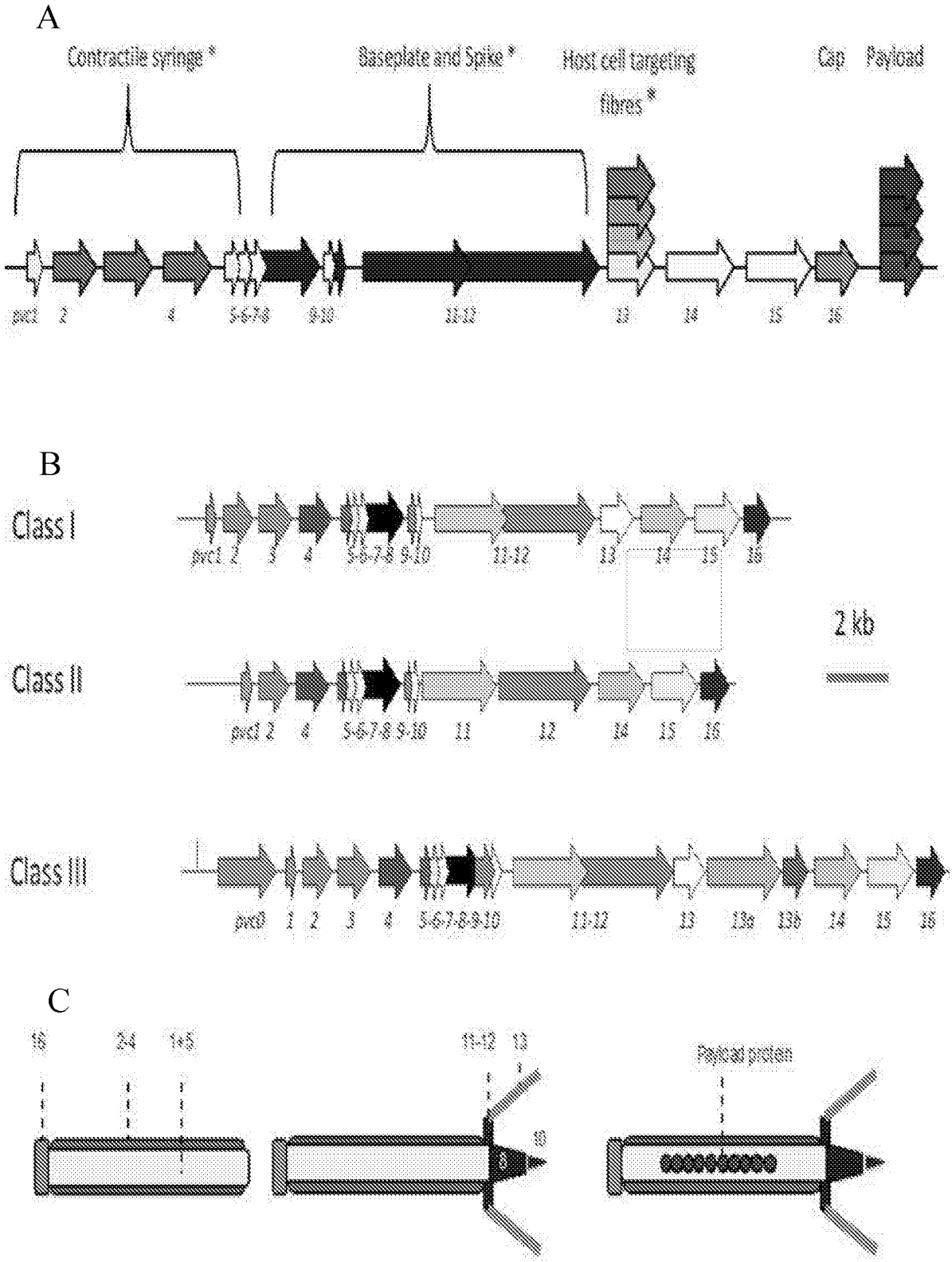
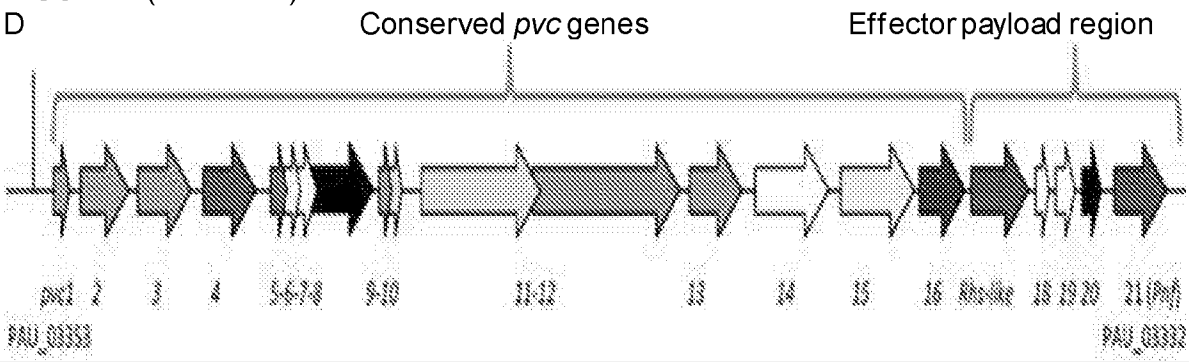

A
Contractile syringe *
Baseplate and Spike *
Host cell targeting fibres *
Cap
Payload
pvc1 2 4 5-6-7-8 9-10 11-12 13 14 15 16
B
Class I
Class II
Class III
2 kb
pvc1 2 3 4 5-6-7-8 9-10 11-12 13 14 15 16
pvc1 2 4 5-6-7-8 9-10 11 12 14 15 16
pvc0 1 2 3 4 5-6-7-8-9-10 11-12 13 13a 13b 14 15 16
C
16
2-4
1+5
11-12
13
10
Payload protein

FIGURE 1 (continued)

D



Locus	Locus Tag	PDB Hit	I Probab	E-Value	P-Value	Score	Protein Function/Description
PVCpnf_1	PAU_03353	6RAP	99.8	3.70E-24	5.90E-29	147.9	Inner sheath tube protein
PVCpnf_2	PAU_03352	6RAP	100	2.30E-60	3.70E-65	427.9	Major outer sheath protein
PVCpnf_3	PAU_03351	6J0N	100	1.70E-74	2.80E-79	524	Minor outer sheath protein and tail fibre docking region
PVCpnf_4	PAU_03350	6RBN	100	4.80E-52	7.60E-57	380.4	Outer sheath tube initiator complex subunit
PVCpnf_5	PAU_03349	6RAO	99.8	5.30E-23	8.40E-28	141.1	Inner sheath tube initiator complex subunit
PVCpnf_6	PAU_03348	3SLS	75.1	1.60E+00	2.50E-05	26.7	Unknown (NR)
PVCpnf_7	PAU_03347	6J0N	99.9	2.10E-28	3.30E-33	183.8	Outer sheath tube initiator complex subunit
PVCpnf_8	PAU_03346	6J0M	100	4.70E-61	7.50E-66	425.4	vgrG-like major spike protein
PVCpnf_9	PAU_03345	6J0N	99.8	1.10E-25	1.80E-30	151.7	Baseplate/spike hub organizing subunit
PVCpnf_10	PAU_03344	1WEY	71	2.40E+00	3.70E-05	26.9	PAAR-like spike tip protein
PVCpnf_11	PAU_03343	6J0N	100	2.00E-130	3.00E-135	1002.4	Major baseplate complex subunit
PVCpnf_12	PAU_03342	6J0N	100	3.00E-246	5.00E-251	1989.6	Major baseplate complex subunit
PVCpnf_13	PAU_03341	2XGF	90.7	7.90E-02	1.30E-06	48.9	Tail fibre
PVCpnf_14	PAU_03340	3C9P	28.5	3.80E+01	6.10E-04	31.5	Putative tape measure protein (NR)
PVCpnf_15	PAU_03339	6FVV	99.8	2.20E-23	3.50E-28	202.1	Putative payload loading AAA+ ATPase (NR)
PVCpnf_16	PAU_03338	6J0F	100	3.10E-62	4.90E-67	425.3	Tube terminator/cap protein complex subunit
PVCpnf_17	PAU_03337	5XNW	97.3	1.40E-06	2.20E-11	82.4	Adenylate cyclase ExoY virulence effector (P. aeruginosa)
PVCpnf_18	PAU_03336	2I0X	74.2	1.70E+00	2.80E-05	25.3	Unknown function
PVCpnf_19	PAU_03334	3L3U	75.5	1.50E+00	2.40E-05	23.4	Unknown function
PVCpnf_20	PAU_03333	5Z72	99.7	1.40E-20	2.20E-25	117.8	Unknown function (likely LysR type regulator)
PVCpnf_21	PAU_03332	1HQ0	100	2.60E-54	4.10E-59	390.4	>1HQ0_A CYTOTOXIC NECROTIZING FACTOR 1

FIGURE 2

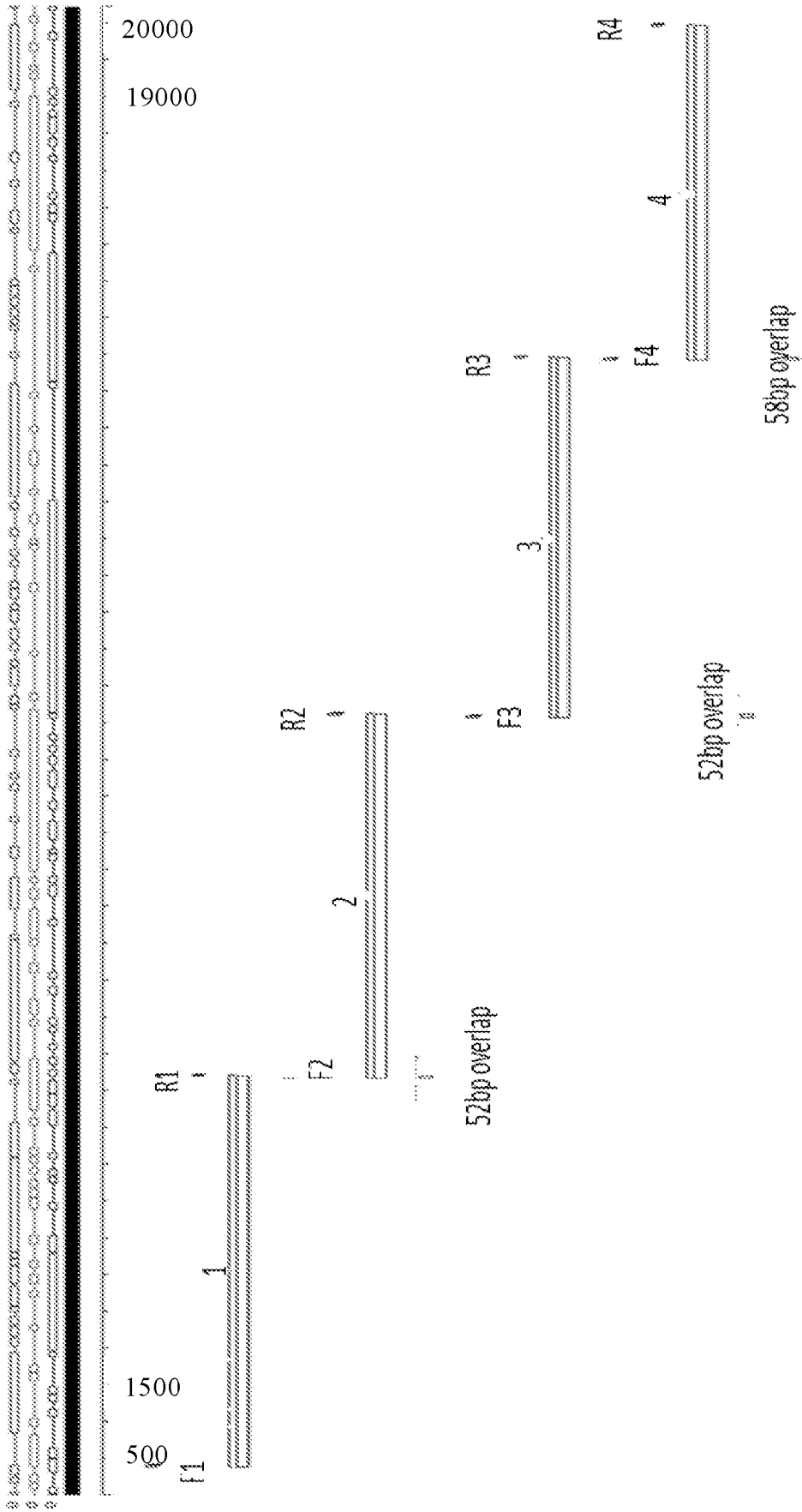

20000
19000
1500
500
F1
R1
1
F2
R2
2
52bp overlap
F3
R3
3
52bp overlap
F4
R4
4
58bp overlap

FIGURE 3

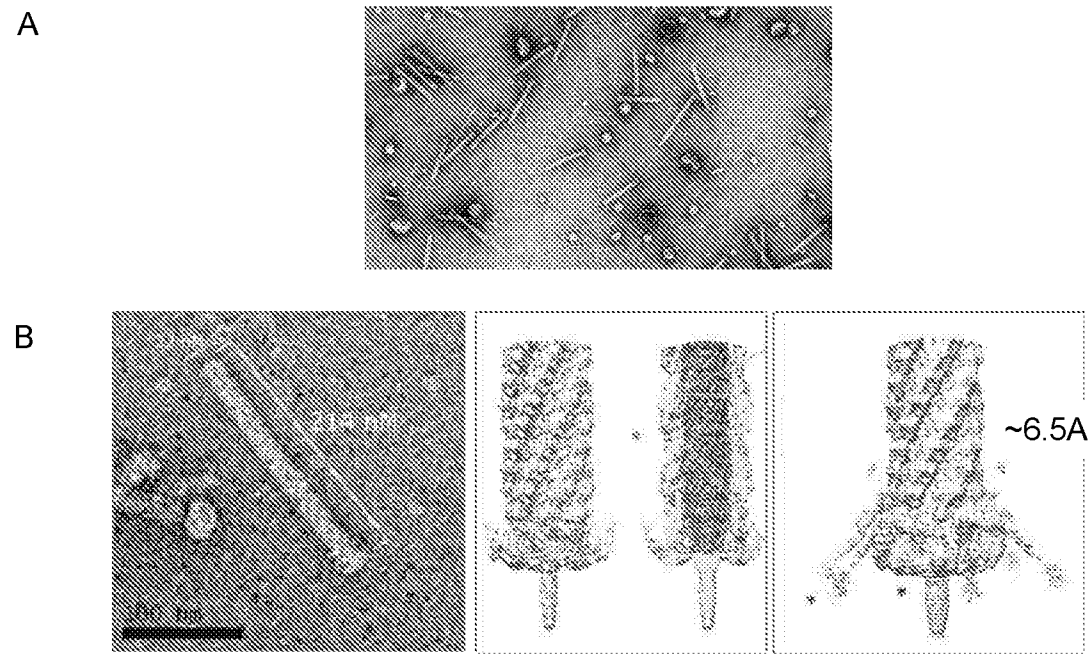


FIGURE 4

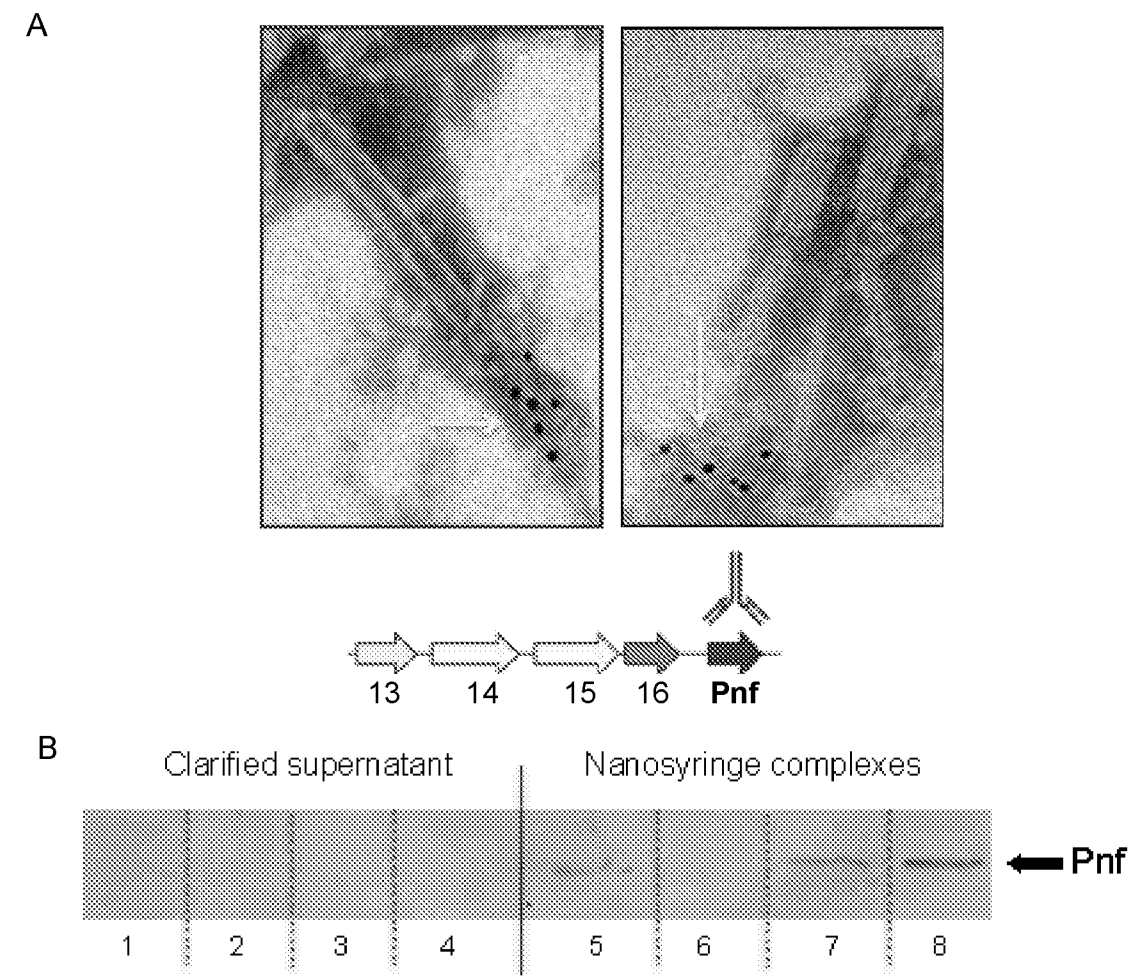


FIGURE 5

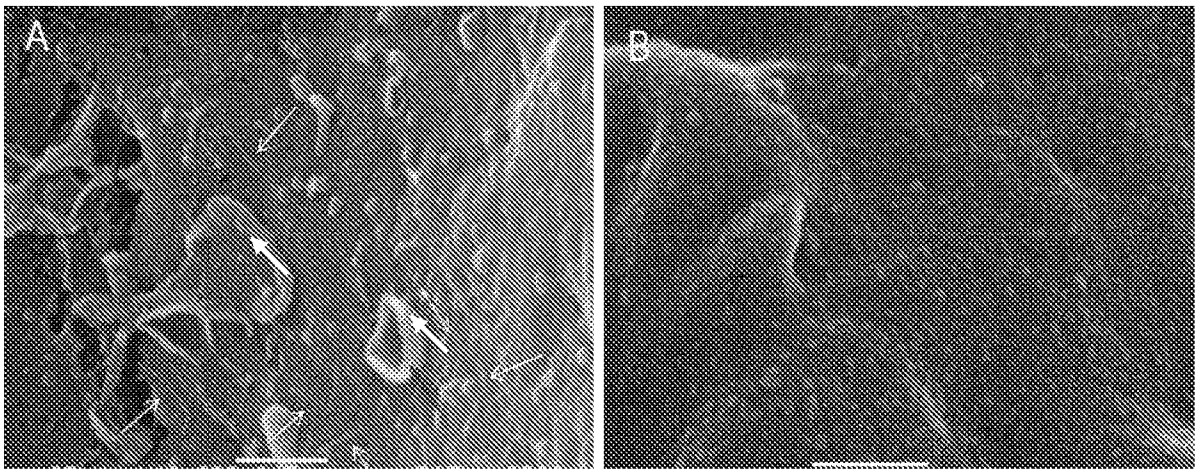


FIGURE 6

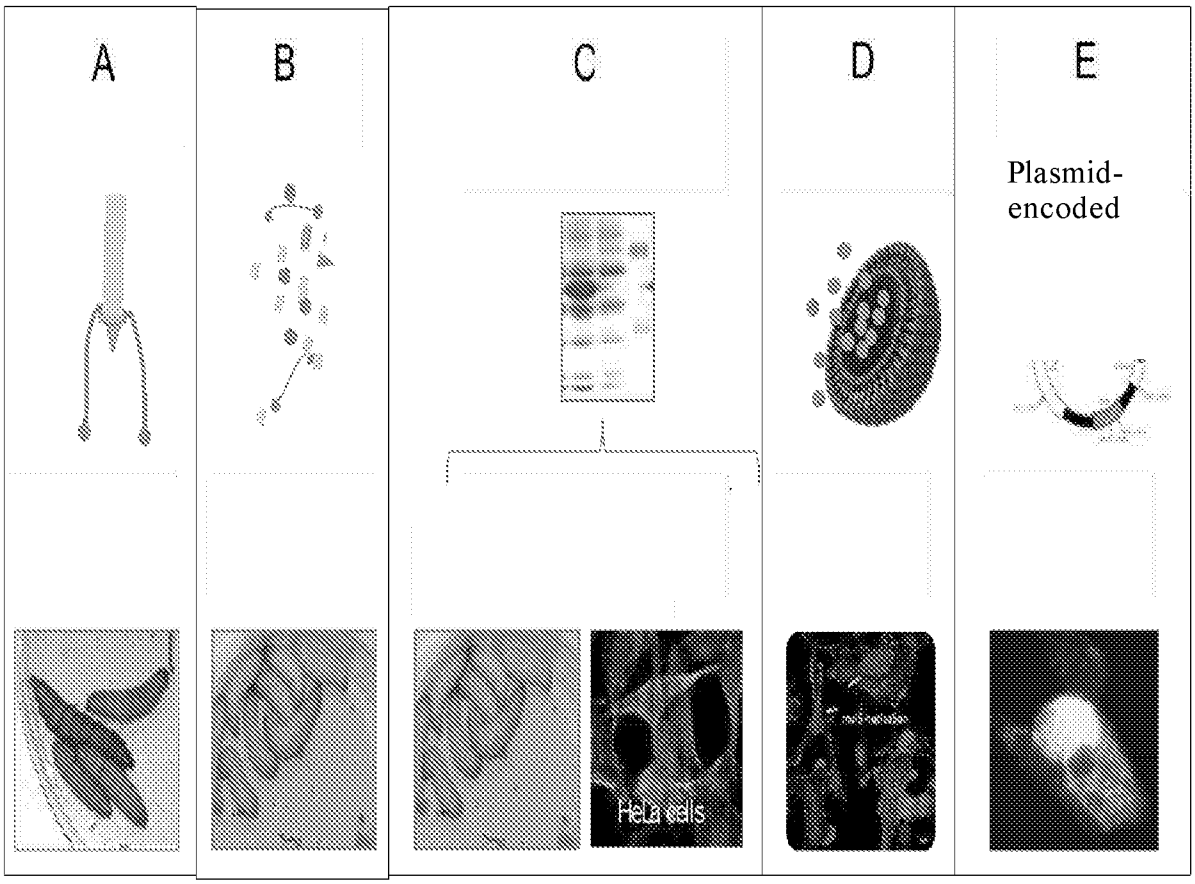


FIGURE 6 (continued)

F

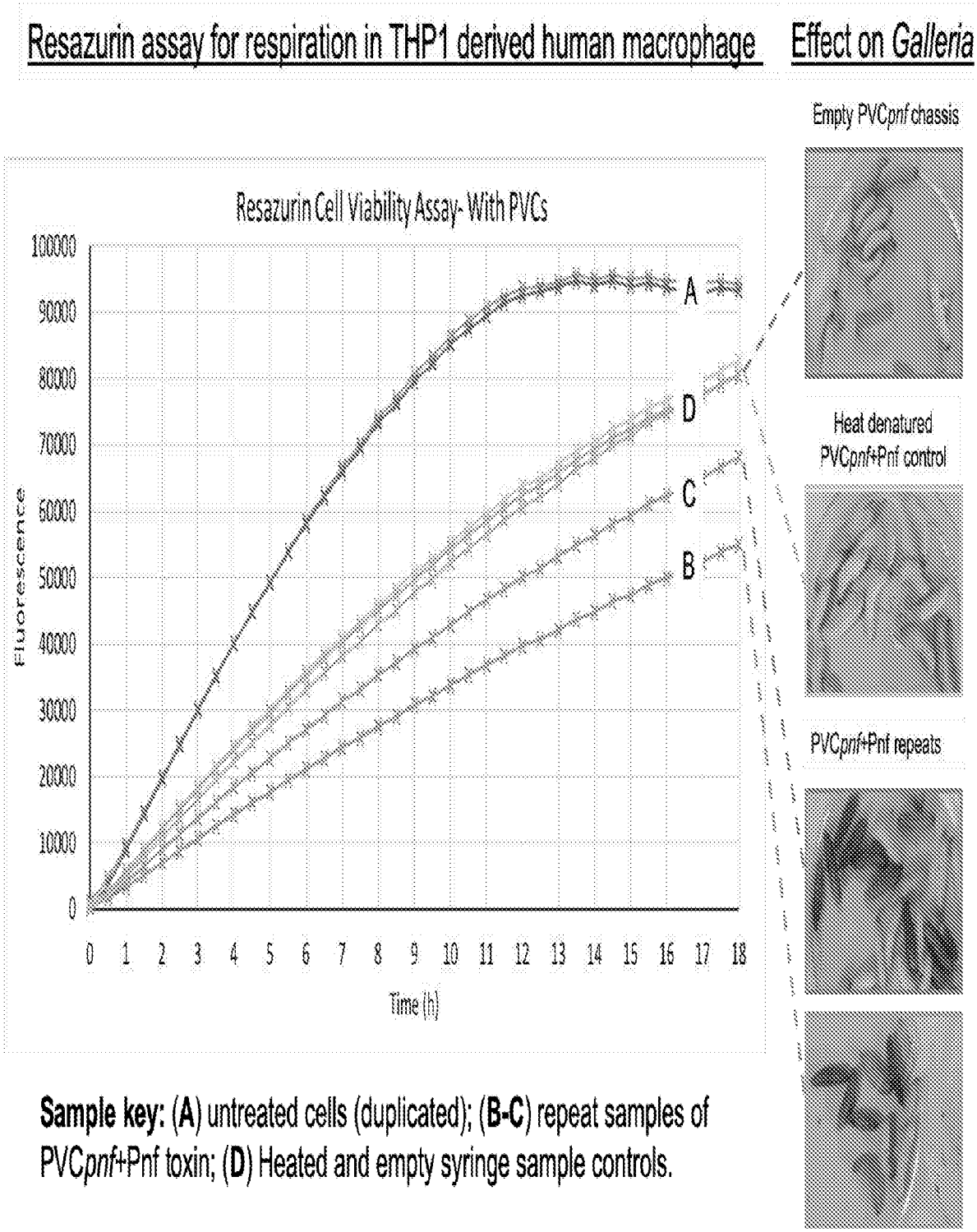


FIGURE 7

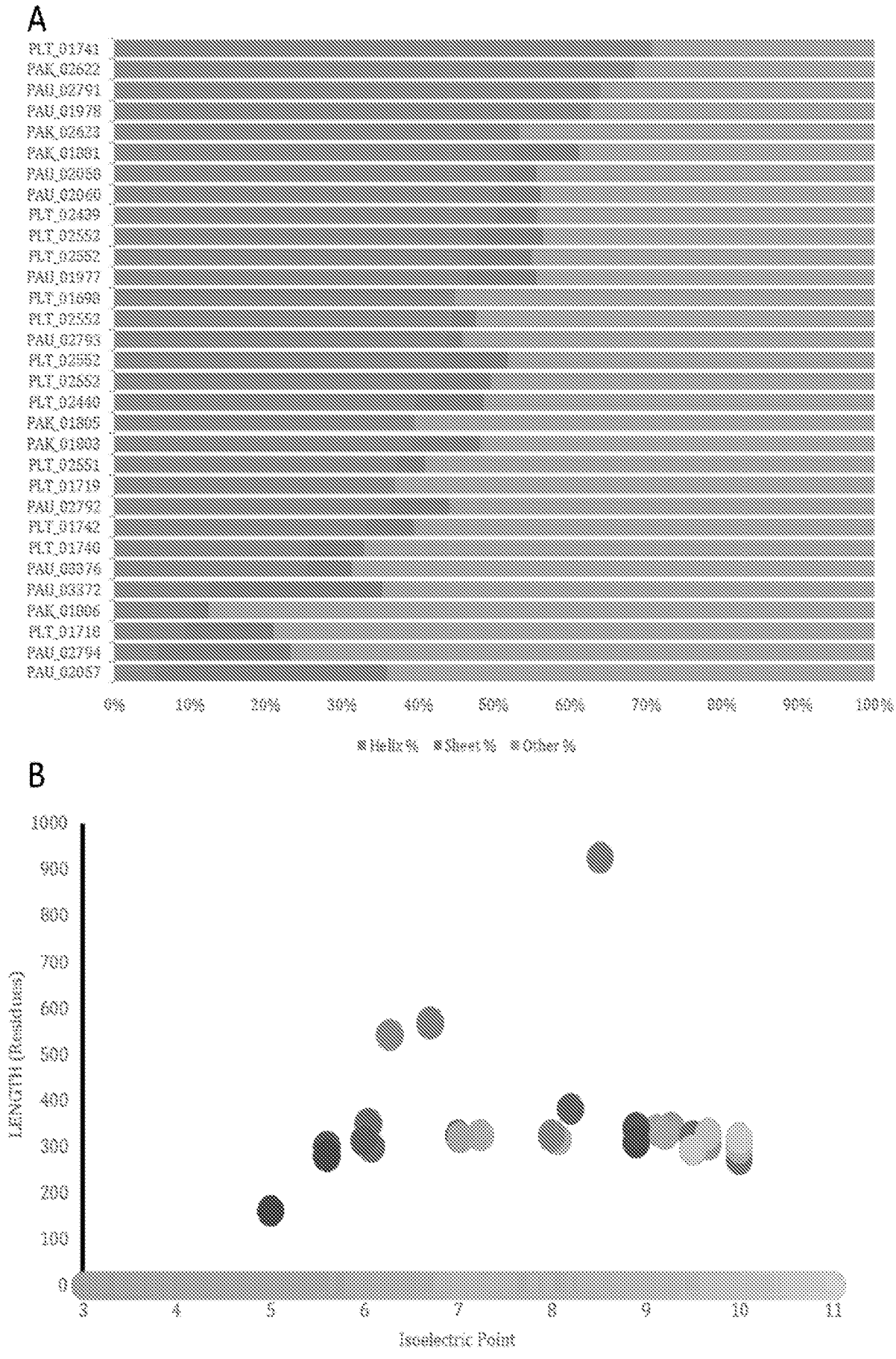

A
PLT_01741
PAK_02622
PAU_02791
PAU_01978
PAK_02623
PAK_01881
PAU_02058
PAU_02060
PLT_02439
PLT_02553
PLT_02552
PAU_01977
PLT_01690
PLT_02553
PAU_02763
PLT_02552
PLT_02552
PLT_02440
PAK_01805
PAK_01803
PLT_02551
PLT_01719
PAU_02792
PLT_01742
PLT_01740
PAU_03076
PAU_03372
PAK_01806
PLT_01718
PAU_02794
PAU_02057
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Helix %
Sheet %
Other %
B
LENGTH (Residues)
1000
900
800
700
600
500
400
300
200
100
0
3
4
5
6
7
8
9
10
11
Isoelectric Point

FIGURE 8

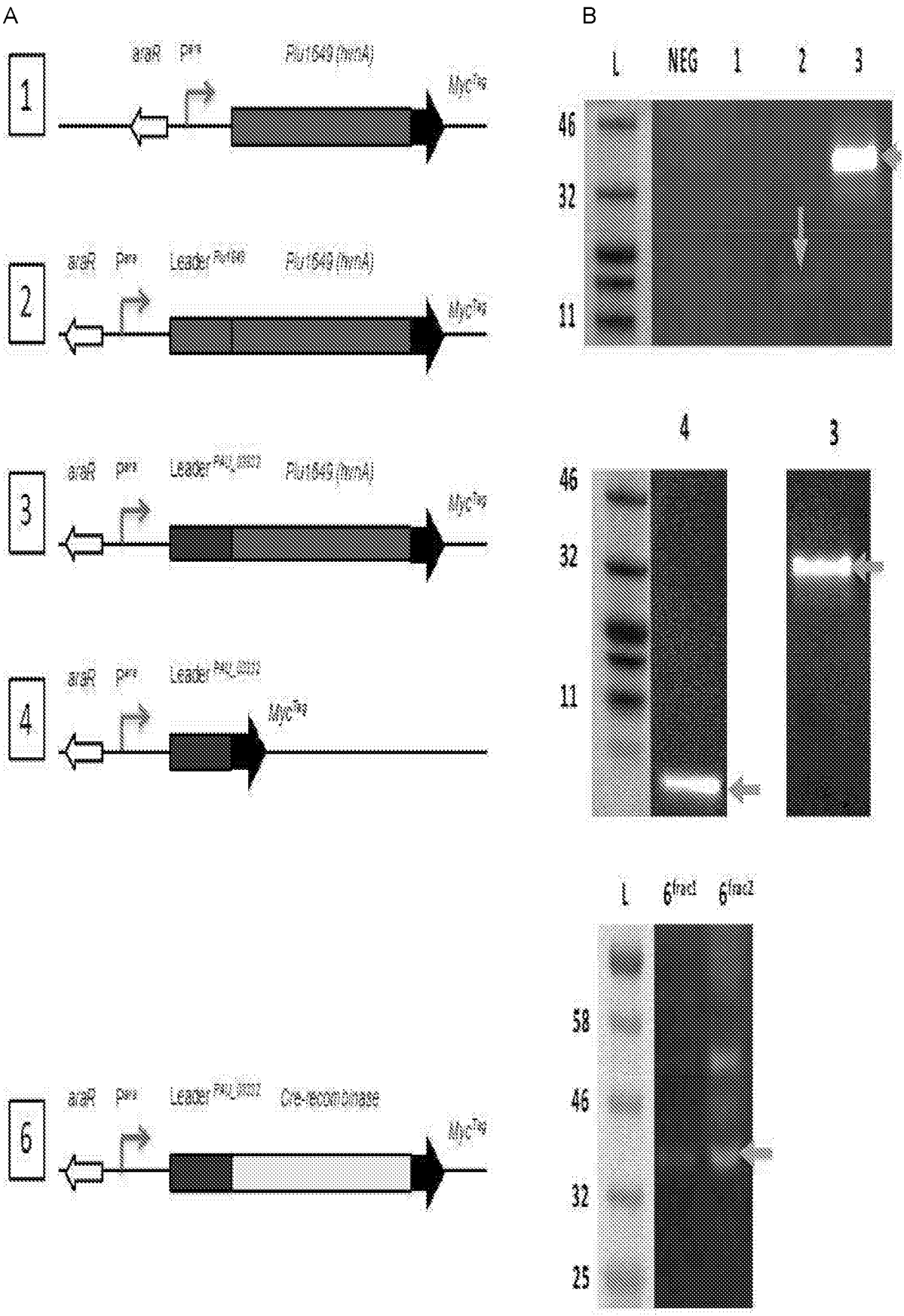

A
B
1
araR
Para
Flu1649 (hrmA)
Myc7xg
2
Leader Flu1649
3
Leader PAU_02622
4
Leader PAU_02622
6
Cre-recombinase
L
NEG
1
2
3
4
3
6frac1
6frac2
46
32
11
58
25

FIGURE 9

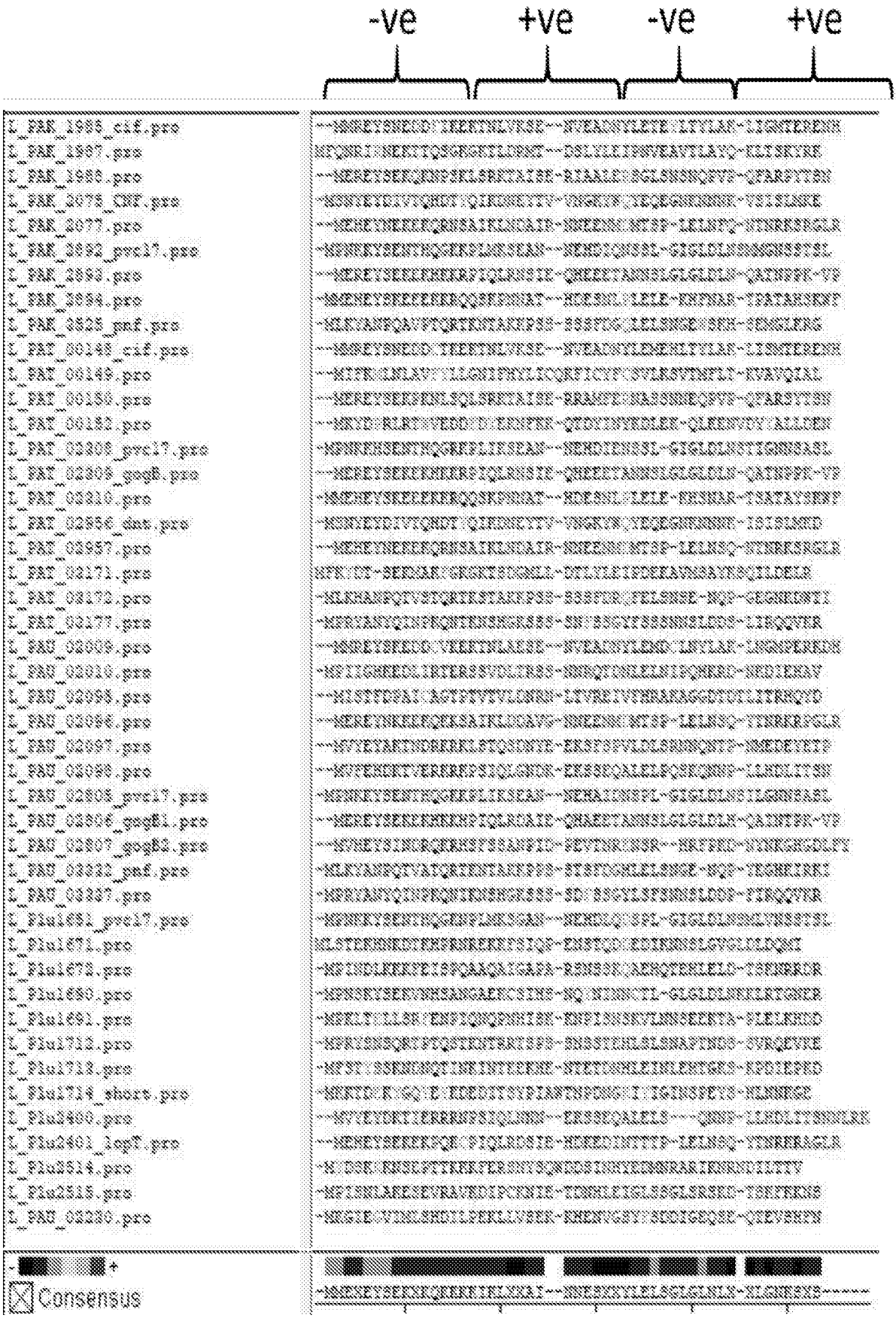
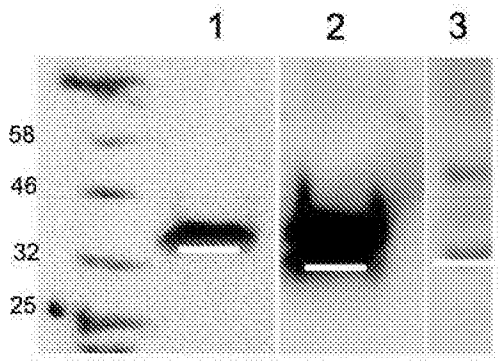


FIGURE 10

A



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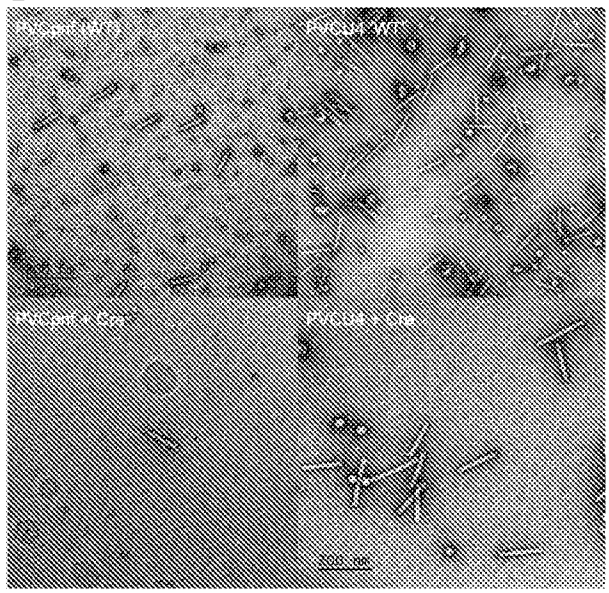

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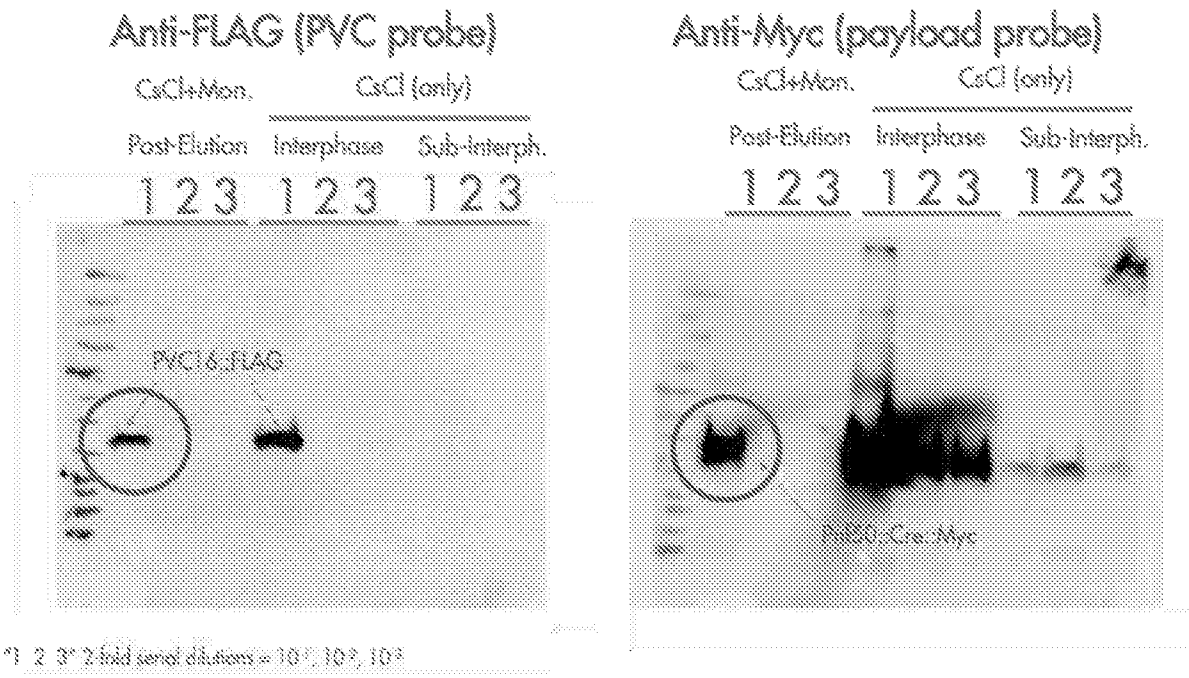

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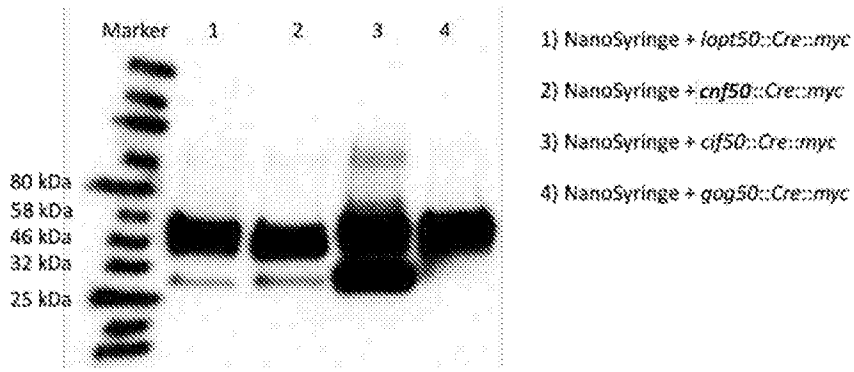


FIGURE 10 (continued)

E

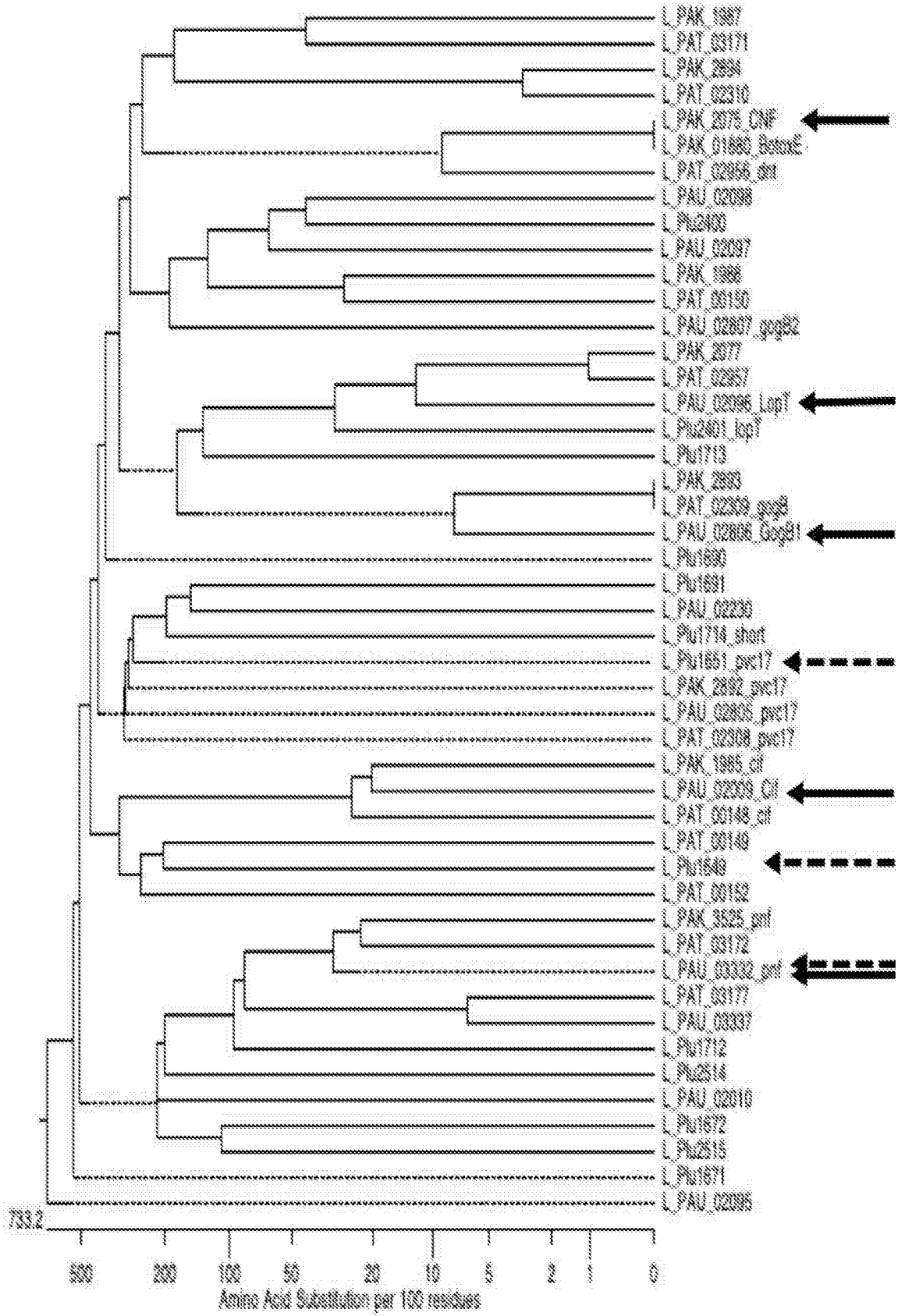


FIGURE 11

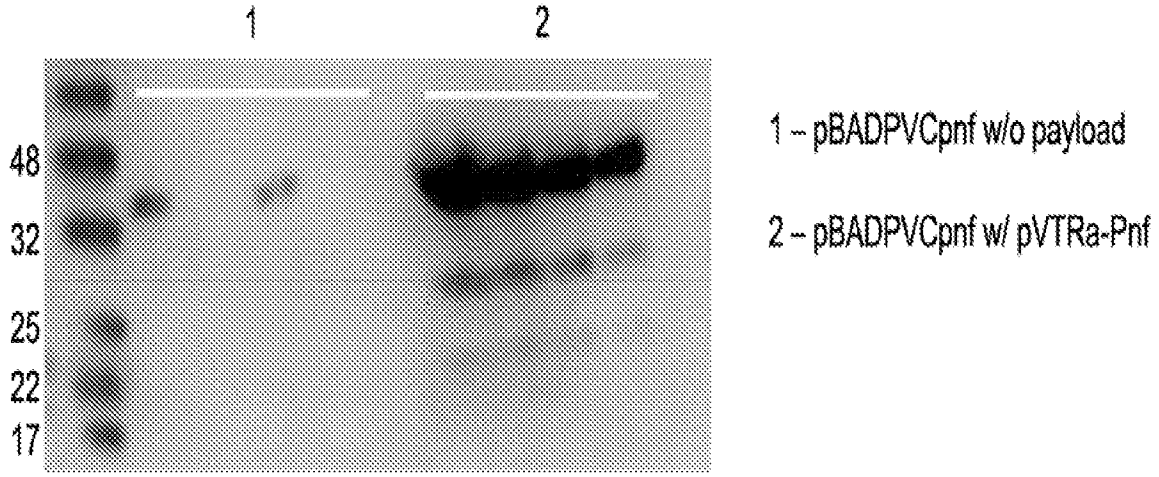


FIGURE 12

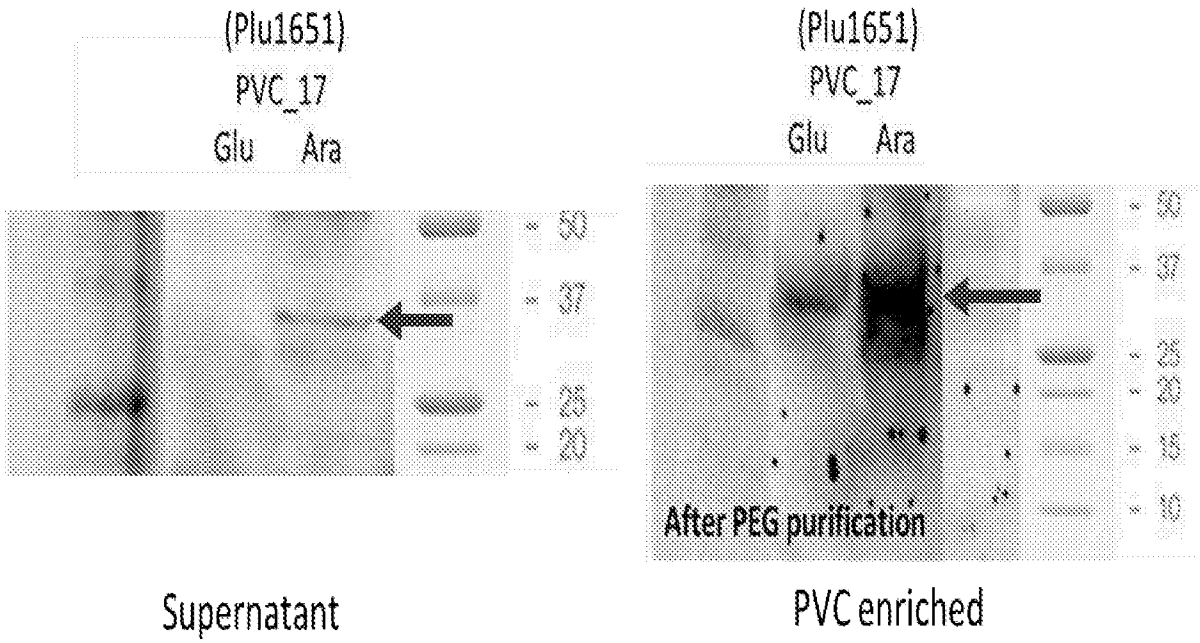


FIGURE 13

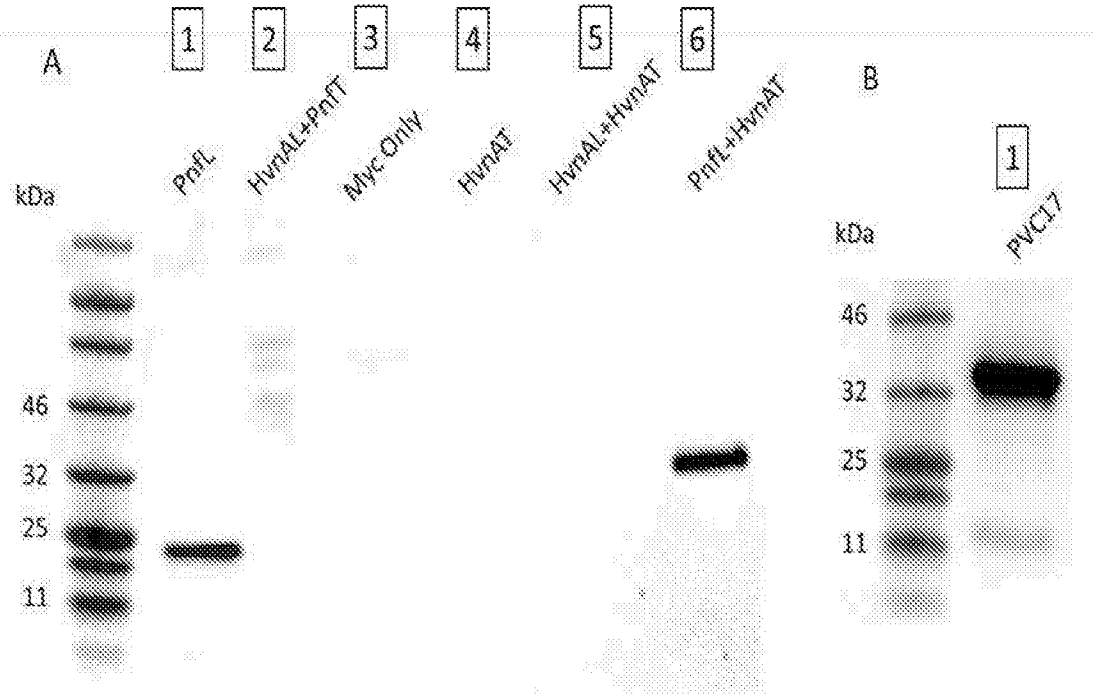


FIGURE 14

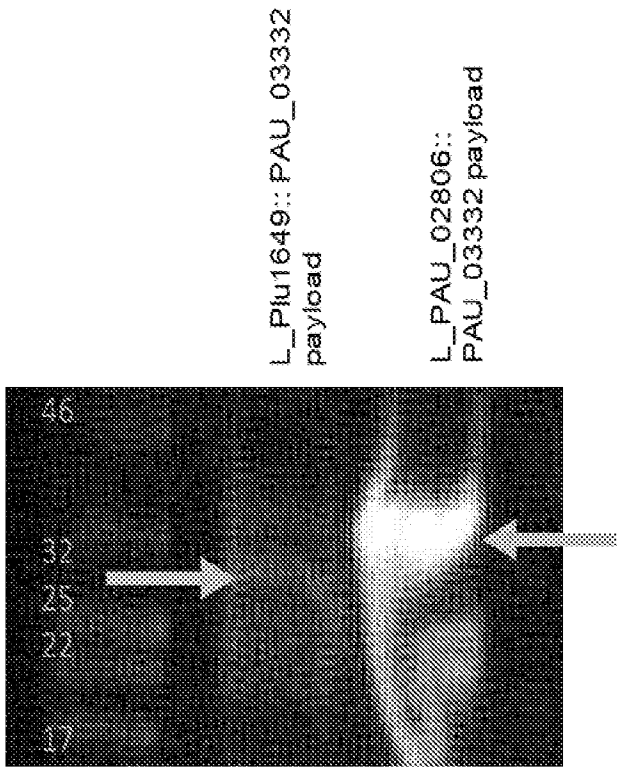


FIGURE 15

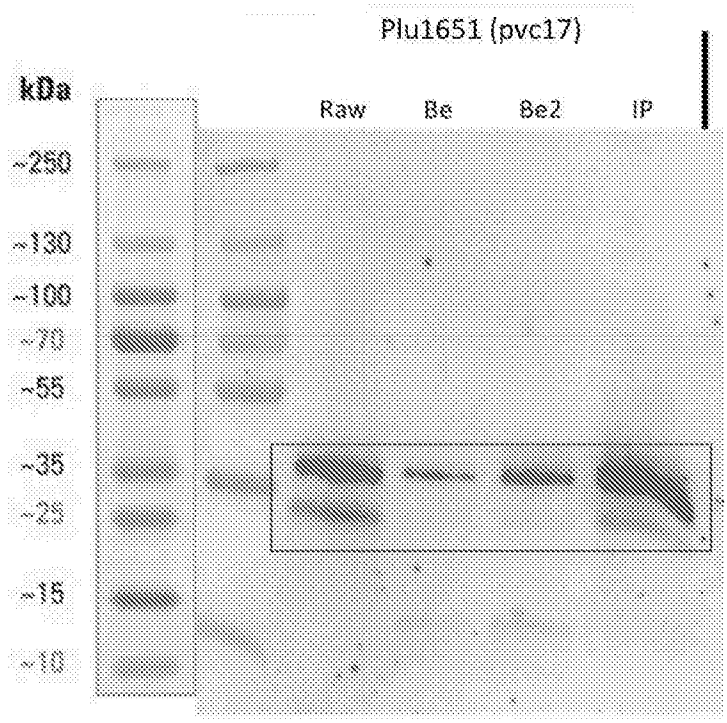


FIGURE 16
A

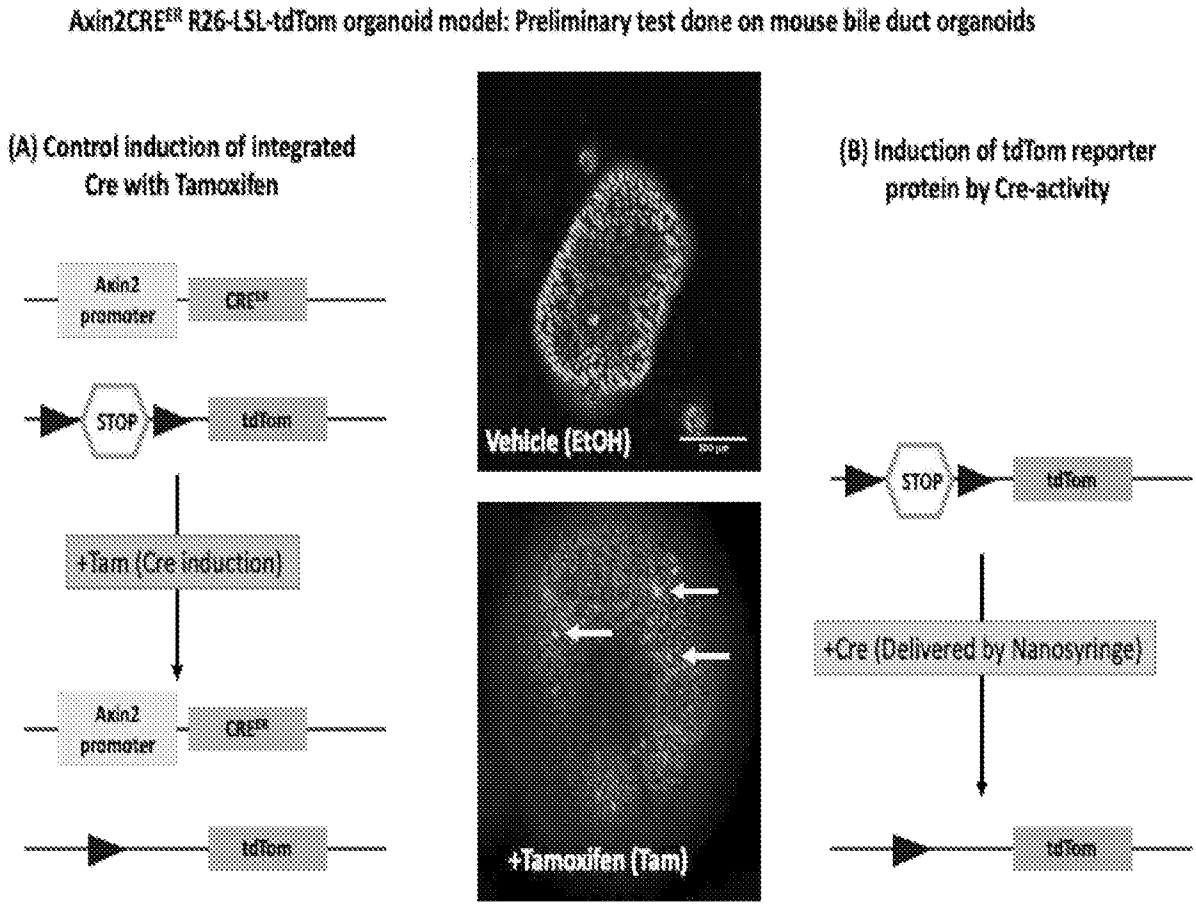


FIGURE 16 (continued)

B

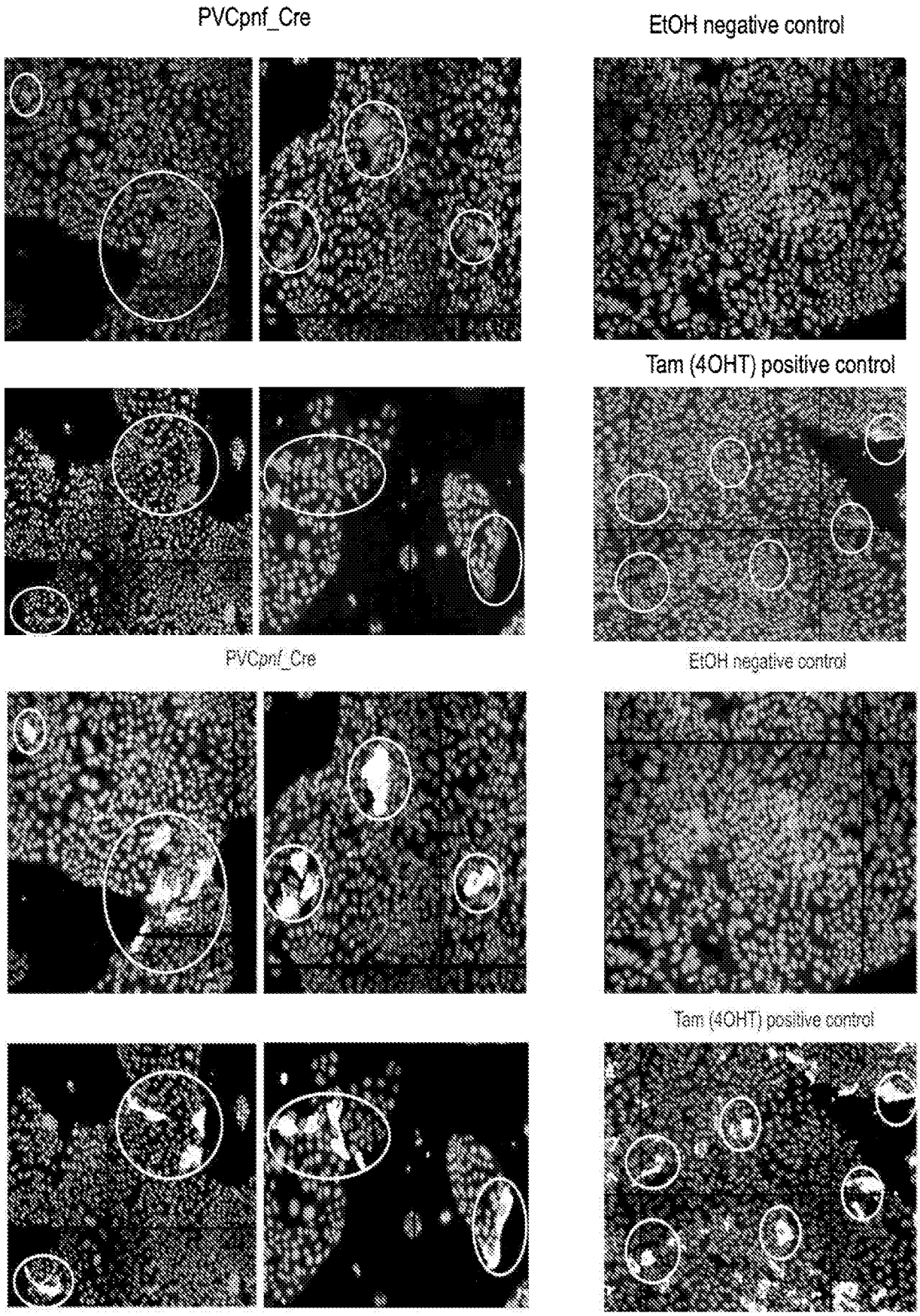


FIGURE 17

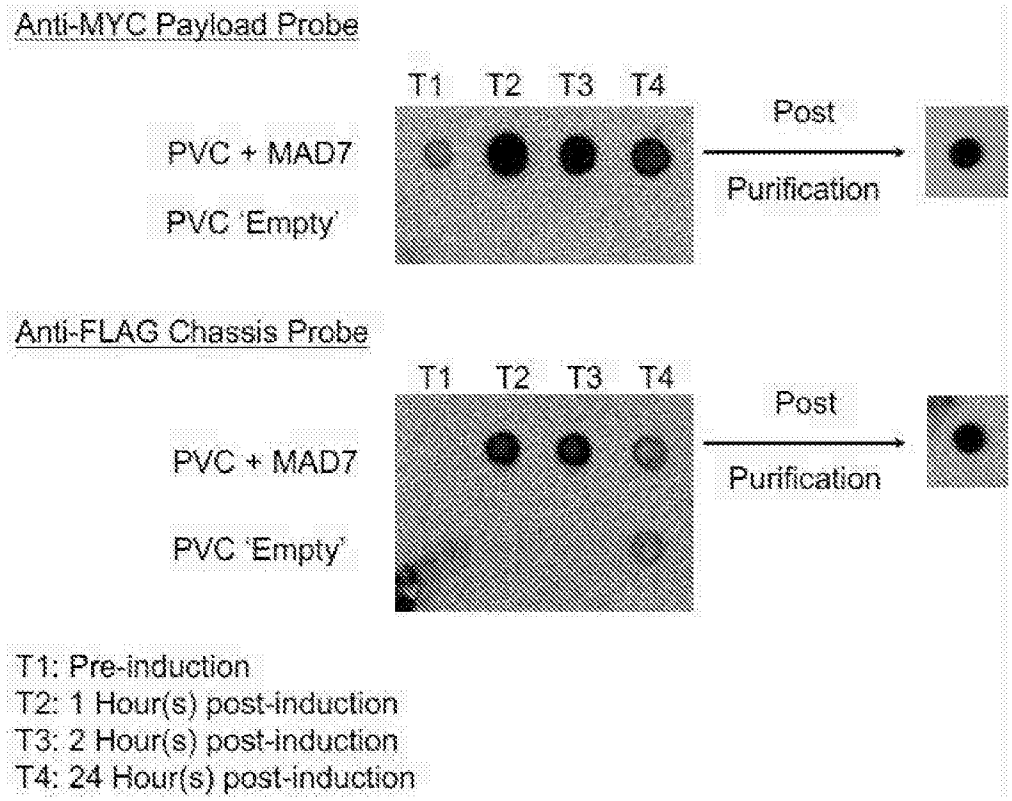


FIGURE 18

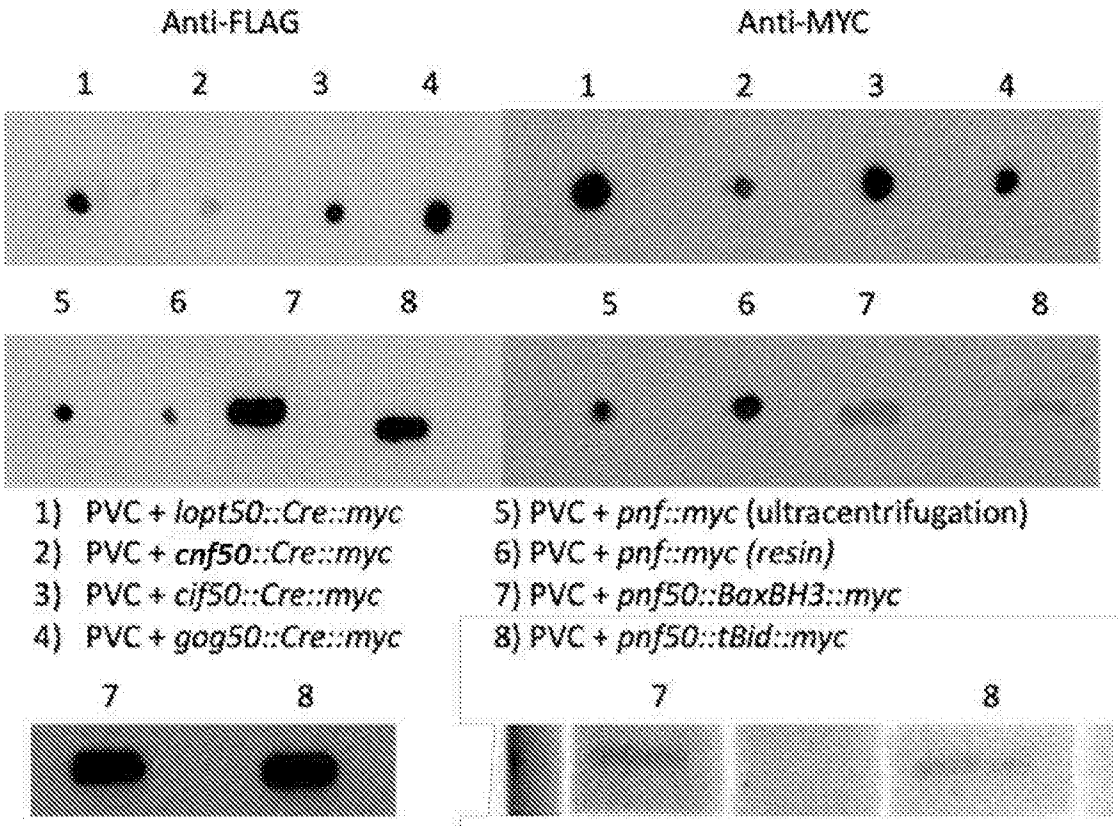
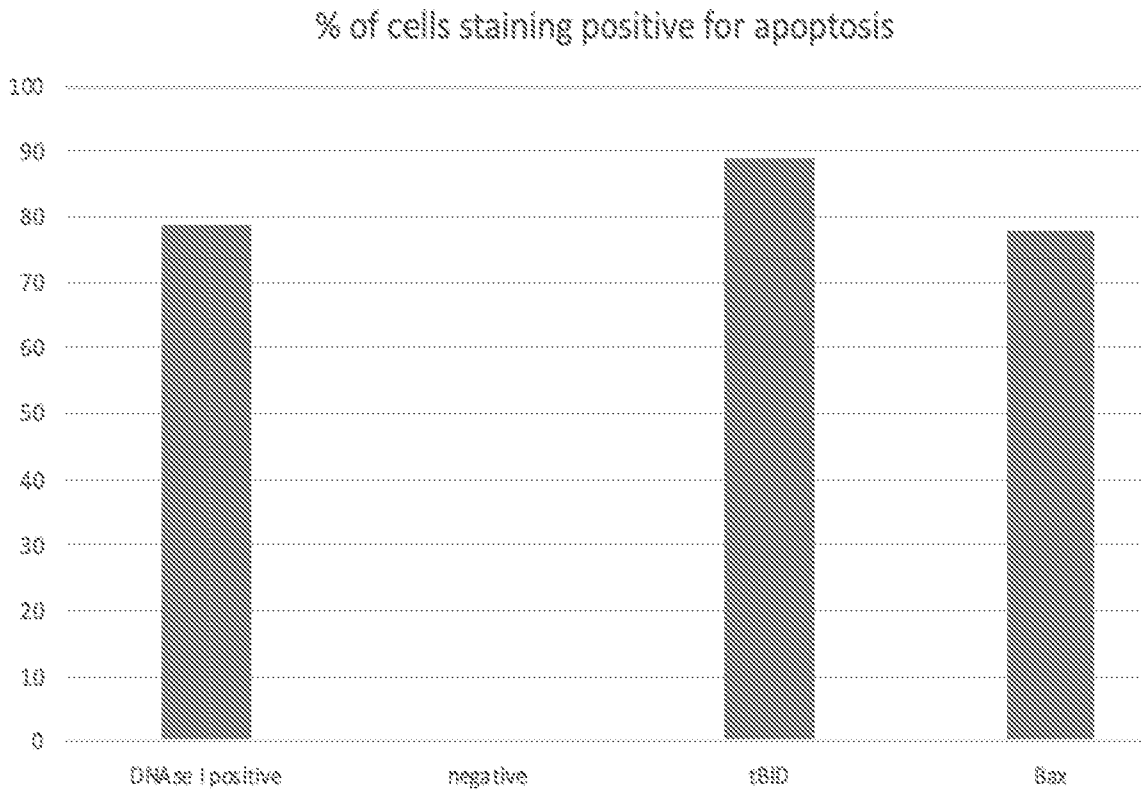
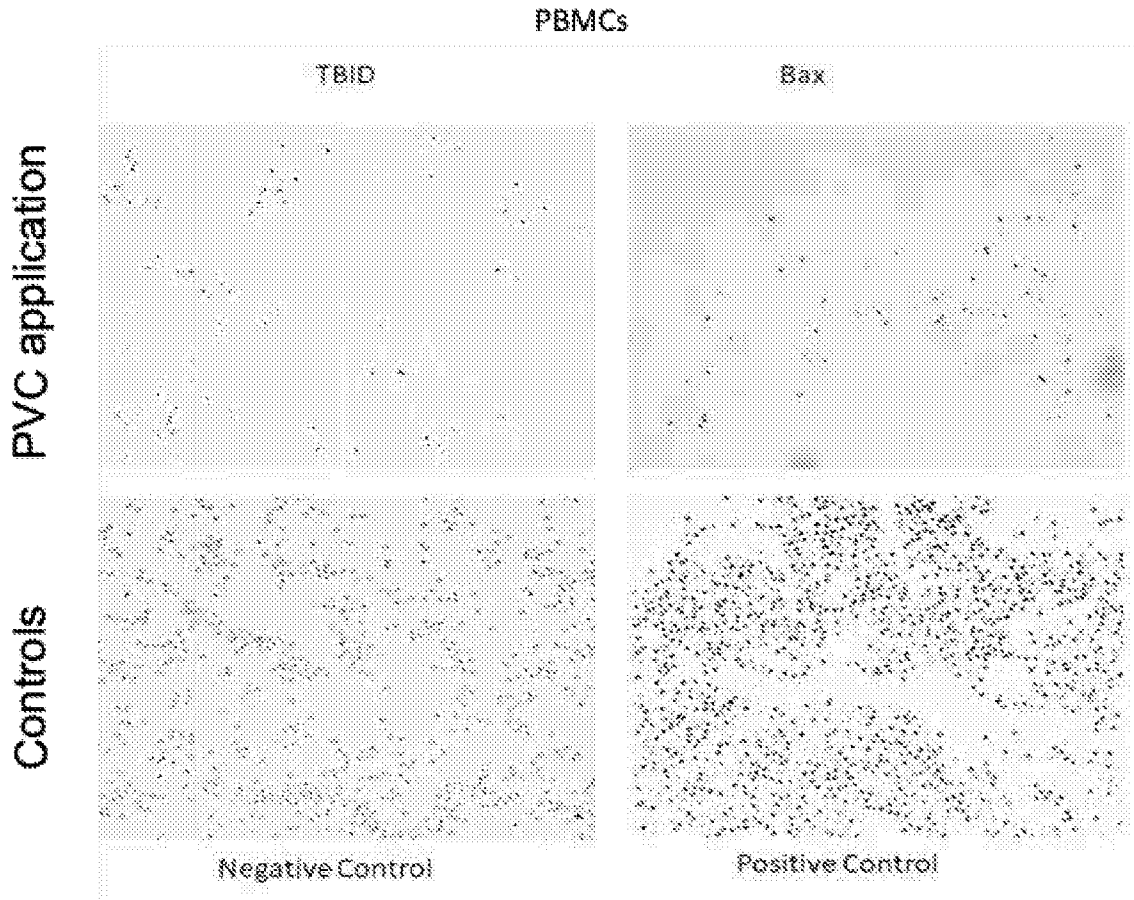


FIGURE 19

A


% of cells staining positive for apoptosis
100
90
80
70
60
50
40
30
20
10
0
DNAse I positive
negative
tBID
Bax

B


PBMCs
TBID
Bax
PVC application
Controls
Negative Control
Positive Control

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<151> 2019-06-07

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Asn Leu Val Lys Ser Glu Asn Val Glu Ala Asp Asn Tyr Leu Glu Thr
            20                  25                  30


Glu Tyr Leu Thr Tyr Leu Ala Lys Leu Ile Gly Met Thr Glu Arg Glu
        35                  40                  45


Asn His His Leu Asn Ser Ile Lys Leu Ile Asp Asp Ile Ile Glu Leu
    50                  55                  60


His Asn Asp Arg Lys Gly Asn Lys Leu Leu Trp Asn Asp Asn Trp Gln
65                  70                  75                  80


Asp Lys Ile Ile Asp Arg Asp Leu Gln Ser Ile Phe Lys Lys Ile Asp
                85                  90                  95


Glu Met Val Ser Glu Phe Gly Gly Leu Glu Ala Tyr Lys Asp Ile Val
            100                 105                 110
```

```
Gly Glu Asn Pro Tyr Asp Pro Thr Glu Pro Val Cys Gly Tyr Ser Ala
        115                 120                 125

Gln Asn Ile Phe Lys Leu Met Thr Glu Gly Glu Tyr Ala Val Asp Pro
    130                 135                 140

Val Lys Met Ala Lys Thr Gly Lys Ile Asn Gly Asn Gln Phe Ala Glu
145                 150                 155                 160

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

Asp His Arg Leu Gly His Met Phe Leu Val Asp Ile Pro Ser Thr Asn
            180                 185                 190

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

Leu Pro Ala Leu Lys Ile Ala Asp Trp Leu Lys Ser Arg Gly Lys Glu
    210                 215                 220

Ser Ile Asn Val Asn Lys Leu Lys Lys Phe Leu Asn Asp Glu Phe Thr
225                 230                 235                 240

Met Leu Pro Asp Asn Glu Gln Lys Gly Leu Ile Ala Glu Ile Phe Asp
                245                 250                 255

Leu Asn Lys Asp Ile Asp Ser Val Lys Ser Gly Lys Ile Lys Lys Asp
            260                 265                 270

Lys Ala Val Asp Ile Tyr Leu Arg Glu Tyr Asp Ile Asn Asp Phe Ile
        275                 280                 285

Ser Asn Ile Glu Lys Leu Lys Thr Lys Leu Ala
    290                 295
```

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<213> Photorhabdus

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Gly Lys Thr Leu Asp Arg Met Thr Asp Ser Leu Tyr Leu Glu Ile Pro
            20                  25                  30

Asn Val Glu Ala Val Thr Leu Ala Tyr Gln Lys Leu Thr Ser Lys Tyr
        35                  40                  45

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

Phe Ser Gln Leu Lys Ser Glu Lys Gln Arg Lys Gly Phe Ser Lys Ser
65                  70                  75                  80

Gly Leu Lys Asn Asn Gly Val Ser Asp Arg Lys Phe Ile Tyr Thr Lys
                85                  90                  95

Asn Ala Leu Lys Asn Phe Ala Ala His Ala Gly Tyr Glu His Asn Gly
            100                 105                 110

His Tyr Glu Asp Glu Phe Val Asn Phe Lys Asp Asn Asn Lys Asn Leu
        115                 120                 125

Ala Lys Gly Lys Leu Phe Pro Gly Ile Ser Leu Ile Glu Arg Arg Lys
    130                 135                 140

Leu Ser Ile Val Lys Asn Lys Glu Gly Lys Trp Glu His Lys Glu Thr
145                 150                 155                 160

Asp Glu Ala Glu Ala Tyr Lys Val Thr Asp Ile Glu Lys Phe Ile Ser
                165                 170                 175

Gly Val Arg Ser Met Tyr Leu Gln Gly Asn Thr Phe Leu His Ala Lys
```

```
            180                 185                 190

Thr Glu Ala Leu Ile Arg Lys His Ile Ala Asn Asn Glu Asn Ile Leu
        195                 200                 205

Pro Thr Met Ala Gly Ile Ala Gly Leu His Ala Glu Val Gln Ala Leu
    210                 215                 220

Asn Asn Leu Phe Ile Ser Gly Asp Lys Gly Thr Lys Lys Arg Glu Lys
225                 230                 235                 240

Trp Lys Tyr Ile Arg Asn Met Leu Glu Ser Ser Ile Phe Thr Gln Arg
                245                 250                 255

Leu Thr Thr Gly Gln Ala Gly Lys Asp Phe Ala Ala Cys His Asn Cys
            260                 265                 270

Ser Gly Ile Leu Ser Ser Pro Val Asn Val Ile Thr Gly Lys Val Glu
        275                 280                 285

Ser Ala Gly Asp Asn Phe Leu Ser Thr Leu Ser Arg Tyr Lys Thr Ser
    290                 295                 300

Gln Glu Ser Pro Ile
305
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1               5                   10                  15

Arg Lys Thr Ala Ile Ser Glu Arg Ile Ala Ala Leu Glu Arg Ser Gly
            20                  25                  30
```

```
Leu Ser Asn Ser Asn Gln Pro Val Pro Gln Phe Ala Arg Pro Tyr Thr
        35                  40                  45

Ser Asn Arg Pro Val Val Asn Ile Asn Pro Gly Arg Ser Ser Ile Ala
    50                  55                  60

Val Ala Thr Ala Asn Ser Thr Ser Pro Val Asn Ile Pro Thr Pro Ala
65                  70                  75                  80

Pro Ala Ser Pro Asp Lys Leu Leu Pro Ser Thr Ser Cys Asp Thr Thr
                85                  90                  95

Ser Ser Ile Leu Ile Val Gly Lys Tyr Asn Leu Glu Leu Thr Ser Gln
            100                 105                 110

Gly Lys Ile Val Val Phe Arg Gly Asp Asn Arg Thr Pro Glu Gln Ile
        115                 120                 125

Val Ala Ala Gly Gly Phe Tyr Pro Trp Ser Lys Gln Asp Val Gly Lys
    130                 135                 140

Ile Lys Lys Glu Leu Ile Asp Glu Phe Ile Glu Ile Gly Pro Ser Ala
145                 150                 155                 160

His Met Met Gly His Val Arg Ser Pro Asn Lys Asn Tyr Val Ser Thr
                165                 170                 175

Gly Met Asn Met Asp Ser Gly Gly Phe Gly Glu Gln Ser Asn Tyr Leu
            180                 185                 190

Tyr Lys Met Glu Ile Pro Gly Leu Lys Pro Gln Asp Met Asn Glu Arg
        195                 200                 205

Thr Leu Gly Glu Lys Ile Arg Gln Asp Lys Arg Gly Ile Asn Tyr Pro
    210                 215                 220

His Phe Leu Met Ser His Leu Thr Leu Ala Glu Ser Glu Phe Val Ala
225                 230                 235                 240
```

```
Met Ile Pro Ala Arg Ser Glu Glu Leu Thr Phe Ile Thr Pro Ile Pro
                245                 250                 255


Leu Ser Tyr Ile Thr Ser Tyr Arg Lys Arg Gly Thr Asn Thr Trp Leu
            260                 265                 270


Pro Met Pro Leu Lys Lys
        275
```

<210> 4
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<400> 4

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Met Ser Asn Tyr Glu Tyr Asp Ile Val Thr Gln His Asp Thr Tyr Gln
1               5                   10                  15


Ile Lys Asp Asn Glu Tyr Thr Val Val Asn Gly Lys Tyr Trp Gln Tyr
            20                  25                  30


Glu Gln Glu Gly Asn Lys Asn Asn Asn Lys Val Ser Ile Ser Leu Met
        35                  40                  45


Lys Glu Asn Gln Asn Asp Pro Val Trp Ile Thr Ser Asp Ile Lys Glu
    50                  55                  60


Ile Ser Leu Tyr Ile Ile Glu Asn Leu Phe Ser Tyr His Lys Phe Ser
65                  70                  75                  80


Ala Glu Leu Gln His Thr Leu Lys Asn Ala Val Lys Ala Val Phe Asn
                85                  90                  95


Glu Tyr Ser Glu Ile Lys Tyr Ser Glu Leu Leu His Asn Ile Asn Asn
            100                 105                 110


Ile Phe Asn Leu Phe Phe Ile Lys Ile Tyr Asn Thr Ser Asp Ile Asp
```

```
        115                 120                 125

Thr Ala Ile Asn Ile Leu Thr Ala Lys Ile Glu Ile Tyr Asp Lys Leu
    130                 135                 140

Glu Lys Ile Asn Gln Asp Lys Thr Asp Ser Asn Asn Thr Asn Val Asp
145                 150                 155                 160

Ile Trp Glu Glu Leu Gly Ile Asn Ala Glu Glu Pro Leu Leu Lys Ile
                165                 170                 175

Tyr Arg Gln Ala Phe Ser Thr Gly Asp Ile Asp Asp Glu Val Tyr Ser
            180                 185                 190

Asp Ala Leu Leu Thr Phe Met Ser Asp Gly Asn Leu Glu Leu Gly Asp
        195                 200                 205

Lys Glu Lys Ser Asp Tyr Asn Gln Arg Ile Lys Asp Lys Thr Asp Leu
    210                 215                 220

Phe Glu Ser Tyr Lys Lys Gly Ile Glu Lys Val Ala Ser Leu Ile Thr
225                 230                 235                 240

Thr Asn Asn Ile Asn Pro Gly Ile Pro Ile Thr Tyr Pro Glu Thr Glu
                245                 250                 255

Lys Ser Ile Asn Ile Gly Asp Asp Leu Leu Leu Ala Gln Leu Ala Lys
            260                 265                 270

Glu Glu Ile Ala Leu Lys Lys Gln Asn Arg Thr Glu Tyr Ser Gln Gln
        275                 280                 285

Asp Ile Phe Glu Leu Gln Thr Leu Gln Ala Ala Lys Tyr His Leu Leu
    290                 295                 300

Ile Leu Ser Ser Leu Gly Ala Leu Leu Tyr Gln Ile Ala Pro Asn Val
305                 310                 315                 320
```

```
Glu Lys Met Thr Lys Gly His Gly Asp Tyr Arg Asp Ile Ile Phe Ser
                325                 330                 335

Gln Glu Gln Ala Glu Ser Leu Phe Lys Lys His Asn Ile Gln Tyr Asp
            340                 345                 350

Thr Asn His Val Leu Ser Gln Glu Ser Lys His Ile Glu Met Glu Gly
        355                 360                 365

Cys Ile Ile Leu Thr Ala Ala Ile Ile Tyr Arg Met Arg Lys Glu Asn
    370                 375                 380

Ala Thr Val Glu Gln Ala Leu Asn Tyr Ser Thr Leu Glu Thr Ile Lys
385                 390                 395                 400

Leu Phe Glu Asn Asp Lys Lys Lys Leu Asn Pro Phe Asn Thr Asn Asn
                405                 410                 415

Val Lys Pro Ala Gly Tyr Phe Ser Phe Ile Asp Phe Lys Lys Arg Asp
            420                 425                 430

Lys Phe Asp Ser Gln Tyr Asn Phe Asn Glu Gln Phe Asn Val Tyr Lys
        435                 440                 445

Asn Lys Tyr Ser His Tyr Glu Ser Ile Ser Phe Ser Lys Leu Ile Leu
    450                 455                 460

Ser Ser Pro Ala Ala Gln Leu Thr Ala Glu Glu Ile Val Asn Pro Pro
465                 470                 475                 480

Glu Glu Ala Phe Leu Tyr Ser Val Glu Gln Gly Met Gly Asn Val Ala
                485                 490                 495

Met Ile Lys Met Tyr Gln Gly Asn Trp Leu Val Ile Ser Thr Ile Gln
            500                 505                 510

Gly Gly Val Lys Ala Lys Lys Tyr Ser Arg Gln Gln Val Asp Ser Asn
```

```
        515                 520                 525

Pro Thr Leu Arg Ala Met Ser Lys Pro Asn Ala Leu Phe Leu Ile Glu
    530                 535                 540

Arg Lys Met Glu Thr Gly Met Gly Ile Leu Met Pro Asn Met Met Val
545                 550                 555                 560

Asn Thr Gly Lys Arg Leu Phe Pro Thr Gly Tyr Glu Arg Ala Lys Thr
                565                 570                 575

Leu Ser Gly Phe Ala Glu Thr Ser Arg Tyr Lys Asn Ser Tyr Asn Ala
            580                 585                 590

Phe Trp Asn Asp Tyr Tyr Gly Ile Thr Ser Gly Met Asn Val Gly Ile
        595                 600                 605

Ser Phe Thr Gly Ser Pro Lys Phe Asn Phe Tyr Lys Glu Glu Asn Leu
    610                 615                 620

Leu Ser Val Thr Ala Thr Ile Ile Gln Gln Gly Leu Asn Asp Ile Ala
625                 630                 635                 640

Ile Lys Ser Lys Gln Ala Leu Asp Ile Thr Ser Gly Trp His Ile Ala
                645                 650                 655

Ala Thr Ile Leu Ile Pro Phe Tyr Asn Val Ile Tyr Lys Ser Thr Thr
            660                 665                 670

Asp Ser Glu Tyr Glu Leu Thr Gly Glu Asp Ile Gly Ser Ile Val Phe
        675                 680                 685

Asp Thr Ala Asn Val Leu Leu Val Val Ala Thr Leu Gly Met Ser Leu
    690                 695                 700

Thr Glu Ser Met Ala Ala Lys Val Thr Gln Thr Thr Leu Arg Leu Arg
705                 710                 715                 720
```

```
Gln Ala Gly Leu Thr Gly Arg Ala Leu Ile Thr Ala Val Val Arg Thr
               725                 730                 735

Leu Pro Glu His Gly Ile Ile Thr Leu Arg Gln Ser Ser Gly Ile Ile
            740                 745                 750

Leu Gly Gly Leu Ile Asp Leu Ile Glu Pro Leu Pro Ile Arg Ser Thr
        755                 760                 765

Leu Thr Leu Thr Tyr Arg Gly Val Ile Asn Ala Val Gly Ala Met Arg
    770                 775                 780

Asn Ser Ile Lys Leu Glu Lys Ser Phe Ala Asp Ile Phe Gly Lys Ser
785                 790                 795                 800

Thr Arg Gly Leu Gly Lys Leu Lys Asn Glu Trp Lys Val Ser Asn Leu
               805                 810                 815

Pro Leu Glu Glu Ile Val Pro His Ser Asn Gly Gly Glu Ile Tyr Lys
            820                 825                 830

Gly Ile Tyr Ser Ile Arg Pro Thr Asn Pro Glu Thr Ala Val Lys Gln
        835                 840                 845

Asn Phe Tyr Ile Lys Glu Ala Gly Ala Asn Tyr Gln Val Lys Trp Asp
    850                 855                 860

Asp Ala Asn His Thr Trp Arg Val Val Asn Pro Thr Tyr Pro Glu Gln
865                 870                 875                 880

Phe Ser Tyr Trp Pro Ala Val Lys Leu Asp Lys Asn Gly His Trp Val
               885                 890                 895

Thr His Ala Asp Val Ser Asn Lys Phe Leu Ile Leu Glu Gln Ser Lys
            900                 905                 910

Arg Ile Asp Gln Glu Leu Glu Ala Ala His Ser Asn Ile Asn Asn Asp
```

```
        915                 920                 925

Asn Ile Leu Asp Ala Phe Ile His Ile Asn Thr Ala Phe Lys Asp Cys
    930                 935                 940

Glu Arg Tyr Asp Ile Asp Lys Leu Ser Asp Ile Thr Asp Thr Leu Thr
945                 950                 955                 960

His Phe Phe Glu Lys Ser Leu Lys Pro Gly Asp Lys Lys Ala Ile Phe
                965                 970                 975

Ser Thr Glu Ile Met Ser Ile Gln Gln Ala Trp Ile Arg Glu Val Ile
            980                 985                 990

Leu Pro Leu Gln Asn Asn Ser Ser  Ile Ser Ile Glu Lys  Ile Asn Ala
        995                 1000                1005

Ile Lys  Thr Glu Leu Pro Tyr  Leu Leu Arg Lys Thr  Phe Pro Ile
    1010                1015                1020

Glu Ser  Gln Leu Pro Asn Gln  Leu Val Ala Asn Lys  Ile Ala Leu
    1025                1030                1035

Ala Ile  Glu Glu Ile Pro Asn  Thr Arg Ile Pro Lys  Tyr Thr Ser
    1040                1045                1050

Gly Asn  Ile Ser Lys Thr Val  Gln Tyr Thr Ser Leu  Leu Glu Asn
    1055                1060                1065

Asn His  Val Asp Ile Pro Pro  Val Gly Ile Thr Ile  Thr Gly Asn
    1070                1075                1080

Asp Thr  Phe Ile Asn Gln Val  Thr Arg Val Leu Ser  Glu Ile Asp
    1085                1090                1095

Glu Ile  Pro Ser Gly Asn Ile  Val Ile Gln Glu Leu  Glu Lys Gln
    1100                1105                1110
```

```
Gly Leu  Asn Ile Gln Pro Pro  Thr Met Asn Asp Ile  Val Arg Glu
    1115                1120                1125

Lys Asn  Gly Gln Phe Tyr Ala  Asn Asn Ser Ala Gly  Ser His Ile
    1130                1135                1140

Ala Phe  Asp Pro Glu Asn His  Leu Ile Gly Thr Glu  Glu Lys Leu
    1145                1150                1155

Ile Asp  Glu Pro Trp Arg Thr  Arg Glu Pro Ala Ile  Ala Leu Tyr
    1160                1165                1170

His Glu  Met Leu His Ile Tyr  Tyr Asn Arg Tyr Pro  Thr Trp Phe
    1175                1180                1185

Thr Ser  Ile Asp Asn Lys Val  Ile Asp Gln Lys Val  Ser Gly Gly
    1190                1195                1200

Phe Ser  Leu Leu Glu Glu Ser  Arg Ile Val Gly Thr  Lys Tyr Tyr
    1205                1210                1215

Val Asn  Asp Lys Asn Thr Leu  Phe Asp Phe Asn Asp  Ser Asp Tyr
    1220                1225                1230

Leu Leu  Glu Asn Asn Ser Ala  Leu Leu Thr Glu Asn  Arg Phe Arg
    1235                1240                1245

Ala Glu  Tyr Ala Ile Phe Lys  Asn Lys Ser Glu Tyr  Val Ile Arg
    1250                1255                1260

Pro Tyr  Ser Gly Lys Gly Asp  Ser Gln Ile Pro Leu  Thr Lys Thr
    1265                1270                1275

Lys Ile  Asn Ile Asn Glu Ser  His Arg Asn Val Met  Gly Val Gly
    1280                1285                1290

Ser Gly  Lys Pro Glu Lys Met  Pro Asn Glu Ser Ala  Thr Asp Tyr
```

```
    1295                1300                1305

Arg Asn  Arg Val Arg Glu Trp  Arg Lys Ala Asn Lys  Gln Pro Glu
    1310                1315                1320

Ala Asp  Ile Gly Thr Gly Asp  Met Arg Lys Thr Lys  Ala Glu Ala
    1325                1330                1335

Arg Val  Lys Leu Leu Lys Glu  Asn Tyr Pro Gln Phe  Glu Pro Gln
    1340                1345                1350

Lys Ile  Glu Leu Gly Gly Ala  Phe Gln Leu Trp Thr  Val Pro Asn
    1355                1360                1365

Glu Pro  Ala Asn Lys Leu Met  Leu Ser Ser His Gly  Tyr Phe Phe
    1370                1375                1380

Ser Asp  Ser Ala Ala Thr Gln  Val Pro Ala Gly Lys  Thr Ile Gln
    1385                1390                1395

Phe Leu  Gly Pro His Gly Lys  Thr Leu Leu Glu Ala  Pro Glu Asn
    1400                1405                1410

Pro Leu  Tyr Ser Pro Phe Asp  Val Thr Leu Gly Asn  Ser Gly Phe
    1415                1420                1425

Thr Val  Gln Pro Tyr Ala Thr  Ile Glu Ser Gly Asn  Lys Ala Gly
    1430                1435                1440

Leu Gly  Ser Val Lys Ile Gly  Asp Lys Thr Phe Thr  Val Asn Asp
    1445                1450                1455

Ile Gln  Asn Ile Ala Thr Asp  Asp Val Glu Asn Tyr  Leu Leu Ala
    1460                1465                1470

Thr Gly  Val Glu Ala Asn Ala  Ser Asn His Gly Lys  Val Arg Asn
    1475                1480                1485
```

```
Tyr Gly  Ile Lys Tyr Tyr Glu  Lys Met Pro Asp Glu  Glu Val Lys
    1490                1495                1500


Ala Ala  Ile Trp Lys Asn Arg  Ala Asp Glu Thr Ser  Thr His Lys
    1505                1510                1515


Tyr Asp  Ala Leu Leu Val Ser  Pro Glu Ala Gly Asn  Arg Lys Lys
    1520                1525                1530


Leu Ser  Asp Ile Phe Ala Leu  Met Lys Thr Asp Glu  Arg Met Ser
    1535                1540                1545


Lys Tyr  Asp Glu Ile Thr Phe  Val Ala Cys Arg Glu  Glu Leu Asn
    1550                1555                1560


Arg Ile  Asn Met Lys Ser Ile  His Asp Thr Gly Leu  Gly Gly Gly
    1565                1570                1575


Tyr Glu  Pro Lys Leu Glu Pro  Thr Val Ile Leu Ser  Arg Arg Arg
    1580                1585                1590


Arg Glu  Ala Thr Phe Thr Ala  Asp Gly Ala Ile Ile  Tyr Ser Ile
    1595                1600                1605


Ile Ala  Val Asn Leu His His  Asn Phe Ile Thr Glu  Glu Ile Val
    1610                1615                1620


Gly Ile  Ala Pro Phe Leu Phe  Ile Asn Asn
    1625                1630


<210>  5
<211>  324
<212>  PRT
<213>  Photorhabdus

<400>  5

Met Glu His Glu Tyr Asn Glu Lys Glu Lys Gln Arg Asn Ser Ala Ile
1               5                  10                  15
```

```
Lys Leu Asn Asp Ala Ile Arg Asn Asn Glu Glu Asn Met Asp Met Thr
            20                  25                  30

Ser Pro Leu Glu Leu Asn Phe Gln Asn Thr Asn Arg Lys Ser Arg Gly
        35                  40                  45

Leu Arg Glu Arg Phe Ser Ala Thr Leu Gln Arg Asn Leu Pro Gly His
    50                  55                  60

Ser Met Leu Asp Arg Glu Leu Thr Thr Asp Gly Gln Lys Asn Gln Glu
65                  70                  75                  80

Ser Arg Phe Ser Pro Gly Met Ile Met Asp Arg Leu Met His Phe Gly
                85                  90                  95

Val Arg Thr Arg Leu Gly Lys Val Arg Asn Ser Ala Ser Lys Tyr Gly
            100                 105                 110

Gly Gln Val Thr Phe Lys Phe Ala Gln Thr Lys Gly Thr Phe Leu Asp
        115                 120                 125

Gln Ile Met Lys His Lys Asp Thr Ser Gly Gly Val Cys Glu Ser Ile
    130                 135                 140

Ser Ala His Trp Ile Ser Ala His Ala Lys Gly Asp Ser Ile Phe Asn
145                 150                 155                 160

Gln Leu Tyr Val Gly Gly Lys Lys Gly Lys Phe His Ile Asp Thr Leu
                165                 170                 175

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

Ser Thr Met Thr Glu Tyr Trp Leu Gly Thr Gln Gly Met Gln Pro Asn
        195                 200                 205
```

```
Ile Gln Arg Asn Asp Asp Thr Asp Glu His Ser Ser Lys Val Val Gly
    210                 215                 220

Glu Thr Gly Asn Arg Gly Thr Lys Asp Leu Leu His Ala Ile Leu Asp
225                 230                 235                 240

Thr Gly Asp Lys Gly Ser Gly Tyr Lys Lys Ile Ser Phe Leu Gly Lys
                245                 250                 255

Met Ala Gly His Thr Val Ala Ala Tyr Val Asp Asp Gln Lys Gly Val
            260                 265                 270

Thr Phe Phe Asp Pro Asn Phe Gly Glu Phe Ser Phe Pro Asp Lys Thr
        275                 280                 285

Ser Phe Ser His Trp Phe Thr Asp Asp Phe Trp Pro Lys Ser Trp Tyr
    290                 295                 300

Ser Leu Glu Ile Gly Leu Gly Gln Glu Phe Glu Val Phe Asn Tyr Ala
305                 310                 315                 320

Pro Glu Ala Pro
```

<210> 6
<211> 287
<212> PRT
<213> Photorhabdus

<400> 6

```
Met Pro Asn Lys Lys Tyr Ser Glu Asn Thr His Gln Gly Lys Lys Pro
1               5                   10                  15

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

Leu Gly Ile Gly Leu Asp Leu Asn Ser Met Met Gly Asn Ser Ser Thr
        35                  40                  45
```

```
Ser Leu Ser His Ile Gln Asp Tyr Ser Phe Trp Lys Glu Asn Ile Ser
    50                  55                  60

Glu Tyr Tyr Lys Trp Met Val Val Val Lys Ala His Leu Lys Gln Leu
65                  70                  75                  80

Asp Trp Thr Leu Lys Ser Met Asp Ser Pro Glu Ser Ala Gly Thr Asn
                85                  90                  95

Ile Ala Lys Asn Thr Gly Thr Thr Ala Leu Gln Thr Leu Leu Asn Thr
            100                 105                 110

Gly Gly Ser Ile Ala Gly Ala Ala Ile Gly Gly Ala Ile Gly Ser Ala
        115                 120                 125

Ile Ala Pro Gly Val Gly Thr Ile Ala Gly Met Gly Ile Gly Ala Leu
    130                 135                 140

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

Asn Glu Lys Leu Glu Ile Ala Tyr Pro Tyr Pro Lys Thr Arg Asn Met
                165                 170                 175

Ile Phe Asp Ile Asn Asn Tyr Asp Lys Asn Pro Ile Ile Lys Ala Ile
            180                 185                 190

Lys Lys Lys Thr Asn Lys Asp Asn Leu Lys Val Thr Ala Gly Ser Ser
        195                 200                 205

Leu Thr Ser Gln Leu Val Gly Lys Val Thr Ser Pro Ile Lys Phe Pro
    210                 215                 220

Ala Tyr Lys Leu Ala Asp Leu Ala Ile Ala Leu Ala Gly Leu Ser Ser
225                 230                 235                 240

Asp Lys Ala Arg His Ile Leu Asp Phe Thr Asp Ser Ile Arg Glu Val
```

```
                245                 250                 255

Leu Asn Glu Ser His Ser Asp Ala Val Ala Phe Met Arg Lys Asn Tyr
            260                 265                 270

Gly Asp Asn Ala Met Gly Leu Ala Gly Leu Ser Ser Arg Ile Lys
        275                 280                 285
```

<210> 7
<211> 322
<212> PRT
<213> Photorhabdus

<400> 7

```
Met Glu Arg Glu Tyr Ser Glu Lys Glu Lys His Lys Lys Arg Pro Ile
1               5                   10                  15

Gln Leu Arg Asn Ser Ile Glu Gln His Glu Glu Glu Thr Ala Asn Asn
            20                  25                  30

Ser Leu Gly Leu Gly Leu Asp Leu Asn Gln Ala Thr Asn Pro Pro Lys
        35                  40                  45

Val Pro Lys Asp Asn Tyr Asn Glu Glu Asn Gly Asp Leu Phe Tyr Gly
    50                  55                  60

Leu Ala Asn Gln Arg Gly Arg Tyr Ile Lys Ser Val Asn Pro Asn Phe
65                  70                  75                  80

Asp Pro Asp Lys Ile Asn Ser Ser Pro Met Ile Ile Asp Val Tyr Asn
                85                  90                  95

Asn Asn Val Ser Asn Thr Ile Leu Asn Lys Tyr Pro Leu Asp Lys Leu
            100                 105                 110

Val Lys Leu Ser Gly Asn Pro Gln Lys Tyr Ala Asn Asn Ile Lys Val
        115                 120                 125
```

```
Glu Asn Ser Leu Gln Gln Asp Val Ala Ser Ser Lys Arg Gly Trp Tyr
    130                 135                 140

Pro Leu Trp Asn Asp Tyr Phe Lys Thr Gly Asn Glu Asn Lys Lys Phe
145                 150                 155                 160

Asn Ile Ala Asp Ile Tyr Lys Glu Thr Arg Asn Gln Tyr Gly Ser Asp
                165                 170                 175

Tyr Tyr His Thr Trp His Thr Pro Thr Gly Ala Ala Pro Lys Leu Leu
            180                 185                 190

Trp Lys Arg Gly Ser Lys Leu Gly Ile Glu Met Ala Ala Ser Asn Glu
        195                 200                 205

Lys Thr Lys Ile His Phe Val Leu Asp Gly Leu Asn Ile Gln Glu Val
    210                 215                 220

Val Asn Lys Gln Lys Gly Ser Thr Pro Leu Glu Gln Gly Arg Gly Glu
225                 230                 235                 240

Ser Ile Thr Ala Ser Glu Leu Arg Tyr Ala Tyr Arg Asn Arg Glu Arg
                245                 250                 255

Leu Ala Gly Lys Ile His Phe Tyr Glu Asn Asp Gln Glu Thr Val Ala
            260                 265                 270

Pro Trp Glu Lys Ser Pro Glu Leu Trp Gln Asn Tyr Ile Pro Lys Asn
        275                 280                 285

Lys Asn Gln Asn Glu Ser Ser Thr Pro Gln Arg Asn Asn Gly Thr Leu
    290                 295                 300

Tyr Arg Leu Gly Gly Pro Phe Arg Lys Leu Arg Ala Ser Leu Arg Lys
305                 310                 315                 320

Arg Ser
```

<210> 8
<211> 308
<212> PRT
<213> Photorhabdus

<400> 8

```
Met Met Glu His Glu Tyr Ser Lys Glu Glu Glu Lys Lys Arg Gln Gln
1               5                  10                  15


Ser Lys Pro Asn Asn Ala Thr His Asp Glu Ser Asn Leu Pro Leu Glu
            20                  25                  30


Leu Glu Lys His Phe Asn Ala Arg Thr Pro Ala Thr Ala His Ser Lys
        35                  40                  45


Trp Phe Thr Tyr Glu Asn Asp Thr Glu Val Glu Leu Thr Thr Glu Arg
    50                  55                  60


Ile Lys Glu Ile Phe Ser Asn Lys Gln Pro Lys Ile Ile Ile Ala Gly
65                  70                  75                  80


Asp Gly His Asn Lys Pro Pro Phe Gln Tyr Ala Lys Asn Ile Pro Asp
                85                  90                  95


Val Asn Ser Ser Phe Asp Ala Gly Thr Leu Gln Leu Tyr Ile Glu Ala
            100                 105                 110


Thr Asp Glu Gln Ile Asn Glu Asn Asn Pro Glu Tyr Ile Pro Lys Glu
        115                 120                 125


Phe Met Ala Lys Pro Gly Leu Phe Thr Asn Lys Asn Arg Arg Ala Glu
    130                 135                 140


Ile Val Gly Trp Glu Asp Ser Glu Leu Ser Asn Ala Met Lys Glu Met
145                 150                 155                 160


Phe Glu Leu Ser Asp Lys Ser Thr Arg Glu Lys Leu Thr Pro Glu Glu
```

```
                165                 170                 175

Thr Ser Ser Phe Tyr Lys Leu His Glu Thr Ala Ile Arg His Phe Phe
            180                 185                 190

Arg Pro Glu Phe Asn Gln Leu Arg Asp Glu Phe Phe Glu Ile Leu Ala
        195                 200                 205

Lys Ala Gly Ser Asn Arg Glu Leu Asp Lys Ile Ala Leu Glu Met Ile
    210                 215                 220

Gly Phe Thr Ser Gly Thr Trp Arg Asp Glu Tyr Ile Asn Pro Thr Leu
225                 230                 235                 240

Ala Glu Lys Ile Ala Lys His Ala Ala Glu Lys Glu Asn His Thr Phe
                245                 250                 255

Val Val Ser Ile Gly Asp Ala His Leu Ser Glu Asn Pro Met Gln Glu
            260                 265                 270

Tyr Leu Asn Lys Arg Arg Asn Gly Gly Glu Phe Lys His Gln Ile Ile
        275                 280                 285

Phe Thr Arg Asp Lys Arg Pro Ile Leu Pro Asp Asn Met Lys Thr Gly
    290                 295                 300

Asn Lys Asn Ser
305
```

<210> 9
<211> 298
<212> PRT
<213> Photorhabdus

<220>
<221> misc_feature
<222> (148)..(148)
<223> Xaa can be any naturally occurring amino acid

<400> 9

```
Met Leu Lys Tyr Ala Asn Pro Gln Ala Val Pro Thr Gln Arg Thr Lys
1               5                   10                  15


Asn Thr Ala Lys Lys Pro Ser Ser Ser Ser Ser Phe Asp Gly Gln Leu
            20                  25                  30


Glu Leu Ser Asn Gly Glu Trp Ser Lys His Ser Glu Met Gly Leu Lys
        35                  40                  45


Arg Gly Gly Leu Ile Asn Ser Ile Arg Arg Arg Ile Ala Arg Asn Gly
    50                  55                  60


Asn Ile Gly Arg Phe Asn Glu Leu Ile Asp Ser Glu Ala Lys Lys Trp
65                  70                  75                  80


Pro Ser Glu Pro Val Asp Lys Asn Ile His Met Ile Trp Ile Gly Thr
                85                  90                  95


Arg Asn Ile Ser Glu Lys Asn Ile Lys Leu Ser Ile Asp Thr Ala Lys
            100                 105                 110


Lys Asn Pro Asp Tyr Asn Thr Ser Ile Ile Tyr Asp Ser Gly Ile Ser
        115                 120                 125


Gly His Glu Gly Ala Arg Asn Phe Met Leu Glu Lys Phe Glu Gly Ser
    130                 135                 140


Asn Val Asn Xaa Ser Leu Ala Phe Pro Lys Gly Ile Gly Val Met Arg
145                 150                 155                 160


Glu Tyr Ala Pro Glu Ala Gly Lys Ala Thr Ala Phe Pro Asn Thr Pro
                165                 170                 175


Ile Ala Val Thr Lys Asn Asn Pro Ile Ile Asn Lys Thr Leu Asp Leu
            180                 185                 190
```

```
Ala Val Gly Asn Tyr Gln Arg Gly Glu Lys Asn Val Leu Lys Leu Ala
        195                 200                 205

Gly Pro Asp Val Phe Thr Gln Ala Leu Tyr Gln Glu Ile Pro Gly Leu
    210                 215                 220

Asn Ser Lys Val Leu Asn Ala Gln Leu Asp Gln Phe Glu Leu Ala Lys
225                 230                 235                 240

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

Glu Lys Leu Thr Ser Val Glu Lys Glu Lys Ile Asn Arg Pro Tyr Gln
            260                 265                 270

Ser Met Arg Gly Leu Ser Gly His Val Met Asn Gly Ala Asp His Ser
        275                 280                 285

Trp Ala Val Asp Thr Glu Val Leu Gly His
    290                 295
```

<210> 10
<211> 299
<212> PRT
<213> Photorhabdus

<400> 10

```
Met Met Arg Glu Tyr Ser Asn Glu Asp Asp Cys Thr Lys Glu Lys Thr
1               5                   10                  15

Asn Leu Val Lys Ser Glu Asn Val Glu Ala Asp Asn Tyr Leu Glu Met
            20                  25                  30

Glu His Leu Thr Tyr Leu Ala Lys Leu Ile Ser Met Thr Glu Arg Glu
        35                  40                  45

Asn His His Leu Asn Ser Ile Lys Leu Ile Asp Asp Ile Ile Glu Leu
    50                  55                  60
```

```
His Asn Asp Arg Lys Gly Asn Lys Leu Leu Trp Asn Asp Asn Trp Gln
65                  70                  75                  80

Asp Lys Ile Ile Asp Arg Asp Leu Gln Ser Ile Phe Lys Lys Ile Asp
                85                  90                  95

Glu Met Val Ser Glu Phe Gly Gly Leu Glu Ala Tyr Lys Asp Ile Val
            100                 105                 110

Gly Glu Ser Pro Tyr Asp Pro Thr Glu Pro Val Cys Gly Tyr Ser Ala
        115                 120                 125

Gln Asn Ile Phe Lys Leu Met Thr Glu Gly Glu Tyr Ala Val Asp Pro
    130                 135                 140

Val Lys Met Ala Lys Thr Gly Lys Ile Asn Gly Asn Gln Phe Ala Glu
145                 150                 155                 160

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

Asp His Arg Leu Gly His Met Phe Leu Val Asp Ile Pro Ser Thr Asn
            180                 185                 190

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

Leu Pro Ala Leu Lys Ile Ala Asp Trp Leu Lys Ser Arg Gly Lys Glu
    210                 215                 220

Ser Ile Asn Val Asn Lys Leu Lys Lys Phe Leu Asn Asp Glu Phe Thr
225                 230                 235                 240

Met Leu Pro Glu Asn Glu Gln Lys Gly Leu Ile Ala Glu Ile Phe Asp
                245                 250                 255

Leu Asn Lys Asp Ile Asp Ser Val Lys Ser Gly Lys Ile Lys Lys Asp
```

260 265 270

Lys Ala Val Asp Ile Tyr Leu Arg Glu Tyr Asp Ile Asn Asp Phe Ile
275 280 285

Ser Asn Val Glu Lys Leu Lys Thr Lys Leu Ala
290 295

<210> 11
<211> 148
<212> PRT
<213> Photorhabdus

<400> 11

Met Ile Phe Lys Met Leu Asn Leu Ala Val Phe Tyr Leu Leu Gly Asn
1 5 10 15

Ile Phe His Tyr Leu Ile Cys Gln Lys Phe Ile Cys Tyr Phe Cys Ser
20 25 30

Val Leu Lys Ser Val Thr Met Phe Leu Thr Lys Val Ala Val Gln Ile
35 40 45

Ala Leu Tyr Leu Asn Ile Leu Pro Thr Met Ala Gly Ile Ala Gly Leu
50 55 60

His Ala Glu Val Gln Ala Leu Asn Asn Leu Phe Ile Ser Gly Asp Arg
65 70 75 80

Gly Thr Glu Lys Arg Glu Asn Trp Lys Tyr Ile Arg Asn Met Leu Glu
85 90 95

Ser Thr Ile Phe Thr Gln Arg Leu Thr Ala Gly Gln Ala Gly Lys Asp
100 105 110

Phe Ala Ala Cys His Asn Cys Ser Gly Ile Leu Ser Ser Pro Val Asn
115 120 125

Val Ile Thr Gly Lys Val Glu Ser Ala Gly Gly Asn Phe Phe Ile Asn
    130   135   140

Ile Ile Ser Ile
145

<210> 12
<211> 170
<212> PRT
<213> Photorhabdus

<400> 12

Met Glu Arg Glu Tyr Ser Glu Lys Pro Lys Asn Leu Ser Gln Leu Ser
1   5   10   15

Arg Lys Thr Ala Ile Ser Glu Arg Arg Ala Met Phe Glu Arg Asn Ala
            20   25   30

Ser Ser Asn Asn Glu Gln Pro Val Pro Gln Phe Ala Arg Ser Tyr Thr
        35   40   45

Ser Asn Arg Ser Val Val Asn Ile Asn Pro Gly Arg Ser Ser Ile Ala
    50   55   60

Val Val Thr Ala Asn Ser Thr Ser Pro Val Asn Ile Ser Thr Pro Ala
65   70   75   80

Ala Ala Ser Pro Asp Lys Leu Leu Pro Ser Thr Ser Cys Asp Thr Thr
                85   90   95

Ser Ser Thr Leu Thr Val Gly Lys Tyr Lys Leu Glu Leu Thr Ser Gln
            100   105   110

Gly Lys Val Val Val Phe Arg Gly Asp Asn Arg Thr Pro Glu Gln Ile
        115   120   125

Val Ala Ala Gly Gly Phe Gly Glu Gln Ser Asn Tyr Leu Tyr Lys Met
    130   135   140

```
Glu Ile Pro Gly Leu Lys Pro Gln Asp Met Asn Glu Arg Thr Leu Gly
145                 150                 155                 160


Glu Lys Ile Arg Gln Asp Ser Arg Gly Asn
                165                 170


<210>  13
<211>  298
<212>  PRT
<213>  Photorhabdus

<400>  13

Met Lys Tyr Asp Pro Arg Leu Arg Thr Trp Val Glu Asp Asp Phe Asp
1               5                   10                  15


Tyr Glu Lys Asn Phe Lys Lys Gln Thr Asp Tyr Ile Asn Tyr Lys Asp
            20                  25                  30


Leu Glu Lys Gln Leu Lys Glu Asn Val Asp Tyr Tyr Ala Leu Leu Asp
        35                  40                  45


Glu Asn Glu Ala Ile Ile Phe Leu Lys Glu Leu Gly Cys Asp Ile Lys
    50                  55                  60


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


Phe Ala Gly Asn Ile Lys Asp Ala Leu Gly Val Phe Lys Val Ala Lys
                85                  90                  95


Asn Phe Lys Pro Ile Asn Ile Gly Ile Phe Thr Tyr Ile Ile Asn Glu
            100                 105                 110


Leu Lys Gly Lys Gly Ile Lys Ala Ile Glu Tyr Leu Gly Lys Asn Gly
        115                 120                 125


Glu Arg Tyr Ile Lys Leu Thr Asp Arg Pro Gly Ile Arg Lys Tyr Leu
    130                 135                 140
```

```
Asn Ala Thr Arg Tyr Leu Ile Asn Asn Lys Lys Ile Met Glu Val Gly
145                 150                 155                 160

Ile Gly Ser Val Ala Met Glu Gly Ser Ile Val Lys Gly Ala Arg Phe
                165                 170                 175

Gly Val Ile Tyr Ser Ala Ala Tyr Arg Ser Val Glu Leu Met Phe Lys
            180                 185                 190

Ser Glu Tyr Asp Leu Thr Asn Phe Phe Val Asn Leu Ser Met Asp Met
        195                 200                 205

Ala Lys Ile Ile Val Ala Thr Ile Ile Ala Lys Ser Thr Val Ala Ala
    210                 215                 220

Ala Thr Ser Phe Val Val Thr Ala Ala Leu Ser Thr Thr Ala Ile Ala
225                 230                 235                 240

Ile Gly Val Phe Ile Ile Gly Ala Leu Val Val Trp Gly Leu Met Trp
                245                 250                 255

Leu Asp Asp Glu Phe Lys Ile Ser Glu Thr Ile Ile Arg Arg Leu Lys
            260                 265                 270

Glu His Lys Val Lys Thr Pro Ile Ser Thr Tyr His Ser Asp Gln Ile
        275                 280                 285

Phe Asn Ala Trp Gly Arg Tyr Tyr Arg Gly
    290                 295
```

<210> 14
<211> 328
<212> PRT
<213> Photorhabdus

<400> 14

```
Met Pro Asn Lys Lys His Ser Glu Asn Thr His Gln Gly Arg Lys Pro
```

```
1               5                   10                  15

Leu Ile Lys Ser Glu Ala Asn Asn Glu His Asp Ile Glu Asn Ser Ser
            20                  25                  30

Leu Gly Ile Gly Leu Asp Leu Asn Ser Thr Ile Gly Asn Asn Ser Ala
        35                  40                  45

Ser Leu Ser Gln Ile Gln Asp Tyr Ser Phe Trp Lys Glu Asn Ile Ser
    50                  55                  60

Glu Tyr Tyr Lys Trp Met Val Val Val Lys Ala His Leu Lys Gln Leu
65                  70                  75                  80

Asp Trp Thr Leu Lys Ser Met Asp Ser Ser Glu Ser Ala Gly Thr Asn
                85                  90                  95

Ile Ala Lys Asn Ile Gly Thr Thr Ala Leu Gln Thr Leu Leu Asn Thr
            100                 105                 110

Gly Gly Ser Ile Ala Gly Gly Ala Ile Gly Gly Ala Ile Gly Ser Ala
        115                 120                 125

Ile Ala Pro Gly Val Gly Thr Ile Ala Gly Met Gly Ile Gly Ala Leu
    130                 135                 140

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

Asn Glu Lys Leu Glu Ile Ala Tyr Pro Tyr Pro Lys Thr Arg Asn Met
                165                 170                 175

Ile Phe Asp Ile Asn Asn Tyr Asp Lys Asn Pro Ile Ile Lys Ala Ile
            180                 185                 190

Lys Lys Lys Thr Asn Lys Asp Asn Leu Lys Val Thr Ala Gly Ser Ser
        195                 200                 205
```

```
Leu Thr Ser Gln Leu Val Gly Lys Val Thr Ser Pro Ile Lys Phe Pro
    210                 215                 220

Ala Tyr Lys Leu Ser Asp Leu Ala Ile Ser His Asn Arg Ala Leu Ala
225                 230                 235                 240

Gly Leu Ser Ser Asp Lys Ala Arg His Ile Leu Asp Phe Thr Asp Ser
                245                 250                 255

Ile Arg Glu Val Leu Asn Glu Ser His Ser Asp Ala Val Ala Phe Met
            260                 265                 270

Arg Lys Asn Tyr Gly Asp Asn Ala Met Gly Leu Ser Gly Leu Ser Ser
        275                 280                 285

Arg Ile Lys Gly Glu Lys Leu Thr Leu Ala Thr Leu Ala Arg Thr Arg
    290                 295                 300

Asn Lys Ile Glu Asn Arg Ile Asn Ser Ile Asn Lys Gln Thr Leu Lys
305                 310                 315                 320

Leu Ser Ser Lys Asn Ser Asn Glu
                325
```

<210> 15
<211> 322
<212> PRT
<213> Photorhabdus

<400> 15

```
Met Glu Arg Glu Tyr Ser Glu Lys Glu Lys His Lys Lys Arg Pro Ile
1               5                   10                  15

Gln Leu Arg Asn Ser Ile Glu Gln His Glu Glu Glu Thr Ala Asn Asn
            20                  25                  30

Ser Leu Gly Leu Gly Leu Asp Leu Asn Gln Ala Thr Asn Pro Pro Lys
        35                  40                  45
```

```
Val Pro Lys Asp Asn Tyr Asn Glu Glu Asn Gly Asp Leu Phe Tyr Gly
    50                  55                  60

Leu Ala Thr Gln Arg Gly Arg Tyr Ile Lys Ser Val Asn Pro Asn Phe
65                  70                  75                  80

Asp Pro Asp Lys Ile Asn Ser Ser Pro Met Ile Ile Asp Val Tyr Asn
                85                  90                  95

Asn Asn Val Ser Asn Thr Ile Leu Asn Lys Tyr Pro Leu Asp Lys Leu
            100                 105                 110

Val Lys Leu Ser Gly Asn Pro Gln Lys Tyr Ala Asn Asn Ile Lys Val
        115                 120                 125

Glu Asn Asn Leu Gln Gln Asp Val Ala Ser Ser Lys Arg Gly Trp Tyr
    130                 135                 140

Pro Leu Trp Asn Asp Tyr Phe Lys Ile Gly Asn Glu Asn Lys Lys Phe
145                 150                 155                 160

Asn Ile Ala Asp Ile Tyr Lys Glu Thr Arg Asn Gln Tyr Gly Ser Asp
                165                 170                 175

Tyr Tyr His Thr Trp His Thr Pro Thr Gly Ala Ala Pro Lys Leu Leu
            180                 185                 190

Trp Lys Arg Gly Ser Lys Leu Gly Ile Glu Met Ala Ala Ser Asn Glu
        195                 200                 205

Lys Thr Lys Ile His Phe Val Leu Asp Gly Leu Asn Ile Gln Glu Val
    210                 215                 220

Val Asn Lys Gln Lys Gly Ser Thr Pro Leu Glu Gln Gly Arg Gly Glu
225                 230                 235                 240
```

```
Ser Ile Thr Ala Ser Glu Leu Arg Tyr Ala Tyr Arg Asn Arg Glu Arg
                245                 250                 255

Leu Ala Gly Lys Ile His Phe Tyr Glu Asn Asp Gln Glu Thr Val Ala
            260                 265                 270

Pro Trp Glu Lys Ser Pro Glu Leu Trp Gln Asn Tyr Ile Pro Lys Asn
        275                 280                 285

Lys Asn Gln Asn Glu Ser Ser Thr Pro Gln Arg Asn Asn Gly Ala Leu
    290                 295                 300

Tyr Arg Leu Gly Gly Pro Phe Arg Lys Leu Arg Ala Ser Leu Arg Lys
305                 310                 315                 320

Arg Ser
```

<210> 16
<211> 308
<212> PRT
<213> Photorhabdus

<400> 16

```
Met Met Glu His Glu Tyr Ser Lys Glu Glu Glu Lys Lys Arg Gln Gln
1               5                   10                  15

Ser Lys Pro Asn Asn Ala Thr His Asp Glu Ser Asn Leu Pro Leu Glu
            20                  25                  30

Leu Glu Lys His Ser Asn Ala Arg Thr Ser Ala Thr Ala Tyr Ser Lys
        35                  40                  45

Trp Phe Thr Tyr Glu Asn Asp Met Glu Val Glu Leu Thr Thr Glu Arg
    50                  55                  60

Val Arg Glu Ile Phe Ser Asn Lys Gln Pro Lys Ile Ile Ile Ala Gly
65                  70                  75                  80
```

```
Asp Gly His Asn Lys Pro Pro Phe Gln Tyr Thr Lys Asn Ile Pro Asp
                85                  90                  95

Val Asn Ser Ser Phe Asp Ala Gly Thr Leu Gln Leu Tyr Ile Glu Ala
            100                 105                 110

Thr Asp Glu Gln Ile Asn Glu Asn Asn Pro Glu Tyr Ile Pro Lys Glu
        115                 120                 125

Phe Met Ala Lys Pro Gly Leu Phe Thr Asn Lys Asn Arg Arg Ala Glu
    130                 135                 140

Ile Val Gly Trp Glu Asp Ser Glu Leu Ser Asn Ala Met Lys Glu Met
145                 150                 155                 160

Phe Glu Leu Ser Asp Lys Ser Thr Arg Glu Lys Leu Thr Pro Glu Glu
                165                 170                 175

Thr Ser Ser Phe Tyr Lys Leu His Glu Thr Ala Ile Arg His Phe Phe
            180                 185                 190

Arg Pro Glu Phe Asn Gln Leu Arg Asp Glu Phe Phe Glu Ile Leu Ala
        195                 200                 205

Lys Ala Gly Ser Asn Arg Glu Leu Asp Lys Ile Ala Leu Glu Met Ile
    210                 215                 220

Gly Phe Thr Ser Gly Thr Trp Arg Asp Glu Tyr Ile Asn Pro Thr Leu
225                 230                 235                 240

Ala Glu Lys Ile Ala Lys His Ala Ala Glu Lys Glu Asn His Thr Phe
                245                 250                 255

Val Val Ser Ile Gly Asp Ala His Leu Ser Glu Asn Pro Met Gln Glu
            260                 265                 270

Tyr Leu Asn Lys Arg Arg Asn Gly Gly Glu Phe Lys His Gln Ile Ile
```

275 280 285

Phe Thr Arg Asp Lys Arg Pro Ile Leu Pro Asp Asn Met Lys Thr Gly
290 295 300

Lys Lys Asn Ser
305

<210> 17
<211> 1633
<212> PRT
<213> Photorhabdus

<400> 17

Met Ser Asn Tyr Glu Tyr Asp Ile Val Thr Gln His Asp Thr Tyr Gln
1 5 10 15

Ile Lys Asp Asn Glu Tyr Thr Val Val Asn Gly Lys Tyr Trp Gln Tyr
20 25 30

Glu Gln Glu Gly Asn Lys Asn Asn Asn Lys Ile Ser Ile Ser Leu Met
35 40 45

Lys Asp Asn Gln Asn Asp Pro Val Trp Ile Thr Ser Asp Ile Lys Glu
50 55 60

Ile Ser Leu Tyr Ile Ile Glu Asn Leu Phe Ser Tyr His Lys Phe Ser
65 70 75 80

Ala Glu Leu Gln His Thr Leu Lys Asn Ala Val Lys Ala Val Phe Asn
85 90 95

Glu Tyr Ser Glu Ile Lys Tyr Ser Glu Leu Leu His Asn Ile Asn Asn
100 105 110

Ile Phe Asn Leu Phe Phe Ile Lys Thr Tyr Asn Thr Ser Asp Ile Asn
115 120 125

```
Thr Ala Ile Asn Ile Leu Thr Ala Lys Ile Glu Ile Tyr Asp Lys Leu
    130                 135                 140

Glu Lys Ile Asn Gln Asp Lys Thr Asp Leu Asn Asn Thr Lys Val Asp
145                 150                 155                 160

Ile Trp Glu Glu Leu Gly Ile Asn Ala Glu Glu Pro Leu Leu Lys Ile
                165                 170                 175

Tyr Arg Gln Ala Phe Ser Thr Gly Asp Ile Asp Asp Glu Val Tyr Ser
            180                 185                 190

Asp Ala Leu Leu Thr Phe Met Ser Asp Gly Asn Leu Lys Leu Gly Asp
        195                 200                 205

Lys Glu Lys Ser Asp Tyr Asn Gln Arg Ile Lys Asp Lys Thr Asp Leu
    210                 215                 220

Phe Glu Ser Tyr Lys Lys Gly Ile Glu Lys Val Ala Ser Leu Ile Thr
225                 230                 235                 240

Thr Asn Asn Ile Asn Pro Gly Ile Pro Ile Thr Tyr Pro Glu Thr Glu
                245                 250                 255

Lys Ser Ile Asn Ile Gly Asp Asp Leu Leu Leu Ala Gln Leu Ala Lys
            260                 265                 270

Glu Glu Ile Ala Leu Lys Lys Gln Asn Arg Thr Glu Tyr Ser Gln Gln
        275                 280                 285

Asp Ile Phe Glu Leu Gln Thr Leu Gln Ala Ala Lys Tyr His Leu Leu
    290                 295                 300

Ile Leu Ser Ser Leu Gly Ala Leu Leu Tyr Gln Ile Ala Pro Asn Val
305                 310                 315                 320

Glu Lys Met Thr Lys Gly His Gly Asp Tyr Arg Asp Ile Ile Phe Ser
                325                 330                 335
```

```
Gln Glu Gln Ala Glu Ser Leu Phe Lys Lys His Asn Ile Gln Tyr Asp
            340                 345                 350

Thr Asn His Val Leu Ser Gln Glu Ser Lys His Ile Glu Met Glu Gly
        355                 360                 365

Cys Ile Ile Leu Thr Ala Ala Ile Ile Tyr Arg Met Arg Lys Glu Asn
    370                 375                 380

Ala Thr Val Glu Gln Ala Leu Asn Tyr Ser Thr Leu Glu Thr Ile Lys
385                 390                 395                 400

Leu Phe Glu Asn Asp Lys Lys Lys Leu Asn Pro Phe Asn Thr Asn Asn
                405                 410                 415

Val Lys Pro Ala Gly Tyr Phe Ser Phe Ile Asp Phe Lys Lys Arg Asp
            420                 425                 430

Lys Phe Asp Ser Gln Tyr Asn Phe Asn Glu Gln Phe Asn Val Tyr Lys
        435                 440                 445

Asn Lys Tyr Ser His Tyr Glu Ser Ile Ser Phe Ser Lys Leu Ile Leu
    450                 455                 460

Ser Ser Pro Ala Ala Gln Leu Thr Ala Glu Glu Ile Val Asn Pro Pro
465                 470                 475                 480

Glu Glu Thr Phe Leu Tyr Ser Val Glu Gln Gly Met Gly Asn Val Ala
                485                 490                 495

Met Ile Lys Met Tyr Gln Gly Asn Trp Leu Val Val Ser Thr Ile Gln
            500                 505                 510

Gly Gly Val Lys Ala Arg Lys Tyr Ser Gln Gln Gln Val Asp Ser Gln
        515                 520                 525
```

```
Pro Thr Leu Arg Ala Met Ser Arg Pro Asn Ala Leu Phe Leu Ile Glu
    530                 535                 540

Arg Lys Ile Met Ile Gly Ile Gly Ile Phe Met Glu Asn Gln Ile Val
545                 550                 555                 560

Asn Thr Gly Lys Arg Leu Phe Pro Thr Gly Tyr Glu Arg Ala Lys Thr
                565                 570                 575

Leu Ser Gly Phe Ala Glu Thr Ser Arg Tyr Lys Asn Ser Tyr Asn Ala
            580                 585                 590

Phe Trp Asn Asp Tyr Tyr Gly Ile Thr Ser Gly Met Asn Val Gly Ile
        595                 600                 605

Ser Phe Thr Gly Ser Pro Lys Phe Asn Phe Tyr Lys Glu Glu Asn Leu
    610                 615                 620

Leu Ser Val Thr Ala Thr Ile Ile Gln Gln Gly Leu Asn Asp Ile Ala
625                 630                 635                 640

Ile Lys Ser Lys Gln Ala Leu Asp Ile Thr Ser Gly Trp His Ile Ala
                645                 650                 655

Ala Thr Ile Leu Ile Pro Phe Tyr Asn Val Ile Tyr Lys Ser Thr Thr
            660                 665                 670

Asp Ser Glu Tyr Glu Leu Thr Gly Glu Asp Ile Gly Ser Ile Val Phe
        675                 680                 685

Asp Thr Ala Asn Val Leu Leu Val Val Ala Thr Leu Gly Met Ser Leu
    690                 695                 700

Thr Glu Ser Met Ala Ala Lys Val Thr Gln Thr Thr Leu Arg Leu Arg
705                 710                 715                 720

Gln Ala Gly Leu Thr Gly Arg Ala Leu Ile Thr Ala Val Val Arg Thr
                725                 730                 735
```

```
Leu Pro Glu His Gly Ile Ile Thr Leu Arg Gln Ser Ser Gly Ile Ile
            740                 745                 750

Leu Gly Gly Leu Ile Asp Leu Ile Glu Pro Leu Pro Ile Arg Ser Thr
        755                 760                 765

Leu Thr Leu Thr Tyr Arg Gly Val Ile Ser Ala Val Gly Ala Met Arg
    770                 775                 780

Asn Ser Ile Lys Leu Glu Lys Ser Phe Ala Asp Ile Phe Gly Lys Ser
785                 790                 795                 800

Thr Arg Gly Leu Gly Lys Leu Lys His Glu Trp Lys Val Ser Asn Leu
                805                 810                 815

Pro Leu Glu Glu Ile Val Pro His Ser Asn Gly Gly Glu Ile Tyr Lys
            820                 825                 830

Gly Ile Tyr Ser Ile Arg His Thr Asn Pro Glu Thr Ala Val Lys Gln
        835                 840                 845

Asn Phe Tyr Ile Lys Glu Ala Gly Ala Asn Tyr Gln Val Lys Trp Asp
    850                 855                 860

Asp Ala Asn His Thr Trp Arg Val Val Asn Pro Thr Tyr Pro Glu Gln
865                 870                 875                 880

Phe Ser Tyr Trp Pro Ala Val Lys Leu Asp Lys Asn Gly His Trp Val
                885                 890                 895

Thr His Ala Asp Ile Ser Asn Lys Phe Leu Ile Leu Glu Lys Ser Lys
            900                 905                 910

Arg Ile Asp Gln Glu Leu Glu Ala Ala His Ser Asn Ile Asn Asn Asp
        915                 920                 925
```

```
Asn Ile Leu Asp Ala Phe Ile His Ile Asn Thr Ala Phe Lys Asp Cys
    930                 935                 940

Glu Arg Tyr Asp Ile Asp Lys Leu Ser Asp Ile Thr Asp Thr Leu Thr
945                 950                 955                 960

His Phe Phe Glu Lys Ser Leu Lys Pro Gly Asp Lys Lys Ala Ile Phe
                965                 970                 975

Ser Thr Glu Ile Met Ser Ile Gln Gln Ala Trp Ile Arg Glu Val Ile
            980                 985                 990

Leu Pro Leu Gln Asn Asn Ser Ser  Ile Ser Ile Glu Lys  Ile Asn Ala
        995                 1000                1005

Ile Lys  Thr Glu Leu Pro Tyr  Leu Leu Arg Lys Thr  Phe Pro Ile
    1010                1015                1020

Glu Ser  Gln Leu Pro Asn Gln  Leu Val Ala Asn Lys  Ile Ala Leu
    1025                1030                1035

Ala Ile  Glu Glu Ile Pro Asn  Thr Arg Ile Pro Lys  Tyr Thr Ser
    1040                1045                1050

Gly Asn  Ile Ser Lys Thr Val  Gln Tyr Thr Ser Leu  Leu Glu Asn
    1055                1060                1065

Asn His  Val Asp Ile Pro Pro  Val Gly Ile Thr Ile  Thr Gly Asn
    1070                1075                1080

Asp Thr  Phe Ile Asn Gln Val  Thr Arg Val Leu Ser  Glu Ile Asp
    1085                1090                1095

Glu Ile  Pro Ser Gly Asn Ile  Val Ile Gln Glu Leu  Glu Lys Gln
    1100                1105                1110

Gly Leu  Asn Ile Gln Pro Pro  Thr Met Asn Asp Ile  Val Arg Glu
    1115                1120                1125
```

```
Lys Asn  Gly Gln Phe Tyr Ala  Asn Asn Ser Ala Gly  Ser His Ile
    1130                1135                1140

Ala Phe  Asp Pro Glu Asn His  Leu Ile Gly Thr Glu  Glu Lys Leu
    1145                1150                1155

Ile Asp  Glu Pro Trp Arg Thr  Arg Glu Pro Ala Ile  Ala Leu Tyr
    1160                1165                1170

His Glu  Met Leu His Ile Tyr  Tyr Asn Arg Tyr Pro  Thr Trp Phe
    1175                1180                1185

Thr Ser  Ile Asp Asn Lys Val  Ile Asp Gln Lys Val  Ser Gly Gly
    1190                1195                1200

Phe Ser  Leu Leu Glu Glu Ser  Arg Ile Val Gly Thr  Lys Tyr Tyr
    1205                1210                1215

Val Asn  Asp Lys Asp Thr Leu  Phe Asp Phe Asn Asp  Ser Asp Tyr
    1220                1225                1230

Leu Leu  Glu Asn Asn Ser Ala  Leu Leu Thr Glu Asn  Arg Phe Arg
    1235                1240                1245

Ala Glu  Tyr Ala Ile Phe Lys  Asn Lys Ser Glu Tyr  Val Ile Arg
    1250                1255                1260

Pro Tyr  Ser Gly Lys Gly Asp  Ser Gln Ile Pro Leu  Thr Lys Thr
    1265                1270                1275

Lys Ile  Asn Ile Asn Glu Ser  His Arg Asn Val Met  Gly Val Gly
    1280                1285                1290

Ser Gly  Lys Pro Glu Lys Met  Pro Asn Glu Ser Ala  Thr Asp Tyr
    1295                1300                1305
```

```
Arg Asn  Arg Val Arg Glu Trp  Arg Lys Ala Asn Lys  Gln Pro Glu
    1310                1315                1320

Ala Asp  Ile Gly Thr Gly Asp  Met Arg Lys Thr Lys  Ala Glu Ala
    1325                1330                1335

Arg Val  Lys Leu Leu Lys Glu  Asn Tyr Pro Gln Phe  Glu Pro Gln
    1340                1345                1350

Lys Ile  Glu Leu Gly Gly Ala  Phe Gln Leu Trp Thr  Val Pro Asn
    1355                1360                1365

Glu Pro  Ala Asn Lys Leu Met  Leu Ser Ser His Gly  Tyr Phe Phe
    1370                1375                1380

Ser Asp  Ser Ala Ala Thr Gln  Val Pro Ala Gly Lys  Thr Ile Gln
    1385                1390                1395

Phe Leu  Gly Pro His Gly Lys  Thr Leu Leu Glu Ala  Pro Glu Asn
    1400                1405                1410

Pro Leu  Asn Ser Pro Phe Asp  Val Thr Leu Gly Asn  Ser Gly Phe
    1415                1420                1425

Thr Val  Gln Pro Tyr Ala Thr  Ile Glu Ser Gly Asn  Lys Ala Gly
    1430                1435                1440

Leu Gly  Ser Val Lys Ile Gly  Asp Lys Thr Phe Thr  Val Asn Asp
    1445                1450                1455

Ile Gln  Asn Ile Ala Thr Asp  Asp Val Glu Asn Tyr  Leu Leu Ala
    1460                1465                1470

Thr Gly  Val Glu Ala Asn Ala  Ser Asn His Gly Lys  Val Arg Asn
    1475                1480                1485

Tyr Gly  Ile Lys Tyr Tyr Glu  Lys Met Pro Asp Glu  Glu Val Lys
    1490                1495                1500
```

```
Ala Ala  Ile Trp Lys Asn Arg  Ala Asp Glu Thr Ser  Thr His Lys
    1505                 1510                 1515


Tyr Asp  Ala Leu Leu Val Ser  Pro Glu Ala Gly Asn  Arg Lys Lys
    1520                 1525                 1530


Leu Ser  Asp Ile Phe Ala Leu  Met Lys Thr Asp Glu  Arg Met Ser
    1535                 1540                 1545


Lys Tyr  Asp Glu Ile Thr Phe  Val Ala Cys Arg Glu  Glu Leu Asn
    1550                 1555                 1560


Arg Ile  Asn Met Lys Ser Ile  His Asp Thr Gly Leu  Gly Gly Gly
    1565                 1570                 1575


Tyr Glu  Pro Lys Leu Glu Pro  Thr Val Ile Leu Ser  Arg Arg Arg
    1580                 1585                 1590


Arg Glu  Ala Thr Phe Thr Ala  Asp Gly Ala Ile Ile  Tyr Ser Ile
    1595                 1600                 1605


Ile Ala  Val Asn Leu His His  Asn Phe Ile Thr Glu  Glu Ile Val
    1610                 1615                 1620


Gly Ile  Ala Pro Phe Leu Phe  Ile Asp Asn
    1625                 1630


<210>  18

<400>  18
000

<210>  19
<211>  293
<212>  PRT
<213>  Photorhabdus

<400>  19
```

```
Met Phe Lys Tyr Asp Thr Ser Glu Lys Met Ala Lys Phe Gly Lys Gly
1               5                   10                  15

Lys Thr Ser Asp Gly Met Leu Leu Asp Thr Leu Tyr Leu Glu Ile Pro
            20                  25                  30

Asp Glu Lys Ala Val Met Ser Ala Tyr Lys Ser Gln Ile Leu Asp Glu
        35                  40                  45

Leu Arg Asn Phe Ser Glu Lys Thr His Ser Phe Phe Ser Gly Lys Lys
    50                  55                  60

Pro Leu Tyr Ser Lys Lys Tyr Leu Ala Asn Leu Ala Ala His Ala Gly
65                  70                  75                  80

Tyr Val His Val Thr Asp Tyr Asn Ser Ile Gly Asn Tyr Lys Asp Gly
                85                  90                  95

Phe Val Asn Phe Lys Asp Asn Ser Arg Asn Leu Ala Glu Gly Lys Leu
            100                 105                 110

Phe Pro Gly Ile Arg Leu Ile Lys Arg Pro Lys Leu Ser Ile Val Arg
        115                 120                 125

Asp Lys Glu Thr Glu Arg Trp Lys Lys Gln Glu Ser Asp Glu Ala Asp
    130                 135                 140

Ala Tyr Glu Ile Thr Asp Ile Glu Ser Phe Ile Ser Gly Val Arg Asp
145                 150                 155                 160

Met Tyr Ser Arg Ala Asn Val Asp Leu His Pro Val Ile Glu Ser Leu
                165                 170                 175

Ile Arg Asn His Ile Val Asn Asn Asp His Val Leu Pro Thr Met Ala
            180                 185                 190

Gly Ile Ala Gly Leu His Ala Glu Val Gln Ala Leu Asn Asn Leu Leu
        195                 200                 205
```

```
Ile Leu Ala Asp Gly Arg Ala Gly Lys Ile Val Gly Gly Arg Lys Ile
    210                 215                 220

Glu Glu Tyr Met Gln Asp Met Leu Lys Ser Phe Ile Phe Thr Gln Arg
225                 230                 235                 240

Leu Thr Thr Lys Gln Ala Gly Asn Asp Phe Ala Ala Cys His Asn Cys
                245                 250                 255

Ser Gly Ile Leu Ser Val Pro Ala Asn Val Ile Thr Gly Lys Val Ala
            260                 265                 270

Ser Ala Gly Ser Asn Phe Ser Leu Ile Leu Ser Arg Tyr Lys Asn Ser
        275                 280                 285

Gln Glu Ser Pro Ile
    290
```

<210> 20
<211> 340
<212> PRT
<213> Photorhabdus

<400> 20

```
Met Leu Lys His Ala Asn Pro Gln Thr Val Ser Thr Gln Arg Thr Lys
1               5                   10                  15

Ser Thr Ala Lys Lys Pro Ser Ser Ser Ser Ser Phe Asp Arg Gln Phe
            20                  25                  30

Glu Leu Ser Asn Ser Glu Asn Gln Pro Gly Glu Gly Asn Lys Asp Trp
        35                  40                  45

Thr Ile Lys Gly Trp Arg Gln Arg Phe Ala Asp Arg Ser Leu Asn Lys
    50                  55                  60

Gly His Ile Ser Pro Leu Met Asn Lys Gly Leu Leu Val Gly Ser Glu
```

```
65                  70                  75                  80

Glu Ala Leu Ile Asn Val Pro Val Val Ala His Arg Tyr Asp Ser Ser
                85                  90                  95

His Gln Leu Thr Asp Ala Gly Pro Leu Lys Ala Asp Ser His Ser Asn
            100                 105                 110

Asn Leu Asp Pro Phe Tyr Gly Val Val Thr Gly Phe Arg Gly Asp Gln
        115                 120                 125

Val Thr Ser Ser Glu Ser Gly Ser Gly Ser Ile Gly Gly His Trp Gly
    130                 135                 140

Lys Asn Thr Leu Asp Ser Asn Ile Thr Gly Ile Asn Val Val Asn Gly
145                 150                 155                 160

Ala Ser Gly Thr Val Gly Ile Arg Ile Ala Leu Lys Asp Ile Gln His
                165                 170                 175

Gly Ala Pro Val Ile Val Thr Ser Gly Ala Leu Ser Gly Cys Thr Met
            180                 185                 190

Val Tyr Ala Val Lys Asn Gly Tyr Phe Phe Ala Tyr His Thr Gly Gln
        195                 200                 205

Lys Pro Gly Asp Lys Glu Trp Lys Thr Gly Arg Gln Gly Val Val Ala
    210                 215                 220

Thr Tyr Arg Ser His Gln Ala Leu Ser Pro Asp Ser Glu Pro Met Ala
225                 230                 235                 240

Val Gly Glu Gln Asn Asn Asp Leu Val Asn Ile Phe Ala Ser Tyr Asp
                245                 250                 255

Gln Gly Ile Ile Thr Tyr Met Gly Lys Pro Gly Val Ile Ile Asp Asn
            260                 265                 270
```

```
Thr Ala Glu Asn Val Gly Val Phe Asn Tyr Asp Glu Val Lys Leu Glu
        275                 280                 285


Lys Pro Asp Ile Arg Ala Gly Tyr Ser Tyr Ala Leu Leu Ala Lys Asp
    290                 295                 300


Asp Lys Gly Lys Val Asn Val Lys Val Leu Ser Glu Asp Val Ile Val
305                 310                 315                 320


Pro Leu Gly Asn Lys Gly Lys Thr Ile Lys Ala Ile Asn Ser Leu Lys
                325                 330                 335


Lys Arg Leu Leu
            340
```

<210> 21
<211> 336
<212> PRT
<213> Photorhabdus

<400> 21

```
Met Pro Arg Tyr Ala Asn Tyr Gln Ile Asn Pro Lys Gln Asn Thr Lys
1               5                   10                  15


Asn Ser His Gly Lys Ser Ser Ser Ser Asn Phe Ser Ser Gly Tyr Phe
            20                  25                  30


Ser Ser Ser Asn Asn Ser Leu Asp Asp Ser Leu Ile Arg Gln Gln Val
        35                  40                  45


Lys Arg Glu Phe Ile Trp Glu Gly His Met Lys Glu Ile Glu Glu Ala
    50                  55                  60


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


Thr Leu Arg Ala Leu Gly Lys Gly Ala Ala Ala Lys Gly His Asp Ile
                85                  90                  95
```

```
Leu Glu Lys Thr Ile Lys Pro Gly Ser Ile Asn Lys Ala Tyr Pro Lys
            100                 105                 110

Asp Glu Ala Ser Asn Val Ile Lys Lys Val Gln Glu Ala Gly Ile Glu
        115                 120                 125

Gly Tyr Val Gly His Trp Asp Lys Lys Thr Gly Arg Leu Leu Gly Ile
    130                 135                 140

Tyr Met Ser Ser Gly His Gly Leu Ser Asp Glu Gln Val Asn Gly Lys
145                 150                 155                 160

Ile Tyr Pro Ile Asp Leu Asn Asn Leu Glu Ala Ser Leu Ser Ala Leu
                165                 170                 175

Lys Thr Lys Glu Asn Trp Ala Ala Leu Pro Phe Thr Gly Asp Tyr Asp
            180                 185                 190

Met His Asp Met Ile Ser Phe Thr Gly Gln Pro His Ser Val Pro Ser
        195                 200                 205

Asn Ser Ser Glu Glu Arg Lys Ile Ile Asp Arg Ile Asn Arg Leu Val
    210                 215                 220

Ala Arg Ser Asp Pro Asn Arg Pro Phe Gly Asp Ile Glu His Asn Val
225                 230                 235                 240

Ile Arg His Gly Ala Gln Val Ser Tyr Pro Ala Phe Ala Met Asp Lys
                245                 250                 255

Glu Lys Glu Glu Ile Lys Lys His Gly Gly Ile Val Lys Ala Val Ala
            260                 265                 270

Glu Pro Gly Glu Phe Pro Val Ala Ile Val Ser Lys Gly Lys Trp Thr
        275                 280                 285
```

```
Ile Ala Asn Asn Ile Asp Glu Leu Asn Gln Phe Tyr Asn Ser Ile Gly
    290                 295                 300

Ala Lys Met Lys Val Ser Trp Lys Pro Gly Ala Glu Asn Pro Gly Phe
305                 310                 315                 320

Val Ser Asn Pro Gln Arg Pro Gly Met Ala Arg Phe Ser Arg Lys Arg
                325                 330                 335
```

<210> 22
<211> 299
<212> PRT
<213> Photorhabdus

<400> 22

```
Met Met Arg Glu Tyr Ser Lys Glu Asp Asp Cys Val Lys Glu Lys Thr
1               5                   10                  15

Asn Leu Ala Glu Ser Glu Asn Val Glu Ala Asp Asn Tyr Leu Glu Met
            20                  25                  30

Asp Cys Leu Asn Tyr Leu Ala Lys Leu Asn Gly Met Pro Glu Arg Lys
        35                  40                  45

Asp His Ser Leu Asn Ser Thr Lys Leu Ile Asp Asp Ile Ile Lys Leu
    50                  55                  60

His Asn Asp Arg Lys Gly Asn Lys Leu Leu Trp Asn Asp Asn Trp Gln
65                  70                  75                  80

Asp Lys Ile Ile Asp Arg Asp Leu Glu Ser Ile Phe Lys Lys Ile Asp
                85                  90                  95

Glu Met Val Ser Glu Phe Gly Gly Ile Glu Ile Tyr Lys Asp Ile Val
            100                 105                 110

Gly Glu Asn Pro Tyr Asp Pro Thr Glu Pro Val Cys Gly Tyr Ser Ala
        115                 120                 125
```

```
Gln Asn Ile Phe Lys Leu Met Thr Glu Gly Glu His Ala Val Asp Pro
    130                 135                 140

Val Lys Met Ala Gln Thr Gly Lys Ile Asn Gly Asn Glu Phe Ala Glu
145                 150                 155                 160

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

Asp His Arg Leu Gly His Met Phe Leu Val Asp Ile Pro Ser Thr Asn
            180                 185                 190

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

Leu Pro Ala Leu Lys Ile Ala Asp Trp Leu Lys Ser Arg Gly Lys Glu
    210                 215                 220

Ser Ile Asn Val Asn Lys Leu Lys Lys Phe Leu Ser Asn Glu Phe Thr
225                 230                 235                 240

Met Leu Ser Glu Ser Glu Gln Lys Glu Leu Ile Ala Glu Ile Phe Asp
                245                 250                 255

Ile Asn Lys Asp Ile Ala Asn Val Lys Leu Gly Lys Ile Lys Lys Asp
            260                 265                 270

Lys Ala Val Asp Val Tyr Leu Arg Glu Tyr Asp Leu Asn Asp Phe Ile
        275                 280                 285

Ser Asn Ile Glu Lys Leu Lys Thr Lys Leu Val
    290                 295
```

<210> 23
<211> 327
<212> PRT
<213> Photorhabdus

<400> 23

```
Met Pro Ile Ile Gly His Lys Glu Asp Leu Ile Arg Thr Glu Arg Ser
1               5                  10                  15

Ser Val Asp Leu Thr Arg Ser Ser Asn Asn Arg Gln Thr Asp Asn Leu
            20                  25                  30

Glu Leu Asn Ile Pro Gln His Lys Arg Asp Asn Lys Asp Ile Glu His
        35                  40                  45

Ala Val Ile Tyr Gly Phe Ser Gln His Arg Gly Pro Glu Met Gln Lys
    50                  55                  60

Ala Phe Ala Asp Asn Lys Asn Pro Val Thr Ile Asp Glu Tyr Asn Ala
65                  70                  75                  80

Gly Leu Gly Ile Met Gly Glu Leu Ser Leu Ser Asp Tyr Phe Arg Ile
                85                  90                  95

Ser Gln Asp Leu Lys Glu Asn Arg Leu Pro Glu Leu Asn Glu Lys Asn
            100                 105                 110

Ile Gln Asn His Ser Leu Lys Tyr Phe Asp Ala Met Gly Val Asn Met
        115                 120                 125

Lys Ser Ala Asp Pro Asn Val Lys Glu Glu Ala Lys Glu Gln Gln Arg
    130                 135                 140

Ala Tyr Thr Arg Ser Trp Gly Phe Tyr Met Met Glu Asn Lys Glu Lys
145                 150                 155                 160

Leu Asp Ile Gln Ser Lys Ile Asn Asn Leu Ile Pro Lys Lys Lys Ser
                165                 170                 175

Phe Phe Ser Lys Ser Pro Gly Glu Asp Glu Tyr Lys Lys Leu Asp Glu
            180                 185                 190
```

```
Phe Ile Leu Lys Asn Ser Asn Gly Ser Asn Leu Thr Ile Pro Lys Gln
        195                 200                 205

Arg Lys Ile Leu Met Lys Phe Ala Ser Ala Lys Asn Ala Val Asp Val
    210                 215                 220

Thr Lys Asn Leu Ser Gly Glu Glu Gln Thr Trp Leu Lys Asp Ile Ile
225                 230                 235                 240

Ala Thr Ala Phe Phe Arg Gln Thr Ser Lys Leu Gly Met Ser Trp Phe
                245                 250                 255

Ile Glu Gln Leu Ala Ser Pro Asp Phe Arg Phe Val Ile Val Gly Phe
            260                 265                 270

Asn Gly Glu Glu Leu Thr Thr Asp Gln Ile Arg Ser Asn Lys Pro Trp
        275                 280                 285

Lys His Gly Asn Arg Arg Lys Glu Gly Ala Ser Glu Tyr Ala Glu Pro
    290                 295                 300

Ile Thr Phe Ser Glu Ile Arg His Ala His Arg Lys Gly Tyr Asp Ser
305                 310                 315                 320

Lys Ile Asn Phe Ile Lys Lys
                325
```

<210> 24
<211> 926
<212> PRT
<213> Photorhabdus

<400> 24

```
Met Ile Ser Thr Phe Asp Pro Ala Ile Cys Ala Gly Thr Pro Thr Val
1               5                   10                  15

Thr Val Leu Asp Asn Arg Asn Leu Thr Val Arg Glu Ile Val Phe His
            20                  25                  30
```

```
Arg Ala Lys Ala Gly Gly Asp Thr Asp Thr Leu Ile Thr Arg His Gln
        35                  40                  45

Tyr Asp Leu Arg Gly Asn Leu Thr Gln Ser Leu Asp Pro Arg Leu Tyr
    50                  55                  60

Asp Leu Met Gln Lys Asp Asn Thr Val Gln Pro Asn Phe Tyr Trp Gln
65                  70                  75                  80

His Asp Leu Leu Gly Arg Val Leu His Thr Val Ser Ile Asp Ala Gly
                85                  90                  95

Gly Thr Val Thr Leu Ser Asp Ile Glu Asp Arg Pro Ala Leu Asn Val
            100                 105                 110

Asn Ala Met Gly Val Val Lys Thr Trp Gln Tyr Glu Ala Asn Ser Leu
        115                 120                 125

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

Pro Arg Val Ile Glu His Phe Ile Trp Ala Gly Asn Ser Gln Ala Glu
145                 150                 155                 160

Lys Asp Leu Asn Leu Ala Gly Gln Tyr Met Arg His Tyr Asp Thr Ala
                165                 170                 175

Gly Leu Asp Gln Leu Asn Ser Leu Ser Leu Thr Gly Ala His Leu Ser
            180                 185                 190

Gln Ser Leu Gln Leu Leu Lys Asp Asp Gln Met Pro Asp Trp Ala Gly
        195                 200                 205

Asp Asn Glu Ser Val Trp Gln Asn Lys Leu Lys Asn Glu Val His Thr
    210                 215                 220

Thr Gln Ser Thr Thr Asp Ala Thr Gly Ala Pro Leu Thr Gln Thr Asp
```

```
225                 230                 235                 240

Ala Lys Glu Asn Met Gln Arg Leu Ala Tyr Asn Val Thr Gly Gln Leu
                245                 250                 255

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

Lys Ser Leu Ala Tyr Ser Glu Ser Gly Gln Lys Ile Arg Glu Glu His
        275                 280                 285

Gly Asn Gly Val Val Thr Lys Tyr Ser Tyr Glu Pro Asp Thr Gln Arg
    290                 295                 300

Leu Ile Asn Ile Thr Thr Gln Arg Ser Lys Gly His Val Phe Ser Glu
305                 310                 315                 320

Lys Leu Leu Gln Asp Leu Leu Tyr Glu Tyr Asp Pro Val Gly Asn Ile
                325                 330                 335

Val Ser Ile Leu Asn Arg Ala Glu Ala Thr His Phe Trp Arg Asn Gln
            340                 345                 350

Lys Val Ser Pro Arg Asn Thr Tyr Thr Tyr Asp Ser Leu Tyr Gln Leu
        355                 360                 365

Ile Gln Ser Thr Gly Arg Glu Met Ala Asp Ile Gly Gln Gln Asn Asn
    370                 375                 380

Lys Met Pro Thr Pro Leu Val Pro Leu Ser Ser Asp Asp Lys Val Tyr
385                 390                 395                 400

Thr Thr Tyr Thr Arg Thr Tyr Ser Tyr Asp Arg Gly Asn Asn Leu Thr
                405                 410                 415

Lys Ile Gln His Arg Ala Pro Ala Ser His Asn Ile Tyr Thr Thr Glu
            420                 425                 430
```

```
Ile Thr Val Ser Asn Arg Ser Asn Arg Ala Val Leu Ser His Asn Gly
        435                 440                 445

Leu Thr Pro Arg Glu Val Asp Ala Gln Phe Asp Ala Ser Gly His Gln
    450                 455                 460

Ile Ser Leu Pro Thr Gly Gln Asn Leu Ser Trp Asn Gln Arg Gly Glu
465                 470                 475                 480

Leu Gln Gln Ala Thr Thr Ile Asn Arg Asp Asn Ser Ala Thr Asp Arg
                485                 490                 495

Glu Trp Tyr Arg Tyr Asn Ala Gly Ser Ala Arg Ile Leu Lys Val Ser
            500                 505                 510

Glu Gln Gln Thr Gly Asn Ser Thr Gln Gln Gln Gln Val Thr Tyr Leu
        515                 520                 525

Pro Gly Leu Glu Leu Arg Thr Thr Lys Ser Gly Thr Asn Thr Thr Glu
    530                 535                 540

Asp Leu Gln Val Ile Thr Met Val Glu Thr Glu Arg Thr Gln Val Arg
545                 550                 555                 560

Ile Leu His Trp Ser Ala Gly Lys Pro Asn Asp Ile Ala Asn Asn Gln
                565                 570                 575

Val Arg Tyr Ser Tyr Asp Asn Leu Ile Glu Ser Asn Val Met Glu Leu
            580                 585                 590

Asp Thr Lys Gly Lys Ile Ile Ser Gln Glu Glu Tyr Tyr Pro Tyr Gly
        595                 600                 605

Gly Thr Ala Ile Trp Thr Ala Arg Asn Gln Ile Glu Ala Ser Tyr Lys
    610                 615                 620

Thr Val Arg Tyr Ser Gly Lys Glu Arg Asp Lys Thr Gly Leu Tyr Tyr
```

625 630 635 640

Tyr Arg His Arg Tyr Tyr Gln Pro Trp Leu Gly Arg Trp Leu Ser Ala
645 650 655

Asp Pro Ala Gly Thr Val Asp Gly Leu Asn Leu Tyr Arg Met Val Lys
660 665 670

Asn Asn Pro Ile Arg Tyr Gln Asp Glu Ser Gly Thr Asn Ala Asn Asp
675 680 685

Lys Ala Gln Ala Ile Phe Lys Glu Gly Lys Lys Ile Ala Ile Asn Gln
690 695 700

Leu Lys Ile Ala Ser Asn Phe Leu Lys Asp Ser Lys Asn Ser Glu Asn
705 710 715 720

Ala Leu Glu Ile Tyr Arg Ile Phe Phe Gly Gly His Gln Asp Ile Glu
725 730 735

Gln Leu Pro Gln Trp Lys Lys Arg Ile Asp Ser Val Ile Tyr Gly Leu
740 745 750

Asp Lys Leu Lys Thr Thr Lys His Val His Tyr Gln Gln Asp Lys Ser
755 760 765

Gly Ser Ser Ser Thr Val Ala Asp Leu Asn Val Asp Glu Tyr Lys Lys
770 775 780

Trp Ser Glu Gly Asn Lys Ser Ile Tyr Val Asn Val Tyr Ala Asp Ala
785 790 795 800

Leu Lys Arg Val Tyr Glu Asp Pro Leu Leu Gly Arg Glu His Val Ala
805 810 815

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

```
His Lys Tyr Ile Gly Val Leu Ser Ser Pro Gly Ser His Asp Leu Thr
        835                 840                 845

Asp Leu Leu Ser Ile Leu Met Pro Pro Ala Asn Glu Gln Asp Arg Thr
    850                 855                 860

Glu Lys Gln Arg Arg Ala Thr Gly Ala Arg Lys Ala Leu Glu Asn Ala
865                 870                 875                 880

Asp Ser Phe Thr Leu Ser Ala Arg Tyr Leu Tyr Tyr Thr Ala Gln Asp
                885                 890                 895

Pro Asn Phe Leu Ser Ser Leu Arg Lys Ala His Arg Asp Phe Asn Asn
            900                 905                 910

Lys Lys Thr Asp Arg Leu Ile Ile Arg Pro Pro Glu Arg Arg
        915                 920                 925
```

<210> 25
<211> 324
<212> PRT
<213> Photorhabdus

<400> 25

```
Met Glu Arg Glu Tyr Asn Lys Lys Glu Lys Gln Lys Lys Ser Ala Ile
1               5                   10                  15

Lys Leu Asp Asp Ala Val Gly Asn Asn Glu Glu Asn Met Asp Met Thr
            20                  25                  30

Ser Pro Leu Glu Leu Asn Ser Gln Tyr Thr Asn Arg Lys Arg Pro Gly
        35                  40                  45

Leu Arg Glu Arg Phe Ser Ala Thr Leu Gln Arg Asn Leu Pro Gly His
    50                  55                  60

Ser Met Leu Asp Arg Glu Leu Thr Thr Asp Gly Gln Lys Asn Gln Glu
65                  70                  75                  80
```

```
Ser Arg Phe Ser Pro Gly Met Ile Met Asp Arg Ile Met His Leu Gly
                85                  90                  95

Val Arg Thr Arg Leu Gly Lys Val Arg Asn Ser Ala Ser Lys Tyr Gly
            100                 105                 110

Gly Gln Val Thr Phe Lys Phe Ala Gln Thr Lys Gly Thr Phe Leu Asp
        115                 120                 125

Gln Ile Met Lys His Lys Asp Thr Ser Gly Gly Val Cys Glu Ser Ile
    130                 135                 140

Ser Ala His Trp Ile Ser Ala His Ala Lys Gly Glu Ser Ile Phe Asp
145                 150                 155                 160

Gln Leu Tyr Val Gly Gly Gln Lys Gly Lys Phe His Ile Asp Thr Leu
                165                 170                 175

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

Ser Thr Met Thr Glu Tyr Trp Leu Gly Thr Gln Gly Ile Gln Pro Asn
        195                 200                 205

Arg Gln Lys Asn Asp Asn Met Asn Glu His Ser Ser Lys Ile Val Gly
    210                 215                 220

Glu Thr Gly Thr Arg Gly Thr Lys Asp Leu Leu Arg Ala Ile Leu Asp
225                 230                 235                 240

Thr Gly Asp Lys Gly Ser Gly Tyr Lys Lys Ile Ser Phe Leu Gly Lys
                245                 250                 255

Met Ala Gly His Thr Val Ala Ala Tyr Val Asp Asp Gln Lys Gly Val
            260                 265                 270
```

```
Thr Phe Phe Asp Pro Asn Phe Gly Glu Phe Asn Phe Pro Asp Lys Val
        275                 280                 285

Ser Phe Ser His Trp Phe Thr Asp Asp Phe Trp Pro Lys Ser Trp Tyr
    290                 295                 300

Ser Leu Glu Ile Gly Leu Gly Gln Glu Phe Glu Val Phe Asn Tyr Glu
305                 310                 315                 320

Pro Lys Glu Pro
```

<210> 26
<211> 304
<212> PRT
<213> Photorhabdus

<400> 26

```
Met Val Tyr Glu Tyr Ala Lys Thr Asn Asp Arg Lys Arg Lys Leu Ser
1               5                   10                  15

Thr Gln Ser Asp Asn Tyr Glu Glu Lys Ser Phe Ser Pro Val Leu Asp
            20                  25                  30

Leu Ser Arg Asn Asn Gln Asn Thr Pro Asn Met Glu Asp Glu Tyr Glu
        35                  40                  45

Thr Pro Gln Asn Phe Ile Asn Arg Thr Gly Arg Glu Lys Leu Phe Arg
    50                  55                  60

Ala Ile Arg Met Val Ala Ser Asn Lys Arg Asp Pro Ile Thr Lys Asp
65                  70                  75                  80

Gln Val Ser Val Pro Pro Asp Gly Asn Leu Phe Thr Glu Leu Lys Asp
                85                  90                  95

Lys His Leu Asp Arg Ala Ala Glu Tyr Lys Lys Leu Lys Thr Trp Pro
            100                 105                 110
```

```
Thr His Ala Ser Ile Ile Ala Thr Ser Pro Ser Ala Asn Thr Pro Ile
        115                 120                 125

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

Gly Asp Lys Pro Gly Ala Val Gln Asn Thr Val Arg Asn Trp Asn Gly
145                 150                 155                 160

Ile Gly Pro Ala Ser Glu Arg Arg Leu Arg Pro Glu Lys Thr Trp Ser
                165                 170                 175

Pro Ile Ile Glu Ile Asp Val Asn Lys Leu Pro Asp Thr Thr Lys Ile
            180                 185                 190

Phe Asp Leu Asn Lys Pro Asn Asn Thr Phe Phe Ser Thr Thr Asn Ser
        195                 200                 205

Asp Ile Ala Gln Asn Ala Phe Ala Asp Lys Glu Val Leu Ile Ser Pro
    210                 215                 220

Glu Ile Pro Gly Leu Ala Ile Thr Arg Val Ile Asn Asp Pro Glu Glu
225                 230                 235                 240

Ile Lys Gln Ile Ala Asn Leu Asn Pro Ser Gln Ser Leu Ile Glu Lys
                245                 250                 255

Lys Asn Thr Ile Pro Glu Glu Lys Ile Ile Phe Glu Glu Lys Lys Ser
            260                 265                 270

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

Phe Pro Lys Arg Lys Lys Pro Arg Asn Ile Arg Ser Arg Thr Asp Ser
    290                 295                 300
```

<210> 27

<211> 542
<212> PRT
<213> Photorhabdus

<400> 27

Met Val Phe Glu His Asp Lys Thr Val Glu Arg Lys Arg Lys Pro Ser
1 5 10 15

Ile Gln Leu Gly Asn Asp Lys Glu Lys Ser Ser Glu Gln Ala Leu Glu
20 25 30

Leu Pro Gln Ser Lys Gln Asn Asn Pro Leu Leu His Asp Leu Ile Thr
35 40 45

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

Pro Ser Tyr Gln Gly Ile Leu Asp Gly Leu Glu His Leu His Asn Leu
65 70 75 80

Ser Gly Asn Glu Gln Leu Thr Ala Gly Phe Glu Leu His Arg Arg Ile
85 90 95

Thr Arg Tyr Leu Glu Glu His Pro Asp Ser Lys Arg Asn Ala Ala Leu
100 105 110

Arg Arg Thr Gln Thr Gln Leu Gly Asp Leu Met Phe Thr Gly Thr Leu
115 120 125

Gln Glu Val Arg His Pro Leu Leu Glu Met Ala Glu Thr Arg Pro Ala
130 135 140

Met Ala Ser Gln Ile Tyr Gln Ile Ala Arg Asp Glu Ala Lys Gly Asn
145 150 155 160

Thr Pro Gly Leu Thr Asp Leu Met Val Arg Trp Val Lys Glu Asp Pro
165 170 175

```
Tyr Leu Ala Ala Lys Ser Gly Tyr Gln Gly Lys Ile Pro Asn Asp Leu
            180                 185                 190

Pro Phe Glu Pro Lys Phe His Val Glu Leu Gly Asp Gln Phe Gly Glu
        195                 200                 205

Phe Lys Thr Trp Leu Asp Thr Ala Gln Asn Gln Gly Leu Leu Thr His
    210                 215                 220

Thr Arg Leu Asp Glu Gln Asn Lys Gln Val His Leu Gly Tyr Ser Tyr
225                 230                 235                 240

Asn Glu Leu Leu Asp Met Thr Gly Gly Val Glu Ser Val Lys Met Ala
                245                 250                 255

Val Tyr Phe Leu Lys Glu Ala Ala Lys Gln Ala Glu Pro Gly Ser Ala
            260                 265                 270

Lys Ser Gln Glu Ala Ile Leu Leu Asn Arg Phe Ala Asn Pro Ala Tyr
        275                 280                 285

Leu Thr Gln Leu Glu Gln Gly Arg Leu Ala Gln Met Glu Ala Ile Tyr
    290                 295                 300

His Ser Ser His Asn Thr Asp Val Ala Ala Trp Asp Gln Gln Phe Ser
305                 310                 315                 320

Pro Asp Ala Leu Thr Gln Phe Asn His Gln Leu Asp Asn Ser Val Asp
                325                 330                 335

Leu Asn Ser Gln Leu Ser Phe Leu Leu Lys Asp Arg Gln Gly Leu Leu
            340                 345                 350

Ile Gly Glu Ser His Gly Ser Asp Leu Asn Gly Leu Arg Phe Val Glu
        355                 360                 365

Glu Gln Met Asp Ala Leu Lys Ala His Gly Val Thr Val Ile Gly Leu
    370                 375                 380
```

```
Glu His Leu Arg Ser Asp Leu Ala Gln Pro Leu Ile Asp Lys Phe Leu
385                 390                 395                 400


Thr Ser Glu Asn Glu Pro Met Pro Ala Glu Leu Ala Ala Met Leu Lys
                405                 410                 415


Thr Lys His Leu Ser Val Asn Leu Phe Glu Gln Ala Arg Ser Lys Gln
            420                 425                 430


Met Lys Ile Ile Ala Leu Asp Asn Asn Ser Thr Thr Arg Pro Ala Glu
        435                 440                 445


Gly Glu His Ser Leu Met Tyr Arg Ala Gly Ala Ala Asn Asn Val Ala
    450                 455                 460


Val Glu Arg Leu Gln Gln Leu Pro Ala Glu Glu Lys Phe Val Ala Ile
465                 470                 475                 480


Tyr Gly Asn Ala His Leu Gln Ser His Glu Gly Ile Asp His Phe Leu
                485                 490                 495


Pro Gly Ile Thr His Arg Leu Gly Leu Pro Ala Leu Lys Val Asp Glu
            500                 505                 510


Asn Asn Arg Phe Thr Ala Gln Ala Asp Asn Ile Asn Gln Arg Lys Cys
        515                 520                 525


Tyr Asp Asp Val Val Glu Val Ser Arg Ile Gln Leu Thr Ser
    530                 535                 540


<210>  28
<211>  2957
<212>  PRT
<213>  Photorhabdus

<400>  28

Met Lys Gly Ile Glu Gly Val Ile Met Leu Ser His Asp Ile Leu Pro
```

```
1               5                   10                  15

Glu Lys Leu Leu Val Ser Glu Lys Lys His Glu Asn Val Gly Ser Tyr
            20                  25                  30

Phe Ser Asp Asp Ile Gly Glu Gln Ser Glu Gln Thr Glu Val Ser His
        35                  40                  45

Phe Asn Leu Ser Leu Asp Asp Ala Phe Asp Ile Tyr Ala Asp Ile Ser
    50                  55                  60

Ile Glu Asn Gln Gln Glu Leu Lys Asn Lys Asp Asn Asn Thr Asn Ile
65                  70                  75                  80

Trp Ser Ser Leu Gly Arg Gly Asp Asp Asp His Asn Leu Lys Lys Ile
                85                  90                  95

Ile Asn Asp Ala Phe Lys Glu Lys Leu Pro Gln Leu Met Glu Tyr Arg
            100                 105                 110

Arg Lys Gly Tyr Asn Val Ile Gly Leu Asp Lys Glu Gly Ile Lys Lys
        115                 120                 125

Leu Glu Gly Met Leu Lys Ala Val Pro Pro Glu Ile Gln Gln Pro Thr
    130                 135                 140

Met Lys Asn Leu Tyr Ser Ala Ala Gln Glu Leu Leu Asn Thr Leu Lys
145                 150                 155                 160

Gln His Pro Leu Leu Pro Glu Asn Gln Asp Met Ile Gln Gln Ser Asn
                165                 170                 175

Leu Val Ile Arg Asn Leu Ser Asp Ala Leu Glu Ala Ile Asn Ala Val
            180                 185                 190

Ser Lys Val Asn Gln Val Glu Trp Trp Glu Glu Val His Lys Thr Asn
        195                 200                 205
```

```
Lys Ala Gln Ser Asp Arg Leu Ile Ala Ala Thr Leu Glu Glu Leu Phe
    210                 215                 220

Phe Lys Val Lys Asp Lys Arg Leu Pro Gly Ser Asn Asp Asp Tyr Cys
225                 230                 235                 240

Gln Gln Glu Arg Glu Glu Thr Glu Arg Lys Ile Lys Asp Leu Leu Leu
                245                 250                 255

Tyr Asp Gly Tyr Gln Leu Thr Ala Glu His Phe Lys Phe Gly Arg Leu
            260                 265                 270

Arg Lys Ser Leu Leu Ala Glu Ser Arg Val Thr Arg Leu Lys Leu Ala
        275                 280                 285

Glu Tyr Leu Glu Lys Lys Ser Val Gly Ile Leu Thr Ala Ala Arg Asp
    290                 295                 300

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

Gly Phe Asn Ala Lys Asp Leu Ile Asn Ala Gly Gln Val Asn Asp Arg
                325                 330                 335

Leu Leu Ser Phe Gln Gln Tyr Ala Arg His Ile Arg Ala Val Asp Gly
            340                 345                 350

Glu Ile Asp Gly Ile Ile Leu Ser Asn Pro Leu Val Val Ala Cys Ile
        355                 360                 365

Lys Glu Thr Asn Asp Glu Pro Ala His Ile Lys Ile Ala Arg Ala Ile
    370                 375                 380

Leu Pro Val Ser Glu Glu Leu Gly Thr Val Ser Lys Val Leu Arg Glu
385                 390                 395                 400

Thr Lys Glu Lys Val Gln Pro Ser Lys Pro Lys Glu Glu Leu Asn His
```

```
                405                 410                 415

Pro His Gln Asp Trp Trp Asn Arg Gly Asp Glu Leu Trp Lys Tyr Ile
            420                 425                 430

Lys Lys Thr Ser Trp Asn Ile Lys Glu Thr Ser Val His Val Thr Gln
        435                 440                 445

Met Val Gly Tyr Glu Ala Ser Lys Thr Ala Ser Arg Ala Lys His Lys
    450                 455                 460

Leu Lys Glu Ser Ser Tyr Ser Glu Ser Ile Asn Gly Ala Val Lys Gly
465                 470                 475                 480

Thr Ala Leu Leu Leu Leu Asp Glu Ile Gln Gln Ala Glu Asn Arg Ile
                485                 490                 495

Arg Gln Ile Pro Gln Phe Ala Trp Asp Val Gln Glu Ala Val Glu Gln
            500                 505                 510

His Ser Ser Val Ile Gln Arg Thr Ala Tyr Pro Asp Glu Leu Pro Glu
        515                 520                 525

Leu Ser Glu Leu Leu Asn Glu Gln Leu Lys His Glu Glu Ala Arg Trp
    530                 535                 540

Gln Ala Val Lys Lys Gln Ser Arg Asp Lys Leu Gln Glu Leu Ile Ala
545                 550                 555                 560

Pro Ile Thr Arg Leu Ala Gln Glu Lys Trp Ala Gln Asp Leu Tyr Phe
                565                 570                 575

Gln Leu Gly Glu Glu Leu Arg Lys Glu Arg Gln Asp Arg Trp Lys Asp
            580                 585                 590

Ile Gln Gln Phe Asp Glu Ile Met Ala Glu Ala Val Gly Gln Phe Ala
        595                 600                 605
```

```
Glu Met Ala Arg Glu Leu Asp Ser Glu Ala Val Arg Leu Ala Glu His
    610                 615                 620

Gly His Ser Gly Gly Lys Glu Leu Gln Glu Lys Val Ala Lys Trp Leu
625                 630                 635                 640

Arg Asp Leu Ser Lys Leu Lys Gly Lys Val Lys Ala Gly Val Ala Lys
                645                 650                 655

Ile Thr Gly Thr Ser Leu Asp Asn Phe Ser Arg Ser Gly Met Leu Ala
            660                 665                 670

Arg Gly Met Ser Glu Trp Ala Glu Asp Leu Lys Gln Ser Tyr Leu Gln
        675                 680                 685

Glu Thr Leu Gln Glu Gly Ser Ala Val Ala Ala Glu Leu Phe Glu Arg
    690                 695                 700

Thr Leu Met Glu Val Val Glu Glu Asn Arg Thr His Phe Ala Lys Glu
705                 710                 715                 720

Ser Asp Pro Glu Ala Glu Arg Phe Leu Lys Arg Leu Ala Leu Ala Leu
                725                 730                 735

Lys His Ala Ala Glu Asn Thr Thr Val Tyr Pro Pro Thr Pro Glu Glu
            740                 745                 750

Ile Leu Ala Gly Ser Arg Ser Leu Pro Glu Asp Ile Arg His Trp Ala
        755                 760                 765

Glu Lys Lys Val Val Ser Gly Ala Ile Ser Ala Ala Phe Arg Gly Gly
    770                 775                 780

Phe Lys Leu Val Thr Gly Thr Phe Ser Leu Pro Val Arg Val Val Ile
785                 790                 795                 800

Arg Gly Ala Lys Thr Gly Gly Thr Leu Tyr Arg Gly Val Arg Ala Ile
```

```
                805                 810                 815

Asn Arg Ser Val Arg Leu Gly Gln Gly Pro Ala Thr Gln Val Lys Ser
            820                 825                 830

Lys Phe Ile Asn Gln Glu Leu Ser Lys Thr Ala Phe Arg Leu Thr Leu
        835                 840                 845

Ser Leu Ser Pro Leu Val Ala Trp Gly Met Ala Ala Ser Ile Thr Ala
    850                 855                 860

Gly Arg Leu Tyr Asn Glu Lys Asp Tyr Pro Glu Lys Ile Ile Lys Asn
865                 870                 875                 880

Ile Val Ile Asp Leu Pro Glu Glu Leu Leu Trp Ile Gly Gly Tyr Ala
                885                 890                 895

Gly Ile Asn Ala Ala Ile Arg Ala His Ala Glu Lys Ala Ile Gln Gln
            900                 905                 910

Ala Ile Gln His Ala Leu Asp Glu Gln Ala Asp Lys Leu Ala Leu Arg
        915                 920                 925

Ile Asn Lys Glu Ile Ala Gly Lys Ser Ala Asp Val Asn Val Glu Ile
    930                 935                 940

Ile Pro Gln Glu Thr Ser Val Ser Pro Ala Glu Thr Ala Gln Ser Thr
945                 950                 955                 960

Pro Glu Pro Leu Ser Asp Phe Ala Ser Thr Ser Gln Leu Thr Met Pro
                965                 970                 975

Glu Leu Ile Asp Ile Gln Asp Asn Asn Ser Ala Gln Gln Pro Lys Val
            980                 985                 990

Arg Arg Lys Arg Asp Val Ser Val  Glu Ser Glu Ile Ser  Ile Asp Asn
        995                 1000                1005
```

```
Leu Asn  Ile Ile Asn Ala Asn  Thr Arg Glu Asp Lys  Val Asn Ser
    1010                1015                1020

Glu Ile  Lys Ser Glu Leu Arg  Ser Glu Leu Lys Arg  Phe Glu Asn
    1025                1030                1035

Ser Asp  Ala Asn Ser Pro Met  Ser Asp Val Glu Arg  Ala Ile Phe
    1040                1045                1050

Ile Asp  Leu Phe Leu Tyr Lys  Asn Lys Tyr Glu Val  Ser Glu Ser
    1055                1060                1065

Gln Gln  Asp Tyr Lys Asn Thr  Trp Leu Lys Phe Arg  Arg Glu Leu
    1070                1075                1080

Glu Ser  Gln Glu Asn Lys Glu  Ile Lys Glu Tyr Leu  Arg Phe Arg
    1085                1090                1095

Ser Ile  Ile Glu Ala Tyr Glu  Ile Tyr Asp Lys Lys  Arg Leu Asp
    1100                1105                1110

Asp Asp  Thr Ile Pro Glu Ala  Gly Thr Ile Ile Lys  Glu Val Ile
    1115                1120                1125

Asp Phe  Phe Gln Lys Leu Lys  Lys Glu Asn Pro Ile  Thr Phe Met
    1130                1135                1140

Lys Leu  Ala Glu Ala Met Val  Lys Phe Gln Tyr Tyr  Tyr Glu Glu
    1145                1150                1155

Glu Asp  Glu Asn Glu Asp Arg  Tyr Phe Lys Met Ala  Glu Ile Tyr
    1160                1165                1170

Tyr Phe  Leu Asn Lys Thr Glu  Asn Glu Lys Lys Ser  Lys Thr Phe
    1175                1180                1185

His Leu  Asp Ile Ile Asp Lys  Tyr Pro Asn Glu Asn  Asn Arg Leu
```

```
    1190                1195                1200

Leu Asp  Glu Phe Phe Leu Asn  Lys Asn Asn Asn Asn  Pro Asp Leu
    1205                1210                1215

Asp Glu  Ile Ile Tyr Lys Leu  Gln Ser Met Gln Glu  Lys Tyr Arg
    1220                1225                1230

Glu Ser  Tyr Glu Met Leu Ser  Lys Val Glu Asn Ile  His Gln Val
    1235                1240                1245

Leu Ser  Asp Asp Ser Lys Asn  Glu Glu Asn Ile Phe  Leu Asp Asn
    1250                1255                1260

Arg Ile  Ile Ala Ala Gln Val  Phe Asp Gly Ser Ile  Asn Ile Ser
    1265                1270                1275

Leu Gln  Asp Lys Lys Lys Trp  Leu Asn Arg Tyr Asp  Gln Ile Arg
    1280                1285                1290

Asn Glu  Glu Gly Ser Asp Gly  Trp Lys Leu Met His  Ile Glu Ser
    1295                1300                1305

Ile Leu  Ile Asn Leu Arg Arg  Ile Asn Thr Ala Ile  Asn Leu Thr
    1310                1315                1320

Ala Met  Lys Ser Glu Ser Ala  Leu Leu Leu Ile Asp  Lys Leu Leu
    1325                1330                1335

Asn Phe  Gln Lys Lys Ala Arg  Glu Asn Ile Leu His  Ile Ser Glu
    1340                1345                1350

Thr Pro  His Glu Asp Phe Thr  Ser Tyr Ser Gln Phe  Lys Thr Arg
    1355                1360                1365

Lys Glu  Leu Gly Asn Asp Asp  Ser Lys Tyr Tyr Ala  Gln Phe Asp
    1370                1375                1380
```

```
Asn Tyr  Lys Asp Asn His Asp  Ala Glu Lys Glu Ala  Lys Glu Ile
    1385                1390                1395

Leu Ser  Gln Val Val Ala Arg  Ala Ser Leu Ser Phe  Ser Glu Leu
    1400                1405                1410

Phe Asp  Lys Val Glu Ser Ile  Lys Leu Phe Ser Phe  Val Tyr Lys
    1415                1420                1425

Asn Arg  Asp Gly Gly Ala Pro  Leu Ala Ala Pro Gly  Arg Thr Val
    1430                1435                1440

Val Ile  Lys Phe Pro Gly Lys  Asp Thr Gly Gly Leu  Val Ile Ser
    1445                1450                1455

Asn Leu  Phe Leu Arg Asn His  Val Lys Arg Ile Ser  Thr Lys Glu
    1460                1465                1470

Met Glu  Asp Leu Lys Pro Leu  Thr Glu Gly Met Tyr  Thr Arg Ala
    1475                1480                1485

Thr Gln  His Arg Ser Leu Gly  Ser Tyr Tyr His Ile  Gly Ser Gln
    1490                1495                1500

Ser Glu  His Thr Asn Ala Leu  Glu Ile Leu Ser Gly  Met Asn Lys
    1505                1510                1515

Glu Glu  Leu Lys Thr His Leu  Lys Lys Gln Gly Ile  Trp Phe Gly
    1520                1525                1530

Glu Pro  Ala Leu Phe Ser Asn  Glu Tyr Pro Lys Gln  Glu Asn Thr
    1535                1540                1545

Gly His  Leu Glu Asn Thr Thr  Leu Lys Asn Ala Ile  Ile Gly Val
    1550                1555                1560

Ser Thr  Ile Gln Asn Asn Ala  Ala Ala Asn Tyr Leu  Arg Ser Thr
```

```
    1565                1570                1575

Met Tyr  Glu Ser Thr Gly Trp  Glu Lys Leu Gly Asp  Arg Phe Ile
    1580                1585                1590

Pro Phe  Tyr Glu Ile Gly Arg  Arg Lys His Tyr Asp  Arg Glu Tyr
    1595                1600                1605

Glu Ile  Asn Ser Glu Gln Leu  Thr Leu Asp Ile Ile  Thr Ser Ile
    1610                1615                1620

Ala Ile  Ala Tyr Pro Ala Ala  Arg Gly Ile Val Ala  Thr Ile Arg
    1625                1630                1635

Ser Ser  Ala Ile Pro Ser Ile  Leu Lys Ser Gly Leu  Arg Gly Ser
    1640                1645                1650

Ala Leu  Phe Lys Ser Leu Ser  Leu Glu Leu Gly Lys  Met Gly Phe
    1655                1660                1665

Asn Ala  Ser Lys Val Phe Gly  Gly Ala Val Tyr Glu  Leu Ile Glu
    1670                1675                1680

Pro Tyr  Pro Ile Asn Ser His  Leu Asn Arg His Asn  Val Phe Asn
    1685                1690                1695

Lys Val  Lys Asp Thr Ala Trp  Glu Phe His Thr Asp  Val Gly Leu
    1700                1705                1710

Lys Gly  Gly Gly Leu Lys Asp  Phe Ile Asp Arg Phe  Thr Lys Glu
    1715                1720                1725

Pro Lys  Glu Ile Thr Ile Ser  Gly Tyr Lys Phe Lys  Arg Ile Lys
    1730                1735                1740

Tyr Asn  Gln Glu Asn Phe Asp  Thr Met Gln Arg Met  Ala Leu Asp
    1745                1750                1755
```

```
Tyr Ala  Tyr Asn Pro Asp Ser  Lys Gly Lys Ile Ala  Gln Ala Gln
    1760                1765                1770

Gln Ala  Tyr Lys Thr Gly Lys  Glu Asp Tyr Asn Ala  Pro Gln Tyr
    1775                1780                1785

Asp Asn  Phe Asn Gly Leu Ser  Leu Asp Lys Lys Ile  Glu Arg Tyr
    1790                1795                1800

Ile Ser  Pro Asp Thr Asp Ala  Thr Thr Lys Gly Val  Leu Ala Gly
    1805                1810                1815

Lys Met  Asn Glu Ser Ile Lys  Asp Ile Asn Ala Phe  Gln Thr Ala
    1820                1825                1830

Lys Asp  Ala Gln Ser Trp Lys  Lys Ser Ala Asn Lys  Ala Asn Lys
    1835                1840                1845

Val Val  Leu Thr Pro Gln Asn  Leu Tyr Leu Lys Gly  Lys Pro Ser
    1850                1855                1860

Glu Cys  Leu Pro Glu Ser Val  Leu Met Gly Trp Ala  Leu Gln Ser
    1865                1870                1875

Ser Gln  Asp Ala Lys Leu Ser  Lys Met Leu Met Gly  Ile Tyr Ser
    1880                1885                1890

Ser Asn  Asp Ile Thr Ser Asn  Pro Leu Tyr Lys Ser  Leu Lys Glu
    1895                1900                1905

Leu His  Ala Asn Gly Asn Ala  Ser Lys Phe Asn Ala  Ser Ala Thr
    1910                1915                1920

Ser Ile  Ser Asn Ile Asn Val  Ser Asn Leu Ala Thr  Ser Glu Thr
    1925                1930                1935

Lys Leu  Phe Pro Thr Glu Ile  Ser Ser Val Arg Val  Asp Ala Pro
```

```
    1940                1945                1950

Lys His  Thr Met Leu Ile Ser  Lys Ile Lys Asn Arg  Glu Asn Lys
    1955                1960                1965

Ile Lys  Tyr Val Phe Tyr Asp  Pro Asn Tyr Gly Met  Ala Tyr Phe
    1970                1975                1980

Asp Lys  His Ser Asp Met Ala  Ala Phe Phe Gln Lys  Lys Met Gln
    1985                1990                1995

Gln Tyr  Asp Phe Pro Asp Asp  Ser Val Ser Phe His  Pro Leu Asp
    2000                2005                2010

Tyr Ser  Asn Val Ser Asp Ile  Lys Ile Ser Gly Arg  Asn Leu Asn
    2015                2020                2025

Glu Ile  Ile Asp Gly Glu Ile  Pro Leu Leu Tyr Lys  Gln Glu Gly
    2030                2035                2040

Val Gln  Leu Glu Gly Ile Thr  Pro Arg Asp Gly Ile  Tyr Arg Val
    2045                2050                2055

Pro Pro  Lys Asn Thr Leu Gly  Val Gln Glu Thr Lys  His Tyr Ile
    2060                2065                2070

Ile Val  Asn Asn Asp Ile Tyr  Gln Val Glu Trp Asp  Gln Thr Asn
    2075                2080                2085

Asn Thr  Trp Arg Val Phe Asp  Pro Ser Asn Thr Asn  Arg Ser Arg
    2090                2095                2100

Pro Thr  Val Pro Val Lys Gln  Asp Thr Asn Gly Glu  Trp Phe Lys
    2105                2110                2115

His Ser  Glu Thr Gly Leu Lys  Gly Gly Gly Pro Ile  Asp Asp Ile
    2120                2125                2130
```

```
Arg Lys  Tyr Ile Ala Arg Lys  Ser Ala Ile Lys Ile  Phe Asn Gln
    2135                2140                2145

Ser Ile  Asn Tyr Ser Ala Thr  Lys Trp Pro Pro Glu  Pro Ile Asp
    2150                2155                2160

Lys Asn  Ile His Met Ile Trp  Ile Gly Thr Lys Asn  Ile Ser Glu
    2165                2170                2175

Lys Asn  Ile Lys Leu Ser Ile  Asp Thr Ala Lys Lys  Asn Pro Asp
    2180                2185                2190

Tyr Asn  Thr Ser Ile Ile Tyr  Asp Ser Gly Ile Ser  Gly His Glu
    2195                2200                2205

Gly Ala  Lys Lys Phe Met Leu  Glu Lys Phe Gln Asp  Ser Asn Val
    2210                2215                2220

Asn Ile  Ile Asp Phe Arg Lys  Lys Ser Tyr Phe Ser  Gln Leu Lys
    2225                2230                2235

Gln Glu  Pro Ser Phe Ala Tyr  Tyr Glu Gln Val Ile  Ala Glu Asn
    2240                2245                2250

Lys Tyr  Ala Gln Ala Ser Asp  Ile Leu Arg Leu Leu  Val Leu Lys
    2255                2260                2265

Tyr Glu  Gly Gly Ile Tyr Lys  Asp Ile Asp Asp Ile  Gln Val Lys
    2270                2275                2280

Gly Phe  Gly Ser Leu Thr Phe  Pro Lys Gly Ile Gly  Val Met Arg
    2285                2290                2295

Glu Tyr  Ala Pro Glu Ala Gly  Lys Ala Thr Ala Phe  Pro Asn Thr
    2300                2305                2310

Pro Ile  Ala Val Thr Lys Asn  Asn Pro Ile Ile Asn  Lys Thr Leu
```

```
    2315                2320                2325

Asp Leu  Ala Val Ser Asn Tyr  Gln Arg Gly Glu Lys  Asn Val Leu
    2330                2335                2340

Lys Leu  Ala Gly Pro Asp Val  Phe Thr Gln Ala Leu  Tyr Gln Glu
    2345                2350                2355

Ile Pro  Gly Leu Asp Ser Lys  Val Leu Asn Ala Gln  Leu Tyr Gln
    2360                2365                2370

Leu Glu  Leu Ala Lys Arg Gln  Ala Leu Gly Val Pro  Leu Glu Lys
    2375                2380                2385

Pro Lys  Asn Phe Ala Asp Glu  Gln Leu Thr Ser Ala  Glu Lys Glu
    2390                2395                2400

Lys Ile  Asn Arg Pro Tyr Gln  Ser Ile Arg Gly Leu  Ser Gly Tyr
    2405                2410                2415

Val Glu  Asn Gly Ala Asp His  Ser Trp Ala Val Asp  Thr Asn Ile
    2420                2425                2430

Pro Ser  Thr Ser Thr Gln Thr  Ser Thr Ile Val Thr  Pro Leu Ala
    2435                2440                2445

Pro Lys  Thr Glu Met Leu Pro  Pro Val Pro Ser Ser  Ser Thr Lys
    2450                2455                2460

Ser Ser  Thr Ser Ala Pro Val  Leu Gln Glu Lys Ile  Ser Tyr Asn
    2465                2470                2475

Leu Ala  Thr Asp Ile Asp Ala  Thr Asp Tyr Leu Asn  Gln Leu Lys
    2480                2485                2490

Gln Lys  Thr Asn Ile Asn Asn  Lys Ile Ser Ser Pro  Ala Gly Gln
    2495                2500                2505
```

```
Cys Glu  Ser Leu Met Lys Pro  Val Ser Asp Phe Met  Arg Glu Asn
    2510                2515                2520

Gly Phe  Thr Asp Ile Arg Tyr  Arg Gly Met Phe Ile  Trp Asn Asn
    2525                2530                2535

Ala Thr  Glu Gln Ile Pro Met  Asn His Phe Val Val  Val Gly Lys
    2540                2545                2550

Lys Val  Gly Lys Asp Tyr Val  Phe Asp Val Ser Ala  His Gln Phe
    2555                2560                2565

Glu Asn  Lys Gly Met Pro Asp  Leu Asn Gly Pro Leu  Ile Leu Ala
    2570                2575                2580

Ala Glu  Asp Trp Ala Lys Lys  Tyr Arg Gly Ala Thr  Thr Arg Lys
    2585                2590                2595

Leu Ile  Tyr Tyr Ser Asp Phe  Lys Asn Ala Ser Thr  Ala Thr Asn
    2600                2605                2610

Thr Tyr  Asn Ala Leu Pro Arg  Glu Leu Val Leu Glu  Ser Met Glu
    2615                2620                2625

Gly Lys  Thr Phe Ile Thr Ser  Pro Asn Trp Tyr Gln  Thr Phe Lys
    2630                2635                2640

Arg Thr  His Asn Ile His Pro  Glu Val Thr Val Ser  Asp Pro Ala
    2645                2650                2655

Thr Phe  Ser Leu Asn Tyr Ser  Val Asn Pro Thr Ala  Glu Asn Leu
    2660                2665                2670

Ser Pro  Pro Pro Pro Pro Pro  Ile Pro Ser His Gly  Gln Val Pro
    2675                2680                2685

Lys Thr  Val Thr Pro Pro Pro  Pro Pro Met Arg Ser  Pro Leu Ser
```

```
    2690                2695                2700

Leu Ser  Gln Pro Leu Glu Arg  Leu Pro Ala Asn Lys  Thr Lys Pro
    2705                2710                2715

Ile Gly  Phe Asn Pro Gly Glu  Asn Lys Ala Ser Phe  Ser Lys Leu
    2720                2725                2730

Glu Glu  Ala Gly Lys His Tyr  Tyr Lys Asp Asp Lys  Ser Arg Gln
    2735                2740                2745

Ala Ala  Pro Val Asn Thr Met  Ser Asp Phe Asp Asn  Arg Tyr Leu
    2750                2755                2760

Ser His  Thr Thr Glu Ala Pro  Ala Pro Ser Asn Val  Ala His Leu
    2765                2770                2775

Ala Pro  Gly Asn Ile Tyr Asn  Thr Lys Val Thr Ala  Lys Gly Ala
    2780                2785                2790

Glu Lys  Pro Ala Tyr Asp Ile  Tyr Ile Ser Lys Asp  Gly Glu Ser
    2795                2800                2805

Leu Ile  Thr Ser Ser Ser Tyr  Lys Val Asp Asp Ile  Thr Thr Asp
    2810                2815                2820

Ser Lys  Phe Gly Lys Pro Leu  Pro Tyr Ser Glu Ile  Met Phe Asn
    2825                2830                2835

Ser Leu  Lys Lys Ser Gly Val  Asp Pro Lys Asn Leu  Lys Arg Ser
    2840                2845                2850

Val Gln  Ala Ser Ile Glu Asn  Lys Val Thr Gln Asp  Val Ile Ser
    2855                2860                2865

Ala Ile  Gly Thr Arg Ile Gln  Arg Gly Gln Val Ile  Arg Val Ser
    2870                2875                2880
```

```
Pro Thr  Glu Asn Pro Asp Ala  Phe Tyr Thr Leu Leu  Gly Thr Asp
    2885                2890                2895


Asn Cys  Lys Ala Thr Leu His  Met Leu Asn Gln His  Ala Glu Glu
    2900                2905                2910


Phe Gly  His Lys Val Val Thr  Ser Ile Glu Phe Lys  Gly Thr Gly
    2915                2920                2925


Tyr Leu  Val Met Asn Ile Gly  Thr Ser Thr Gln Thr  Ser Thr Ile
    2930                2935                2940


Val Thr  Pro Pro Pro Met Pro  Gly Thr Ser Gln Leu  Val Gln
    2945                2950                2955
```

<210> 29
<211> 327
<212> PRT
<213> Photorhabdus

<400> 29

```
Met Pro Asn Lys Lys Tyr Ser Glu Asn Thr His Gln Gly Lys Lys Pro
1               5                   10                  15


Leu Ile Lys Ser Glu Ala Asn Asn Glu His Ala Ile Asp Asn Ser Pro
            20                  25                  30


Leu Gly Ile Gly Leu Asp Leu Asn Ser Ile Leu Gly Asn Asn Ser Ala
        35                  40                  45


Ser Leu Ser Gln Ile His Asp Tyr Ser Phe Trp Lys Glu Asn Ile Ser
    50                  55                  60


Glu Tyr Tyr Lys Trp Met Val Val Val Lys Ala His Leu Lys Gln Leu
65                  70                  75                  80


Asp Trp Thr Leu Lys Ser Met Asp Ser Pro Glu Ser Ala Gly Ala Asn
                85                  90                  95
```

```
Ile Ala Lys Asn Ile Gly Thr Thr Thr Leu Gln Thr Leu Leu Asn Thr
            100                 105                 110

Gly Gly Ser Ile Ala Gly Gly Ala Ile Gly Gly Ala Ile Gly Ser Ala
        115                 120                 125

Ile Ala Pro Gly Val Gly Thr Ile Ala Gly Met Gly Ile Gly Ala Leu
    130                 135                 140

Ala Gly Thr Gly Leu Asn Tyr Leu Asn Asp Thr Ala Ile Glu Lys Leu
145                 150                 155                 160

Asn Glu Lys Leu Glu Ile Ala Tyr Pro Tyr Pro Lys Thr Arg Asn Met
                165                 170                 175

Ile Phe Asp Ile Asn Asn Tyr Asp Lys Asn Pro Leu Ile Lys Ala Ile
            180                 185                 190

Lys Lys Lys Thr Lys Lys Asp Asn Leu Lys Val Met Ala Gly Ser Ser
        195                 200                 205

Leu Thr Ser Gln Leu Leu Gly Arg Ile Thr Pro Ile Lys Ile Pro Ala
    210                 215                 220

Tyr Lys Leu Ala Asp Leu Ala Val Ser His His Arg Ala Leu Ala Gly
225                 230                 235                 240

Leu Ser Ser Asp Lys Ala Arg His Ile Leu Asp Phe Thr Asn Ser Ile
                245                 250                 255

Arg Glu Val Leu Asn Glu Ser His Ser Asp Ala Val Ala Phe Met Arg
            260                 265                 270

Lys Asn Tyr Gly Asp Asn Ala Met Gly Leu Ser Gly Leu Ser Ser Lys
        275                 280                 285
```

```
Ile Lys Gly Asp Lys Leu Thr Leu Asp Thr Leu Ala Arg Thr Arg Asn
    290                 295                 300

Lys Ile Glu Asn Arg Ile Asn Ser Ile Asn Lys Gln Thr Leu Lys Leu
305                 310                 315                 320

Ser Ser Lys Asn Ser Asn Glu
                325
```

<210> 30
<211> 322
<212> PRT
<213> Photorhabdus

<400> 30

```
Met Glu Arg Glu Tyr Ser Glu Lys Glu Lys His Lys Lys His Pro Ile
1               5                   10                  15

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

Ser Leu Gly Leu Gly Leu Asp Leu His Gln Ala Ile Asn Thr Pro Lys
        35                  40                  45

Val Pro Lys Asp Asn Tyr Asn Glu Glu Asn Gly Asp Leu Phe Tyr Gly
    50                  55                  60

Leu Ala Ala Gln Arg Gly Arg Tyr Ile Lys Ser Val Asn Pro Asn Phe
65                  70                  75                  80

Asp Pro Asp Lys Thr Asn Ser Ser Pro Met Val Ile Asp Val Tyr Asn
                85                  90                  95

Asn His Val Ser Asn Thr Ile Leu Asn Lys Tyr Pro Leu Asp Lys Leu
            100                 105                 110

Gly Lys Leu Tyr Gly Asn Pro Gln Lys Tyr Ala Lys Asp Ile Lys Val
        115                 120                 125
```

```
Thr Asn Ser Leu Gln Gln Asp Val Ala Ala Ser Lys Arg Gly Trp Tyr
    130                 135                 140

Pro Leu Trp Asn Asp Tyr Phe Lys Ala Gly Asn Glu Asn Lys Lys Phe
145                 150                 155                 160

Asn Ile Ala Asp Ile Tyr Lys Glu Thr Arg Asn Gln Tyr Gly Ser Asp
                165                 170                 175

Tyr Tyr His Thr Trp His Glu Pro Thr Gly Ala Ala Pro Lys Leu Leu
            180                 185                 190

Trp Lys Arg Gly Ser Lys Leu Gly Ile Ala Met Ala Ala Ser Asn Glu
        195                 200                 205

Lys Thr Lys Ile His Phe Val Leu Asp Gly Leu Asn Ile Gln Glu Val
    210                 215                 220

Val Asn Lys Gln Lys Gly Ser Thr Pro Leu Glu Gln Gly Arg Gly Glu
225                 230                 235                 240

Ser Ile Thr Ala Ser Glu Leu Arg Tyr Ala Tyr Arg Asn Arg Glu Arg
                245                 250                 255

Leu Ala Gly Lys Ile His Phe Tyr Glu Asn Asp Gln Glu Thr Ile Ala
            260                 265                 270

Pro Trp Glu Lys Ser Pro Glu Leu Trp Gln Asn Tyr Ile Pro Lys Asn
        275                 280                 285

Lys Ser Gln Asn Glu Ser Ser Thr Pro Gln Arg Asn Asn Gly Ala Leu
    290                 295                 300

Tyr Arg Leu Gly Gly Pro Phe Arg Lys Leu Arg Ala Ser Leu Arg Lys
305                 310                 315                 320

Arg Ser
```

<210> 31
<211> 297
<212> PRT
<213> Photorhabdus

<400> 31

```
Met Val His Glu Tyr Ser Ile Asn Asp Arg Gln Lys Arg His Ser Phe
1               5                  10                  15


Ser Ser Ala Asn Pro Ile Asp Pro Glu Val Thr Asn Arg Glu Asn Ser
            20                  25                  30


Arg His Arg Phe Pro Lys Asp Asn Tyr Asn Lys Gly His Gly Asp Leu
        35                  40                  45


Phe Tyr Gly Leu Ala Pro Glu Arg Gly Lys Tyr Ile Lys Glu Ala Asn
    50                  55                  60


Pro Lys Phe Asp Pro Asn Asn Pro Glu Asn Ala Ala Met Ile Ile Asp
65                  70                  75                  80


Val Tyr Asn Asp Glu Ile Ser Arg Val Ile Leu Asn Asn Asn Ala Asn
                85                  90                  95


Lys Ile Ser Thr Asn Arg Leu Leu Asn Phe Ile Tyr Asn Phe Arg Lys
            100                 105                 110


Asn Arg Leu Glu Asn Leu Met Lys Asn Pro Glu Lys Tyr Ala Lys Asp
        115                 120                 125


Ile Lys Val Lys Asp Asn Leu Arg Glu Asn Ile Ser Pro Lys Lys Ile
    130                 135                 140


Glu Lys Tyr Pro Leu Trp Asn Asp Tyr Phe Glu Ala Gly Ile Arg Asn
145                 150                 155                 160
```

```
Lys Lys Phe Asn Ile Ala Glu Ile Phe Lys Glu Thr Ala Ser Gln Tyr
                165                 170                 175


Asn Ser Asp Tyr Tyr His Ala Trp His Ile Gly Gly Asn Ser Ala Pro
            180                 185                 190


Arg Leu Leu Trp Lys Arg Gly Ser Lys Leu Gly Ile Glu Ile Ala Ala
        195                 200                 205


Ser Asn Gln Arg Thr Lys Ile His Phe Ile Leu Asp Gly Leu Lys Ile
    210                 215                 220


Glu Asp Val Val Asn Lys Thr Lys Gly Pro Ala Pro Leu Lys Ala Gly
225                 230                 235                 240


Pro Gly Glu Ser Ile Thr Ala Ser Glu Leu Arg Tyr Ala Tyr Arg Asn
                245                 250                 255


Arg Ala Arg Leu Ala Gly Arg Ile His Phe Tyr Glu Asn Gly Lys Glu
            260                 265                 270


Thr Ile Ala Pro Trp Asp Lys Asp Pro Glu Leu Trp Gln Lys Tyr Thr
        275                 280                 285


Pro Lys Asn Arg Ser Gly Met Glu Leu
    290                 295


<210>  32
<211>  340
<212>  PRT
<213>  Photorhabdus

<400>  32

Met Leu Lys Tyr Ala Asn Pro Gln Thr Val Ala Thr Gln Arg Thr Lys
1               5                   10                  15


Asn Thr Ala Lys Lys Pro Pro Ser Ser Thr Ser Phe Asp Gly His Leu
            20                  25                  30
```

```
Glu Leu Ser Asn Gly Glu Asn Gln Pro Tyr Glu Gly His Lys Ile Arg
        35                  40                  45

Lys Ile Lys Gly Leu Arg Gln His Leu Ala Asp Arg Ser Leu Asn Lys
    50                  55                  60

Gly His Ile Ser Pro Leu Met Asn Lys Gly Leu Leu Val Gly Ser Lys
65                  70                  75                  80

Asp Val Ser Ile Asp Ile Pro Val Ile Ala His Arg Tyr Asp Ser Ser
                85                  90                  95

His Gln Leu Thr Asp Ala Glu Pro Leu Lys Ala Asp Ser His Ser Asn
            100                 105                 110

His Leu Asp Pro Phe Tyr Gly Val Ile Ala Gly Phe Arg Gly Asp Gln
        115                 120                 125

Val Thr Ser Ser Glu Ser Gly Ser Gly Ser Ile Gly Val His Trp Gly
    130                 135                 140

Lys Asn Thr Leu Asp Ser Asn Ile Met Gly Val Asn Val Val Asn Gly
145                 150                 155                 160

Ala Ser Gly Thr Val Gly Ile Arg Ile Ala Leu Lys Asp Ile Gln His
                165                 170                 175

Gly Ser Pro Val Ile Val Thr Ser Gly Ala Leu Ser Gly Cys Thr Met
            180                 185                 190

Val Tyr Ser Val Lys Asn Gly Tyr Phe Phe Ala Tyr His Thr Gly Gln
        195                 200                 205

Lys Pro Gly Asn Asn Glu Trp Lys Thr Gly Arg Gln Gly Val Val Ala
    210                 215                 220

Thr Tyr Leu Ser His Gln Ala Leu Ser Pro Asp Ser Glu Pro Met Thr
```

225 230 235 240

Val Gly Glu Gln Asn Asn Asp Leu Val Asn Ile Phe Ala Asn Tyr Asp
245 250 255

Gln Ser Val Ile Thr Tyr Met Gly Lys Pro Gly Val Leu Ile Asp Lys
260 265 270

Met Ala Glu Asn Val Gly Val Phe Asn Tyr Asp Glu Ile Lys Pro Glu
275 280 285

Lys Pro Ala Ile Arg Ala Gly Tyr Ser Tyr Ala Leu Leu Ala Lys Asp
290 295 300

Asp Lys Gly Lys Val Asn Val Lys Val Leu Ser Glu Asp Val Ile Val
305 310 315 320

Ser Ser Gly Lys Gln Gly Asn Thr Val Lys Ala Ile Asn Ser Leu Lys
325 330 335

Lys Arg Leu Leu
340

<210> 33
<211> 336
<212> PRT
<213> Photorhabdus

<400> 33

Met Pro Arg Tyr Ala Asn Tyr Gln Ile Asn Pro Lys Gln Asn Ile Lys
1 5 10 15

Asn Ser His Gly Lys Ser Ser Ser Ser Asp Phe Ser Ser Gly Tyr Leu
20 25 30

Ser Phe Ser Asn Asn Ser Leu Asp Asp Pro Phe Ile Arg Gln Gln Val
35 40 45

```
Lys Arg Glu Phe Ile Trp Glu Gly His Met Lys Glu Ile Glu Glu Ala
    50                  55                  60

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

Thr Leu Arg Ala Leu Gly Lys Gly Ala Ala Ala Lys Gly His Asp Ile
                85                  90                  95

Leu Glu Lys Thr Ile Lys Pro Gly Ser Ile Asn Lys Ala Tyr Pro Lys
            100                 105                 110

Asp Glu Ala Ser Asp Val Ile Lys Lys Val Gln Glu Ala Gly Ile Glu
        115                 120                 125

Gly Tyr Val Gly His Trp Asp Lys Lys Thr Gly Arg Leu Leu Gly Ile
    130                 135                 140

Tyr Met Ser Ser Gly His Gly Leu Ser Asp Glu Gln Val Asn Gly Lys
145                 150                 155                 160

Ile Tyr Pro Ile Asp Leu Asn Asn Leu Glu Ala Ser Leu Ser Ala Leu
                165                 170                 175

Lys Ala Lys Glu Asn Trp Ala Ala Leu Pro Phe Thr Gly Asp Tyr Asp
            180                 185                 190

Met His Asp Met Ile Ser Phe Thr Gly Gln Pro His Ser Val Pro Ser
        195                 200                 205

Asn Ser Ser Glu Glu Arg Lys Ile Ile Asp Arg Ile Asn Arg Leu Val
    210                 215                 220

Ala Arg Ser Asp Ser Asn Arg Pro Phe Gly Asp Ile Glu His Asn Val
225                 230                 235                 240

Ile Arg His Gly Ala Gln Val Ser Tyr Pro Ala Phe Ala Met Asp Lys
                245                 250                 255
```

```
Glu Lys Glu Glu Ile Lys Lys His Gly Gly Ile Val Lys Ala Val Ala
            260                 265                 270

Glu Pro Gly Glu Phe Pro Val Ala Ile Val Ser Lys Gly Lys Trp Thr
        275                 280                 285

Ile Ala Asn Asn Ile Asp Glu Leu Asn Gln Phe Tyr Asn Ser Ile Gly
    290                 295                 300

Ala Lys Met Lys Val Ser Trp Lys Pro Gly Ala Glu Asn Pro Gly Phe
305                 310                 315                 320

Val Ser Asn Pro Gln Arg Pro Gly Met Ala Arg Phe Ser Arg Lys Arg
                325                 330                 335
```

<210> 34
<211> 328
<212> PRT
<213> Photorhabdus

<400> 34

```
Met Pro Asn Lys Lys Tyr Ser Glu Asn Thr His Gln Gly Lys Asn Pro
1               5                   10                  15

Leu Met Lys Ser Gly Ala Asn Asn Glu His Asp Leu Gln Asp Ser Pro
            20                  25                  30

Leu Gly Ile Gly Leu Asp Leu Asn Ser Met Leu Val Asn Ser Ser Thr
        35                  40                  45

Ser Leu Ser Gln Ile Gln Asp Tyr Ser Phe Trp Lys Glu Asn Ile Ser
    50                  55                  60

Glu Tyr Tyr Lys Trp Met Val Val Val Glu Ser His Leu Lys Gln Leu
65                  70                  75                  80

Asp Trp Thr Leu Lys Ser Met Asp Ser Pro Glu Ser Ala Gly Thr Asn
```

```
                85                  90                  95

Val Ala Lys Asn Met Gly Val Thr Ala Leu Gln Ser Leu Leu Asn Thr
            100                 105                 110

Gly Ser Ser Ile Ala Gly Gly Ala Ile Gly Gly Ala Ile Gly Ser Ala
        115                 120                 125

Ile Ala Pro Gly Val Gly Thr Ile Ala Gly Ala Gly Ile Gly Ala Leu
    130                 135                 140

Ala Gly Thr Gly Leu Asn Tyr Leu Asn Asp Thr Ala Met Ser Lys Leu
145                 150                 155                 160

Ser Lys Lys Leu Glu Ile Ala His Pro Tyr Pro Lys Thr Arg Asn Met
                165                 170                 175

Ile Leu Asp Ile Asn Asn Tyr Asp Lys Asn Pro Ile Ile Lys Ala Ile
            180                 185                 190

Lys Lys Asn Val Asn Lys Asp Asn Leu Lys Val Thr Ala Gly Ser Ser
        195                 200                 205

Leu Thr Ser Lys Leu Val Gly Thr Val Thr Ser Pro Ile Lys Phe Pro
    210                 215                 220

Ala Tyr Lys Phe Ala Glu Leu Ala Val Ser His His Arg Ala Leu Glu
225                 230                 235                 240

Gly Leu Ser Asp Asp Lys Ala Arg His Ile Leu Asp Phe Thr Asn Ser
                245                 250                 255

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

Arg Lys Asn Tyr Gly Asp Asn Ala Met Gly Leu Ser Gly Phe Ser Ser
        275                 280                 285
```

```
Lys Ile Lys Arg Glu Lys Leu Thr Leu Asn Thr Leu Ala Lys Thr Lys
    290                 295                 300

Asn Glu Ile Glu Asn Arg Ile Asn Ser Ile Asn Lys Gln Thr Leu Lys
305                 310                 315                 320

Val Ser Ser Arg Ser Arg Asn Glu
                325
```

<210> 35
<211> 324
<212> PRT
<213> Photorhabdus

<400> 35

```
Met Leu Ser Thr Glu Lys His Asn Lys Asp Thr Lys His Pro Arg Asn
1               5                   10                  15

Arg Glu Lys Lys Phe Ser Ile Gln Pro Glu Asn Ser Thr Gln Asp Asp
            20                  25                  30

Glu Asp Ile Lys Asn Asn Ser Leu Gly Val Gly Leu Asp Leu Asp Gln
        35                  40                  45

Met Ile Arg Asn Thr Ser Ser Thr Leu Thr Asn Ala Pro Gln Lys Pro
    50                  55                  60

Glu Asp Gly Tyr Tyr Tyr His Ile Ser Arg Gly Asn Asn Leu Gln Ser
65                  70                  75                  80

Phe Leu Gln Asn Gly Phe Lys Pro Gln Gly Ser Pro Gly Pro Thr Leu
                85                  90                  95

Ser Glu Glu Asp Phe Ser Arg Arg Lys Ile Gly Ile Ile Lys Leu Ile
            100                 105                 110

Tyr Ser Ile Ile Ala Thr Thr Ile Asn Lys Asn Arg Lys Ala Lys Lys
        115                 120                 125
```

```
Ile Ser Lys Asp Asn Phe Leu Met Pro Gln Glu Phe Trp His Glu Phe
    130                 135                 140

Lys Asn Phe Tyr Gln Asn Ile Pro Thr Gln Thr Asn Ile Asp Asp Gln
145                 150                 155                 160

Leu Leu Lys Lys Ser Ile Thr Glu Ser Ile Asp Lys Leu Asp Gln Asn
                165                 170                 175

Lys Phe Met Glu Lys His Ser Asp Arg Lys Gln Thr Ile Ile Asn Asn
            180                 185                 190

Glu Arg Glu Ala Ile Leu Gln Gln Asp Glu Arg Ile Asn Glu Ile Ile
        195                 200                 205

Ser Ser Arg Ala Lys Met Ile Gln Gln Arg Glu Ala Glu Asn Thr Glu
    210                 215                 220

Gly Tyr Ile Tyr Leu Ala Pro His Lys Asn Thr Leu Leu Glu Tyr Met
225                 230                 235                 240

Lys His Leu Gln Glu Glu Lys Asn Leu Phe Leu Ile Leu Ala Val Lys
                245                 250                 255

Glu Asp Ile Phe Thr Glu Lys Gly Leu Glu Gln Asp Pro Gln Glu Pro
            260                 265                 270

His Gly Ala Val Arg Tyr Lys Gly Ala Leu Ser Thr Glu Glu Leu Asn
        275                 280                 285

Phe Val Asn Gln Glu Gly Gln Ile Cys Ala Ile Pro Ala Ser Ile Gly
    290                 295                 300

Glu Met Asp Tyr Gly Asp Phe Ile Leu Asn Gln Gln Gln Val Ile Asp
305                 310                 315                 320
```

Phe Cys Lys Lys

<210> 36
<211> 336
<212> PRT
<213> Photorhabdus

<400> 36

```
Met Pro Ile Asn Asp Leu Lys Lys Lys Phe Glu Ile Ser Pro Gln Ala
1               5                  10                  15

Ala Gln Ala Ile Gly Ala Pro Ala Arg Ser Asn Ser Ser Lys Gln Ala
            20                  25                  30

Glu His Gln Thr Glu His Leu Glu Leu Asp Thr Ser Lys Asn Arg Arg
        35                  40                  45

Asp Arg Lys Asp Leu Asn Ala Gln Ala Thr Pro Asn Gln Gln His Thr
    50                  55                  60

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

Gln Ala His Thr Pro Asp Leu Val Met Lys Lys Glu Ser Ser Val Thr
                85                  90                  95

Pro Asn Thr Arg Lys Ser Pro Asn Glu Lys Ile Lys Ala Glu Asp Ile
            100                 105                 110

Phe His Arg Tyr Lys Asp Arg Phe Ser Pro Ser Asp Arg Glu Leu Pro
        115                 120                 125

Phe Glu Ile Met Asn Glu Ile Thr Asn Asn Gly Ile Ala Phe Ser Ser
    130                 135                 140

Glu Lys Ala Pro Glu Ser His Leu Asp Lys Val Lys Asp Lys Lys Phe
145                 150                 155                 160
```

```
Thr Leu Arg His Tyr Thr Ser Gly Asn Gly Gln Glu Lys Pro Thr Phe
                165                 170                 175

Asn Glu Ile Gly Ser Asn Phe Asn Leu Val Asn Glu Gly Ile Lys Thr
            180                 185                 190

Leu Lys Arg Thr Gln Gly Ser Asn Thr Asn Glu Asp Asp Trp Asn Arg
        195                 200                 205

Leu Gly Asn Thr Ala Phe Thr Phe Phe Leu Leu Ala Ile Asp Gly Glu
    210                 215                 220

Val Ser Asp Arg Lys Phe Leu Ser Asn Thr Thr His Phe Ala Glu Ile
225                 230                 235                 240

Asp Ile Glu Asn Pro Ala Glu Leu Lys Glu Leu Gly Leu Asp Glu Thr
                245                 250                 255

Glu Phe Phe Ala Ser Pro Asp Leu Leu His Glu Lys Asn Leu Ser Gln
            260                 265                 270

Ala Pro Ala Val Lys Gly Lys Leu Ser Asp Leu Lys Ser Leu Leu Leu
        275                 280                 285

Lys Gln Ser Gly Ile Lys Pro Val Gln Leu Gln Ser Leu Gly Ala Lys
    290                 295                 300

Gly Ile Leu Glu Arg Ile Asp Ser Lys Phe Asn Gly Ser Leu Glu Ile
305                 310                 315                 320

Lys Ile Pro Gly Asn Val Lys Val Lys Glu Trp Lys Lys Val Glu Lys
                325                 330                 335
```

<210> 37
<211> 315
<212> PRT
<213> Photorhabdus

<400> 37

```
Met Pro Asn Ser Lys Tyr Ser Glu Lys Val Asn His Ser Ala Asn Gly
1               5                   10                  15

Ala Glu Lys Cys Ser Ile His Ser Asn Gln Tyr Asn Ile Asn Asn Cys
            20                  25                  30

Thr Leu Gly Leu Gly Leu Asp Leu Asn Lys Lys Leu Arg Thr Gly Asn
        35                  40                  45

Glu Arg Asn Ile Glu Gly Ala Gln Pro Phe Ile Pro Phe Pro Ser Lys
    50                  55                  60

Gln Lys Gln Tyr Ser Thr Ser Pro Ile Ala Met Ala Asp Ile Leu Asn
65                  70                  75                  80

Glu Ser Ala Leu Thr Ser Gln Pro Ile Ile Thr Asp Leu Ile Asn Pro
                85                  90                  95

Gln Lys Ile Lys Met Ser Asp Gly Val Lys Asn Ile Leu Asn Asn Lys
            100                 105                 110

Glu Gly Gly Gly Asp Leu Val Phe Lys Ala Leu Gln Ile Lys Pro Ser
        115                 120                 125

Asp Glu Thr Leu Pro Phe Asn Ala Leu Lys Ile Val Asp Thr Tyr Gln
    130                 135                 140

Glu Glu Met Pro Asn Lys Asp Met Ser Ile Ser Ala Tyr Trp Ala Pro
145                 150                 155                 160

Gln Gly Gly Tyr Val Asp Ile Pro Ala Gln Pro Asp Ile Ser Arg His
                165                 170                 175

Pro Gln Tyr Val Phe Thr Pro Asn Phe Ser Gly Cys Ser Phe Val Val
            180                 185                 190
```

```
Asp Lys Met Asn Glu Asp Thr Leu Arg Val Arg His Val Gln Gly Gly
        195                 200                 205

Gln Glu Asp Val Glu Tyr Asn Asn Gln Asn Ile Asp His Gly Met Gly
    210                 215                 220

Met Ile Thr Ala Met Glu Phe Arg Asp Tyr Gly Tyr His Glu Ala Asp
225                 230                 235                 240

Asp Lys Val Ile Glu Asn Thr Tyr Gly Phe Ala Phe Leu Lys Phe Asn
                245                 250                 255

Gln Glu Lys Lys Gln Trp Gln Leu His Tyr Gln Lys Ile Ala Ala Ala
            260                 265                 270

Pro Asn Ile Ile Asn Ile Lys Thr Lys Ser Ser Trp Leu Pro Phe Ser
        275                 280                 285

Lys Pro Ser Ile Glu Ala Asp Thr Phe Thr Phe Lys Asn Met Lys Val
    290                 295                 300

Pro Gly Tyr Ser Arg Lys Asn Ile Asn Asn Asn
305                 310                 315
```

<210> 38
<211> 309
<212> PRT
<213> Photorhabdus

<400> 38

```
Met Pro Lys Leu Thr Glu Leu Leu Ser Arg Phe Glu Asn Pro Ile Gln
1               5                   10                  15

Asn Gln Pro Asn His Ile Ser Lys Lys Asn Pro Ile Ser Asn Ser Lys
            20                  25                  30

Val Leu Asn Asn Ser Glu Glu Lys Thr Ala Pro Leu Glu Leu Lys His
        35                  40                  45
```

```
Asp Asp Ser Lys Ile Lys Ser Gln Val Ser Ile Pro Asn Leu Val Lys
    50                  55                  60

Lys Asn Glu Lys Pro Ala Ala Ser Asn Thr Pro Asn Asn Ser His Glu
65                  70                  75                  80

Lys Val Lys Ala Glu Asp Ile Phe Asn Arg Phe Lys Ser Lys Phe Asp
                85                  90                  95

Pro Tyr Asp Arg Glu Leu Pro Phe Asp Ile Met Asn Lys Ile Thr Asn
            100                 105                 110

Asn Glu Ile Lys Phe Ser Ser Glu Lys Ser Lys Asp Asp Tyr Leu Ala
        115                 120                 125

Lys Val Lys Asp Lys Lys Phe Thr Leu Arg His Tyr Thr Ala Gly Thr
    130                 135                 140

Gly Gln Glu Lys Pro Thr Phe Asp Glu Ile Ser Ser Asn Phe Asn Leu
145                 150                 155                 160

Val Asn Lys Gly Ile Lys Thr Leu Asn Arg Thr Gln Gly Ser Asn Thr
                165                 170                 175

Asn Glu Asp Asp Trp Asn Arg Leu Gly Asn Thr Ala Phe Thr Phe Tyr
            180                 185                 190

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

Thr Thr His Phe Ala Glu Ile Asn Ile Glu Asp Ser Glu Glu Leu Lys
    210                 215                 220

Glu Leu Gly Leu Asp Gln Ala Glu Phe Phe Ala Ser Pro Asp Leu Leu
225                 230                 235                 240

His Glu Lys Asn Leu Ser Gln Ala Pro Ala Val Lys Gly Lys Leu Ser
```

```
                245                 250                 255

Asp Leu Lys Ser Leu Leu Leu Lys Arg Ser Gly Ile Ser Ser Val Gln
            260                 265                 270

Leu Gly Arg Leu Asp Ala Lys Ala Ile Leu Lys Ser Ile Asp Asn Glu
        275                 280                 285

Phe Gly Asn Ser Leu Glu Ile Lys Ile Pro Gly Asn Val Lys Val Asn
    290                 295                 300

Lys Trp Asn Lys Ile
305
```

<210> 39
<211> 340
<212> PRT
<213> Photorhabdus

<400> 39

```
Met Pro Arg Tyr Ser Asn Ser Gln Arg Thr Pro Thr Gln Ser Thr Lys
1               5                   10                  15

Asn Thr Arg Arg Thr Ser Pro Ser Ser Asn Ser Ser Thr Glu His Leu
            20                  25                  30

Ser Leu Ser Asn Ala Pro Thr Asn Asp Ser Ser Val Arg Gln Glu Val
        35                  40                  45

Lys Glu Lys Phe Ile Trp Glu Gly His Trp Glu Gly His Met Glu Ala
    50                  55                  60

Ile Glu Lys Ala Ser Ile Leu Gly Asn Phe Ala Val Ser Phe Arg Ala
65                  70                  75                  80

Ala Gly Lys Pro Thr Leu Glu Ala Leu Gly Lys Gly Ala Ala Ala Lys
                85                  90                  95
```

```
Gly His Asp Ile Leu Glu Lys Thr Ile Lys Pro Gly Ser Ile Glu Lys
            100                 105                 110

Ala Tyr Pro Glu Asn Glu Ala Ser Asp Val Ile Lys Lys Val Arg Glu
        115                 120                 125

Ala Gly Ile Glu Gly Tyr Val Gly His Trp Asn Lys Glu Thr Gly Arg
    130                 135                 140

Leu Glu Gly Ile Tyr Met Ser Ser Gly His Gly Leu Pro Asn Gly Gln
145                 150                 155                 160

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

Leu Ala Pro Leu Lys Glu Lys Lys Asn Trp Ala Ala Leu Pro Phe Thr
            180                 185                 190

Gly Asp Tyr Asp Met His Asp Met Ile Ser Phe Thr Thr Gln Pro His
        195                 200                 205

Ser Val Pro Ser Asn Ser Ser Glu Glu Lys Lys Ile Ile Asp Arg Ile
    210                 215                 220

Asn Glu Tyr Ile Ala Lys Ser Asp Ser Asn Arg Pro Phe Glu Asp Ile
225                 230                 235                 240

Glu His Asn Val Ile Arg His Gly Pro Gln Val Ser Tyr Pro Ala Phe
                245                 250                 255

Ala Met Asp Lys Glu Lys Lys Glu Ile Lys Glu Arg Gly Gly Ile Val
            260                 265                 270

Lys Ala Val Ala Glu Pro Gly Glu Phe Pro Val Ala Ile Val Ser Lys
        275                 280                 285

Gly Lys Trp Thr Ile Ala Asn Asn Ile Asn Glu Leu Glu Gln Phe Tyr
    290                 295                 300
```

```
Asn Ser Ile Gly Ala Lys Met Lys Ala Ser Trp Lys Pro Gly Ala Gly
305                 310                 315                 320


Asn Pro Gly Phe Val Ser Asn Pro Gln Lys Pro Gly Met Ala Arg Phe
                325                 330                 335


Ser Arg Lys Lys
            340


<210>  40
<211>  280
<212>  PRT
<213>  Photorhabdus

<400>  40

Met Phe Ser Thr Tyr Ser Ser Lys Asn Asp Asn Gln Thr Ile Asn Lys
1               5                   10                  15


Ile Asn Thr Glu Glu Lys His Glu Asn Thr Glu Thr Asp Asn His Leu
            20                  25                  30


Glu Ile Asn Leu Glu His Thr Gly Lys Ser Lys Pro Asp Ile Glu Pro
        35                  40                  45


Lys Asp Val Thr Thr Gly Thr Ile Asn Ala Gly Thr Leu Leu Tyr Lys
    50                  55                  60


Thr Thr Ala Ile Pro Glu Phe Leu Asp Asn Ala Lys Ser Leu Gly Leu
65                  70                  75                  80


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


Gly Lys Ala Glu Asp Ala Glu Lys Leu Lys Asn Lys Ser Gln Trp Ala
            100                 105                 110


Gly Gln Tyr Phe Ala Leu Glu Lys Ser Tyr Asp Glu Tyr Ala Asn Glu
```

```
        115                 120                 125

Ala Pro Asp Ser Tyr Asn Asn Leu Leu Lys Asn Ala Gly Lys Asp Leu
    130                 135                 140

Leu Glu Asn Thr Glu Glu Val Lys Val Phe Leu Tyr Thr Phe Lys Val
145                 150                 155                 160

Thr Lys Asp Ile Lys Val Leu Lys Pro His Asn Asn Ser Asn Ser Tyr
                165                 170                 175

Tyr Val Gly Asp Thr Glu Gly Trp Glu Lys Ala Lys Glu Ile Met Asn
            180                 185                 190

Asp Val Gln Ser Gln Ser Glu Lys Asn Asp Asn Pro Phe Pro Glu Leu
        195                 200                 205

Lys Asn Leu Glu Asp Lys Asn Phe Leu Leu Glu Glu Leu Gly Glu Lys
    210                 215                 220

Gly Tyr Ala Trp Met Gly Pro Leu His Ala Lys Glu Gly Ala Glu Lys
225                 230                 235                 240

Gly Thr Glu Phe Ser Tyr Glu Leu Ala Ile Ser Pro Asn Leu Leu Arg
                245                 250                 255

Gln His Leu Thr Leu Glu Ser Glu Glu Leu Leu Gly Thr Tyr Lys Asn
            260                 265                 270

Arg Tyr Gly Tyr Trp Asp Lys Lys
        275                 280
```

<210> 41
<211> 138
<212> PRT
<213> Photorhabdus

<400> 41

```
Met Lys Lys Thr Asp Glu Lys Tyr Gly Gln Tyr Glu Tyr Lys Asp Glu
1               5                   10                  15


Asp Ile Thr Ser Tyr Pro Ile Ala Trp Thr Asn Pro Asp Asn Gly Lys
            20                  25                  30


Ile Tyr Ile Gly Ile Asn Ser Pro Glu Tyr Ser His Leu Asn Asn Lys
        35                  40                  45


Gly Glu Ser Glu Leu Asn Leu Ala Lys Ile Ile Ser Thr Ile Ile His
    50                  55                  60


Glu Ser Leu His Ala Ser Ser His Gln His Lys Gly Leu Gln Ser Gln
65                  70                  75                  80


Thr Asp Thr Gly Ala Asp Asn Leu Asn Tyr Asp Glu Tyr Val Thr Asp
                85                  90                  95


Tyr Phe Ala Arg Glu Val Tyr Lys Gln Ile Leu Pro Asp Lys Asp Tyr
            100                 105                 110


Val Ala Asn Cys Phe Thr Lys Gly Leu Gly Gly Glu Asn Lys Ile Trp
        115                 120                 125


Gly Gly Asn Ile Val Glu Phe Met Ile Gln
    130                 135


<210>  42
<211>  539
<212>  PRT
<213>  Photorhabdus

<400>  42

Met Val Tyr Glu Tyr Asp Lys Thr Ile Glu Arg Arg Arg Asn Pro Ser
1               5                   10                  15


Ile Gln Leu Asn Asn Asn Glu Lys Ser Ser Glu Gln Ala Leu Glu Leu
            20                  25                  30
```

```
Ser Gln Asn Asn Pro Leu Leu His Asp Leu Ile Thr Ser Asn Asn Leu
        35                  40                  45

Arg Lys Glu Ala Ala Val Phe Ala Lys Arg Ile Gly Pro Ser Tyr Gln
    50                  55                  60

Glu Ile Leu Asp Glu Leu Glu His Leu His His Leu Ser Gly Asn Glu
65                  70                  75                  80

Gln Leu Ala Ala Gly Phe Glu Leu His Arg Arg Ile Thr His Tyr Leu
                85                  90                  95

Glu Glu His Pro Asp Ser Lys Arg Asn Thr Ala Leu Arg Arg Thr Gln
            100                 105                 110

Thr Gln Phe Gly Asp Leu Met Phe Thr Gly Thr Leu Gln Lys Ile Arg
        115                 120                 125

His Ser Leu Leu Glu Met Ala Glu Thr Arg Pro Glu Met Ala Ser His
    130                 135                 140

Ile Tyr Gln Ile Ala Arg Glu Glu Val Lys Gly Asn Thr Pro Gly Leu
145                 150                 155                 160

Thr Asp Leu Met Val Arg Trp Val Lys Glu Asp Pro Tyr Leu Ala Ala
                165                 170                 175

Lys Thr Gly Tyr Gln Gly Lys Ile Pro Asn Asp Leu Pro Phe Glu Pro
            180                 185                 190

Lys Phe His Val Glu Leu Gly Ala Gln Phe Asp Asp Phe Lys Lys Trp
        195                 200                 205

Leu Asp Thr Ala Gln Ser Lys Glu Leu Leu Thr His Thr Arg Leu Asp
    210                 215                 220

Glu Gln Asn Lys Gln Val His Leu Gly Tyr Ser Tyr Asn Glu Leu Leu
```

```
225                 230                 235                 240

Asp Met Thr Gly Val Glu Ser Val Gln Met Ala Val Tyr Phe Leu Lys
                245                 250                 255

Glu Ala Ala Lys Gln Ala Glu Pro Gly Ser Thr Lys Ser Gln Glu Asp
            260                 265                 270

Ile Leu Leu His Arg Phe Ala Asn Pro Thr Tyr Leu Ala Gln Leu Glu
        275                 280                 285

His Ser Arg Leu Ala Gln Ile Glu Ala Ile Tyr His Ser Ser His Asp
    290                 295                 300

Thr Asp Val Thr Ala Trp Asp Gln Gln Phe Ala Ser Asp Ala Leu Thr
305                 310                 315                 320

Gln Phe Asn His Gln Leu Asn Asn Thr Val Asp Leu Asn Ser Gln Leu
                325                 330                 335

Ser Leu Leu Leu Lys Asp Arg Gln Gly Leu Leu Ile Gly Glu Ser His
            340                 345                 350

Gly Ser Asp Leu Asn Gly Leu Arg Phe Val Glu Glu Gln Met Glu Val
        355                 360                 365

Leu Lys Ala His Gly Val Thr Val Ile Gly Leu Glu His Leu Arg Ser
    370                 375                 380

Asp Leu Ala Gln Pro Leu Ile Asp Lys Phe Leu Ala Ser Gly Asn Glu
385                 390                 395                 400

Pro Met Pro Ala Glu Leu Ala Ala Leu Leu Lys Thr Lys His Leu Ser
                405                 410                 415

Ala Asn Leu Phe Glu Gln Ala Arg Ser Lys Gln Met Lys Ile Ile Ala
            420                 425                 430
```

```
Leu Asp Asn Asn Ser Thr Thr Arg Pro Thr Val Glu Gly Thr Gln His
        435                 440                 445

Gly Leu Met Tyr Arg Ala Gly Ala Ala Asn Asn Val Ala Val Glu Arg
    450                 455                 460

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

Ala His Leu Gln Ser His Glu Gly Ile Asp His Phe Leu Pro Gly Ile
                485                 490                 495

Thr His Arg Leu Gly Leu Pro Ala Leu Lys Val Asp Glu Asn Asn Arg
            500                 505                 510

Phe Thr Ala Gln Val Asp Asn Ile Asn Gln Arg Lys Arg Tyr Asp Asp
        515                 520                 525

Val Val Glu Leu Pro Arg Ile Gln Leu Thr Ser
    530                 535
```

<210> 43
<211> 323
<212> PRT
<213> Photorhabdus

<400> 43

```
Met Glu His Glu Tyr Ser Glu Lys Glu Lys Pro Gln Lys Cys Pro Ile
1               5                   10                  15

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

Thr Pro Leu Glu Leu Asn Ser Gln Tyr Thr Asn Arg Lys Arg Ala Gly
        35                  40                  45

Leu Arg Glu Arg Phe Ser Thr Thr Leu Gln Arg Asn Leu Pro Gly His
    50                  55                  60
```

```
Ser Met Leu Asp Arg Glu Leu Thr Thr Asp Gly Met Lys Asn Gln Glu
65                  70                  75                  80

Ser Arg Phe Ser Pro Ala Met Ile Met Asp Arg Met Met His Phe Gly
                85                  90                  95

Val Arg Thr Arg Leu Gly Lys Val Arg Asn Ser Ala Ser Lys His Gly
            100                 105                 110

Gly Gln Val Thr Phe Lys Phe Ala Gln Thr Lys Gly Thr Phe Leu Asp
        115                 120                 125

Gln Ile Met Lys His Lys Asp Thr Ser Gly Gly Val Cys Glu Ser Ile
    130                 135                 140

Ser Ala His Trp Ile Ser Ala His Ala Lys Gly Glu Ser Ile Phe Asp
145                 150                 155                 160

Gln Leu Tyr Val Gly Gly Gln Lys Gly Lys Phe His Ile Asp Ser Leu
                165                 170                 175

Val Ser Ile Lys Gln Leu Gln Met Asp Ser Tyr Leu Asp Asp Glu Gln
            180                 185                 190

Ser Thr Met Thr Glu Tyr Trp Leu Gly Thr Gln Gly Ile Gln Pro Ile
        195                 200                 205

Met Gln Lys Asn Asp Val Asp Glu His Ser Ser Lys Val Val Gly Gln
    210                 215                 220

Thr Gly Asn Lys Gly Thr Thr Asp Leu Leu Arg Ala Ile Leu Asp Thr
225                 230                 235                 240

Gly Asp Lys Gly Ser Gly Tyr Lys Lys Ile Ser Phe Leu Gly Lys Met
                245                 250                 255
```

```
Ala Gly His Thr Val Ala Ala Tyr Val Asp Asp Gln Lys Gly Val Ile
            260                 265                 270

Phe Phe Asp Pro Asn Phe Gly Glu Phe Ser Phe Pro Ser Ile Thr Ser
        275                 280                 285

Phe Ser Arg Trp Phe Thr Asp Asp Phe Trp Pro Lys Ser Trp Tyr Asn
    290                 295                 300

Leu Glu Ile Gly Leu Gly Gln Gln Phe Glu Val Phe Asn Tyr Glu Leu
305                 310                 315                 320

Lys Lys Ser
```

<210> 44
<211> 381
<212> PRT
<213> Photorhabdus

<400> 44

```
Met Tyr Asp Ser Lys Lys Lys Asn Ser Glu Pro Thr Thr Lys Lys Lys
1               5                   10                  15

Phe Glu Arg Ser Asn Tyr Ser Gln Trp Asp Asp Ser Ile Asn His Tyr
            20                  25                  30

Glu Asp Met Asn Arg Ala Arg Ile Lys Asn Arg Asn Asp Ile Leu Thr
        35                  40                  45

Thr Val Asp Tyr Phe Gly Glu Lys Lys Lys Thr Met His Thr Phe Glu
    50                  55                  60

Tyr Gln Ser Asp Ile Lys His Asp Thr Asn Phe Asn Asn Lys Asn Lys
65                  70                  75                  80

Ser Leu Phe Glu Ser Phe Ala Ala Ser Phe Val Leu Gln Asn Pro Ser
                85                  90                  95
```

```
Phe Phe Ser Gly Val Ile Asp Lys Leu Ser Lys Lys Leu Phe Asn Ile
            100                 105                 110

Ile Ser Lys Ile Asp Glu Arg Asn Asn Phe Gln Lys Lys Leu Tyr Asp
        115                 120                 125

Phe Ile Glu Lys Asp Thr Ser Pro Glu Gly Gln Phe Gly Arg Phe Thr
    130                 135                 140

Leu Gly Lys Asn Glu Ile Leu Asn Val Leu Gln Val Lys Ser Asp Thr
145                 150                 155                 160

Pro Gln Leu Phe Val Lys Lys Met Leu Leu Ile Lys Ser Leu Gly Ala
                165                 170                 175

Phe Ile Ile Asp Phe Ser Ser Lys Asp Ile Gly Asn Tyr Asp Phe Ile
            180                 185                 190

Phe Asp Gly Lys Gly Arg Glu Val Asn Asp Ile Ile Glu Lys Asn Arg
        195                 200                 205

Pro Thr Asn Leu Phe Lys Val Arg Gly Arg Thr Asn Ile Lys Ser Ser
    210                 215                 220

Gln His Arg Ser Asp Ile Gly Ile Leu Asp Thr Pro Thr Phe Asp Ser
225                 230                 235                 240

Leu Thr Glu Glu Gln Lys Ser Phe Leu Thr Ile Pro Glu Leu Thr Lys
                245                 250                 255

Arg Arg Pro Leu Phe Arg Thr Phe Thr His Glu Leu Asp Ala Glu Asp
            260                 265                 270

Lys Arg Val Val Glu Ser Val Phe Val Asn Arg Thr Phe Asp Cys Asp
        275                 280                 285

Ser Pro Leu Ile Gly Ser Val Ser Gly Ser Thr Ser Cys Val Leu Val
```

```
    290                 295                 300

Ala Ala Asp Ile Leu Phe Pro Asp Met Thr Met Val Glu Arg Lys Lys
305                 310                 315                 320

Leu Ala Ile Ala Thr Phe Ala Phe Leu Val Gly Gly Gly Tyr His Ser
                325                 330                 335

Ala Thr Glu Val Phe Asp Val Ala Tyr Pro Gly Leu Asp Leu Asn Lys
            340                 345                 350

Glu Ile Glu Glu Leu Ile Glu Asn Asn Pro Ile Gln Glu Asn Ala Gly
        355                 360                 365

Val Ala Thr Leu Arg Gln Leu Ile Gly Asn Ser Gly Phe
    370                 375                 380


<210>  45
<211>  308
<212>  PRT
<213>  Photorhabdus

<400>  45

Met Pro Ile Ser Asn Leu Ala Lys Glu Ser Glu Val Arg Ala Val Lys
1               5                   10                  15

Asp Ile Pro Cys Lys Asn Ile Glu Thr Asp Asn His Leu Glu Ile Gly
            20                  25                  30

Leu Ser Ser Gly Leu Ser Arg Ser Lys Asp Thr Ser Lys Phe Lys Lys
        35                  40                  45

Asn Ser Ile Asn Thr Ile Lys Leu Ile Asp Asp Ile Ile Ala Leu His
    50                  55                  60

Asn Asp Pro Lys Gly Asn Lys Leu Leu Trp Asn Asp Asn Trp Gln Asp
65                  70                  75                  80
```

```
Lys Ile Ile Asn Arg Asp Leu Ala Asn Ile Phe Glu Lys Ile Asp Glu
                85                  90                  95

Ser Val Ser Glu Leu Gly Gly Leu Glu Met Tyr Gln Glu Met Val Gly
            100                 105                 110

Val Asn Pro Tyr Asp Pro Thr Glu Pro Val Cys Gly Leu Ser Ala Gln
        115                 120                 125

Asn Ile Phe Lys Leu Met Thr Glu Gly Glu His Ala Val Asp Pro Val
    130                 135                 140

Glu Met Ala Gln Thr Gly Lys Ile Asp Gly Asn Glu Phe Ala Glu Ser
145                 150                 155                 160

Val Asp Gln Leu Ser Ser Ala Lys Asn Tyr Val Ala Leu Val Asn Asp
                165                 170                 175

Arg Arg Leu Gly His Met Phe Leu Ile Asp Ile Pro Ser Asn Asp Gln
            180                 185                 190

Glu Thr Val Gly Tyr Ile Tyr Gln Ser Asp Leu Gly Gln Gly Ala Leu
        195                 200                 205

Pro Pro Leu Lys Ile Ala Asp Trp Leu Asn Ser Arg Gly Lys Asp Ala
    210                 215                 220

Val Ser Leu Asn Lys Leu Lys Lys Leu Leu Ser Arg Glu Phe Asn Leu
225                 230                 235                 240

Leu Ser Asp Asp Glu Lys Arg Ala Leu Ile Ser Glu Thr Leu Asp Ile
                245                 250                 255

His Lys Asp Val Ser Asn Val Glu Leu Asp Arg Ile Lys Arg Asp Arg
            260                 265                 270

Gly Val Asp Ile Tyr Leu Thr Glu Tyr Asp Val Asn Asn Phe Tyr Glu
        275                 280                 285
```

Asn Ile Glu Thr Leu Lys Ser Lys Leu Ser Asn Tyr Asp Lys Lys Leu
290 295 300

Ser Lys Pro Lys
305

<210> 46
<211> 295
<212> PRT
<213> Photorhabdus

<400> 46

Met Leu Ala Asn Val Leu Pro Asn Leu Ala Ser Phe Leu Lys Tyr Glu
1 5 10 15

Lys Glu Thr Pro Leu Phe Phe Ile Glu Asp Gly Phe Asn Phe Gln Asn
20 25 30

Leu Asn Pro Gly Arg Val Pro Leu Ile Lys Thr Pro Glu Gln Arg Lys
35 40 45

Ala Gly Asp Thr Gln Ser Pro Ala Phe Leu Cys Ser Gly Val Ile Leu
50 55 60

Arg Gly Thr Ile His Ser Asn Asp Tyr Lys Phe Trp Gln Pro Ser Pro
65 70 75 80

Ser Ser Ile Lys Ser Gly Gly Val Ser Phe Ser Tyr Leu Arg Lys Asp
85 90 95

Ala Lys Phe Lys Arg Leu Ala Tyr Gly Tyr Lys Asn Gly Phe Ile Ile
100 105 110

Phe Pro Glu His Ile Ala Pro Glu Asp Arg Val Asp Phe Ser Val Leu
115 120 125

Cys Ala Phe Pro Ile Asp Gly Tyr Thr Asn Glu Arg Ala Asn Gln Gly

```
    130                 135                 140

Cys Gly Glu Asn Ile Thr Lys Ala Lys Asp Lys Gly Lys Ser Cys Gln
145                 150                 155                 160

Glu Gln Asn Val Thr Asn Ser Asp Asp Trp Ile Lys Asn Tyr Arg Lys
                165                 170                 175

Val Asn Ser Gln Asp Phe Phe Gln Cys Gly Phe Asn Val Thr Lys Asp
            180                 185                 190

Val Asn Asn Pro Ala Ile Ala Phe Tyr Gln Met Leu Glu Ser Ile Lys
        195                 200                 205

Lys Leu Pro Arg Thr Pro Asn Thr Pro Pro Lys Gln Asn Glu Ile Arg
    210                 215                 220

Ile Ser Thr Trp Glu Glu Ser Asp Pro Asn Lys Leu Pro Ile Glu Ala
225                 230                 235                 240

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

Arg Asp Tyr Lys Asn Ala Thr Gly Lys Phe Leu Pro Ile Val Lys Met
            260                 265                 270

Leu Leu Pro Arg Thr Leu Asn Glu Asp Ala Leu Phe Lys Phe Asn Ile
        275                 280                 285

Lys Asp Gln Val Ile Asn Pro
    290                 295
```

<210> 47
<211> 50
<212> PRT
<213> Photorhabdus

<400> 47

```
Met Met Arg Glu Tyr Ser Asn Glu Asp Asp Phe Ile Lys Glu Lys Thr
1               5                   10                  15


Asn Leu Val Lys Ser Glu Asn Val Glu Ala Asp Asn Tyr Leu Glu Thr
            20                  25                  30


Glu Tyr Leu Thr Tyr Leu Ala Lys Leu Ile Gly Met Thr Glu Arg Glu
        35                  40                  45


Asn His
    50
```

<210> 48
<211> 50
<212> PRT
<213> Photorhabdus

<400> 48

```
Met Phe Gln Asn Arg Ile Arg Asn Glu Lys Thr Thr Gln Ser Gly Lys
1               5                   10                  15


Gly Lys Thr Leu Asp Arg Met Thr Asp Ser Leu Tyr Leu Glu Ile Pro
            20                  25                  30


Asn Val Glu Ala Val Thr Leu Ala Tyr Gln Lys Leu Thr Ser Lys Tyr
        35                  40                  45


Arg Lys
    50
```

<210> 49
<211> 50
<212> PRT
<213> Photorhabdus

<400> 49

```
Met Glu Arg Glu Tyr Ser Glu Lys Gln Lys Asn Pro Ser Lys Leu Ser
1               5                   10                  15
```

Arg Lys Thr Ala Ile Ser Glu Arg Ile Ala Ala Leu Glu Arg Ser Gly
            20   25   30

Leu Ser Asn Ser Asn Gln Pro Val Pro Gln Phe Ala Arg Pro Tyr Thr
        35   40   45

Ser Asn
    50

<210> 50
<211> 50
<212> PRT
<213> Photorhabdus

<400> 50

Met Ser Asn Tyr Glu Tyr Asp Ile Val Thr Gln His Asp Thr Tyr Gln
1   5   10   15

Ile Lys Asp Asn Glu Tyr Thr Val Val Asn Gly Lys Tyr Trp Gln Tyr
            20   25   30

Glu Gln Glu Gly Asn Lys Asn Asn Asn Lys Val Ser Ile Ser Leu Met
        35   40   45

Lys Glu
    50

<210> 51
<211> 50
<212> PRT
<213> Photorhabdus

<400> 51

Met Glu His Glu Tyr Asn Glu Lys Glu Lys Gln Arg Asn Ser Ala Ile
1   5   10   15

Lys Leu Asn Asp Ala Ile Arg Asn Asn Glu Glu Asn Met Asp Met Thr
            20   25   30

Ser Pro Leu Glu Leu Asn Phe Gln Asn Thr Asn Arg Lys Ser Arg Gly
        35   40   45

Leu Arg
    50

<210> 52
<211> 50
<212> PRT
<213> Photorhabdus

<400> 52

Met Pro Asn Lys Lys Tyr Ser Glu Asn Thr His Gln Gly Lys Lys Pro
1   5   10   15

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

Leu Gly Ile Gly Leu Asp Leu Asn Ser Met Met Gly Asn Ser Ser Thr
        35   40   45

Ser Leu
    50

<210> 53
<211> 50
<212> PRT
<213> Photorhabdus

<400> 53

Met Glu Arg Glu Tyr Ser Glu Lys Glu Lys His Lys Lys Arg Pro Ile
1   5   10   15

Gln Leu Arg Asn Ser Ile Glu Gln His Glu Glu Glu Thr Ala Asn Asn
            20   25   30

Ser Leu Gly Leu Gly Leu Asp Leu Asn Gln Ala Thr Asn Pro Pro Lys
        35   40   45

Val Pro
    50

<210> 54
<211> 50
<212> PRT
<213> Photorhabdus

<400> 54

Met Met Glu His Glu Tyr Ser Lys Glu Glu Glu Lys Lys Arg Gln Gln
1   5   10   15

Ser Lys Pro Asn Asn Ala Thr His Asp Glu Ser Asn Leu Pro Leu Glu
            20   25   30

Leu Glu Lys His Phe Asn Ala Arg Thr Pro Ala Thr Ala His Ser Lys
        35   40   45

Trp Phe
    50

<210> 55
<211> 50
<212> PRT
<213> Photorhabdus

<400> 55

Met Leu Lys Tyr Ala Asn Pro Gln Ala Val Pro Thr Gln Arg Thr Lys
1   5   10   15

Asn Thr Ala Lys Lys Pro Ser Ser Ser Ser Ser Phe Asp Gly Gln Leu
            20   25   30

Glu Leu Ser Asn Gly Glu Trp Ser Lys His Ser Glu Met Gly Leu Lys
        35   40   45

Arg Gly
    50

<210> 56
<211> 50
<212> PRT
<213> Photorhabdus

<400> 56

Met Met Arg Glu Tyr Ser Asn Glu Asp Asp Cys Thr Lys Glu Lys Thr
1   5   10   15

Asn Leu Val Lys Ser Glu Asn Val Glu Ala Asp Asn Tyr Leu Glu Met
            20   25   30

Glu His Leu Thr Tyr Leu Ala Lys Leu Ile Ser Met Thr Glu Arg Glu
        35   40   45

Asn His
    50

<210> 57
<211> 50
<212> PRT
<213> Photorhabdus

<400> 57

Met Ile Phe Lys Met Leu Asn Leu Ala Val Phe Tyr Leu Leu Gly Asn
1   5   10   15

Ile Phe His Tyr Leu Ile Cys Gln Lys Phe Ile Cys Tyr Phe Cys Ser
            20   25   30

Val Leu Lys Ser Val Thr Met Phe Leu Thr Lys Val Ala Val Gln Ile
        35   40   45

Ala Leu
    50

<210> 58
<211> 50
<212> PRT
<213> Photorhabdus

<400> 58

Met Glu Arg Glu Tyr Ser Glu Lys Pro Lys Asn Leu Ser Gln Leu Ser
1   5   10   15

Arg Lys Thr Ala Ile Ser Glu Arg Arg Ala Met Phe Glu Arg Asn Ala
            20   25   30

Ser Ser Asn Asn Glu Gln Pro Val Pro Gln Phe Ala Arg Ser Tyr Thr
        35   40   45

Ser Asn
    50

<210> 59
<211> 50
<212> PRT
<213> Photorhabdus

<400> 59

Met Lys Tyr Asp Pro Arg Leu Arg Thr Trp Val Glu Asp Asp Phe Asp
1   5   10   15

Tyr Glu Lys Asn Phe Lys Lys Gln Thr Asp Tyr Ile Asn Tyr Lys Asp
            20   25   30

Leu Glu Lys Gln Leu Lys Glu Asn Val Asp Tyr Tyr Ala Leu Leu Asp
        35   40   45

Glu Asn
    50

<210> 60
<211> 50
<212> PRT
<213> Photorhabdus

<400> 60

Met Pro Asn Lys Lys His Ser Glu Asn Thr His Gln Gly Arg Lys Pro

```
1               5                   10                  15


Leu Ile Lys Ser Glu Ala Asn Asn Glu His Asp Ile Glu Asn Ser Ser
            20                  25                  30


Leu Gly Ile Gly Leu Asp Leu Asn Ser Thr Ile Gly Asn Asn Ser Ala
        35                  40                  45


Ser Leu
    50
```

<210> 61
<211> 50
<212> PRT
<213> Photorhabdus

<400> 61

```
Met Glu Arg Glu Tyr Ser Glu Lys Glu Lys His Lys Lys Arg Pro Ile
1               5                   10                  15


Gln Leu Arg Asn Ser Ile Glu Gln His Glu Glu Glu Thr Ala Asn Asn
            20                  25                  30


Ser Leu Gly Leu Gly Leu Asp Leu Asn Gln Ala Thr Asn Pro Pro Lys
        35                  40                  45


Val Pro
    50
```

<210> 62
<211> 50
<212> PRT
<213> Photorhabdus

<400> 62

```
Met Met Glu His Glu Tyr Ser Lys Glu Glu Glu Lys Lys Arg Gln Gln
1               5                   10                  15


Ser Lys Pro Asn Asn Ala Thr His Asp Glu Ser Asn Leu Pro Leu Glu
```

```
            20                  25                  30

Leu Glu Lys His Ser Asn Ala Arg Thr Ser Ala Thr Ala Tyr Ser Lys
        35                  40                  45

Trp Phe
    50
```

<210> 63
<211> 50
<212> PRT
<213> Photorhabdus

<400> 63

```
Met Ser Asn Tyr Glu Tyr Asp Ile Val Thr Gln His Asp Thr Tyr Gln
1               5                   10                  15

Ile Lys Asp Asn Glu Tyr Thr Val Val Asn Gly Lys Tyr Trp Gln Tyr
            20                  25                  30

Glu Gln Glu Gly Asn Lys Asn Asn Asn Lys Ile Ser Ile Ser Leu Met
        35                  40                  45

Lys Asp
    50
```

<210> 64
<211> 50
<212> PRT
<213> Photorhabdus

<400> 64

```
Met Glu His Glu Tyr Asn Glu Lys Glu Lys Gln Arg Asn Ser Ala Ile
1               5                   10                  15

Lys Leu Asn Asp Ala Ile Arg Asn Asn Glu Glu Asn Met Asp Met Thr
            20                  25                  30

Ser Pro Leu Glu Leu Asn Ser Gln Asn Thr Asn Arg Lys Ser Arg Gly
```

```
        35                  40                  45


Leu Arg
    50


<210>  65
<211>  50
<212>  PRT
<213>  Photorhabdus

<400>  65

Met Phe Lys Tyr Asp Thr Ser Glu Lys Met Ala Lys Phe Gly Lys Gly
1               5                   10                  15


Lys Thr Ser Asp Gly Met Leu Leu Asp Thr Leu Tyr Leu Glu Ile Pro
            20                  25                  30


Asp Glu Lys Ala Val Met Ser Ala Tyr Lys Ser Gln Ile Leu Asp Glu
        35                  40                  45


Leu Arg
    50


<210>  66
<211>  50
<212>  PRT
<213>  Photorhabdus

<400>  66

Met Leu Lys His Ala Asn Pro Gln Thr Val Ser Thr Gln Arg Thr Lys
1               5                   10                  15


Ser Thr Ala Lys Lys Pro Ser Ser Ser Ser Ser Phe Asp Arg Gln Phe
            20                  25                  30


Glu Leu Ser Asn Ser Glu Asn Gln Pro Gly Glu Gly Asn Lys Asp Trp
        35                  40                  45


Thr Ile
```

50

<210> 67
<211> 50
<212> PRT
<213> Photorhabdus

<400> 67

Met Pro Arg Tyr Ala Asn Tyr Gln Ile Asn Pro Lys Gln Asn Thr Lys
1 5 10 15

Asn Ser His Gly Lys Ser Ser Ser Ser Asn Phe Ser Ser Gly Tyr Phe
20 25 30

Ser Ser Ser Asn Asn Ser Leu Asp Asp Ser Leu Ile Arg Gln Gln Val
35 40 45

Lys Arg
50

<210> 68
<211> 50
<212> PRT
<213> Photorhabdus

<400> 68

Met Arg Glu Tyr Ser Lys Glu Asp Asp Cys Val Lys Glu Lys Thr Asn
1 5 10 15

Leu Ala Glu Ser Glu Asn Val Glu Ala Asp Asn Tyr Leu Glu Met Asp
20 25 30

Cys Leu Asn Tyr Leu Ala Lys Leu Asn Gly Met Pro Glu Arg Lys Asp
35 40 45

His Ser
50

<210> 69

<211> 50
<212> PRT
<213> Photorhabdus

<400> 69

Met Pro Ile Ile Gly His Lys Glu Asp Leu Ile Arg Thr Glu Arg Ser
1 5 10 15

Ser Val Asp Leu Thr Arg Ser Ser Asn Asn Arg Gln Thr Asp Asn Leu
20 25 30

Glu Leu Asn Ile Pro Gln His Lys Arg Asp Asn Lys Asp Ile Glu His
35 40 45

Ala Val
50

<210> 70
<211> 50
<212> PRT
<213> Photorhabdus

<400> 70

Met Ile Ser Thr Phe Asp Pro Ala Ile Cys Ala Gly Thr Pro Thr Val
1 5 10 15

Thr Val Leu Asp Asn Arg Asn Leu Thr Val Arg Glu Ile Val Phe His
20 25 30

Arg Ala Lys Ala Gly Gly Asp Thr Asp Thr Leu Ile Thr Arg His Gln
35 40 45

Tyr Asp
50

<210> 71
<211> 50
<212> PRT
<213> Photorhabdus

<400> 71

Met Glu Arg Glu Tyr Asn Lys Lys Glu Lys Gln Lys Lys Ser Ala Ile
1 5 10 15

Lys Leu Asp Asp Ala Val Gly Asn Asn Glu Glu Asn Met Asp Met Thr
20 25 30

Ser Pro Leu Glu Leu Asn Ser Gln Tyr Thr Asn Arg Lys Arg Pro Gly
35 40 45

Leu Arg
50

<210> 72
<211> 50
<212> PRT
<213> Photorhabdus

<400> 72

Met Val Tyr Glu Tyr Ala Lys Thr Asn Asp Arg Lys Arg Lys Leu Ser
1 5 10 15

Thr Gln Ser Asp Asn Tyr Glu Glu Lys Ser Phe Ser Pro Val Leu Asp
20 25 30

Leu Ser Arg Asn Asn Gln Asn Thr Pro Asn Met Glu Asp Glu Tyr Glu
35 40 45

Thr Pro
50

<210> 73
<211> 50
<212> PRT
<213> Photorhabdus

<400> 73

Met Val Phe Glu His Asp Lys Thr Val Glu Arg Lys Arg Lys Pro Ser
1 5 10 15

```
Ile Gln Leu Gly Asn Asp Lys Glu Lys Ser Ser Glu Gln Ala Leu Glu
            20                  25                  30


Leu Pro Gln Ser Lys Gln Asn Asn Pro Leu Leu His Asp Leu Ile Thr
        35                  40                  45


Ser Asn
    50


<210>  74
<211>  50
<212>  PRT
<213>  Photorhabdus

<400>  74

Met Lys Gly Ile Glu Gly Val Ile Met Leu Ser His Asp Ile Leu Pro
1               5                   10                  15


Glu Lys Leu Leu Val Ser Glu Lys Lys His Glu Asn Val Gly Ser Tyr
            20                  25                  30


Phe Ser Asp Asp Ile Gly Glu Gln Ser Glu Gln Thr Glu Val Ser His
        35                  40                  45


Phe Asn
    50


<210>  75
<211>  50
<212>  PRT
<213>  Photorhabdus

<400>  75

Met Pro Asn Lys Lys Tyr Ser Glu Asn Thr His Gln Gly Lys Lys Pro
1               5                   10                  15


Leu Ile Lys Ser Glu Ala Asn Asn Glu His Ala Ile Asp Asn Ser Pro
            20                  25                  30
```

Leu Gly Ile Gly Leu Asp Leu Asn Ser Ile Leu Gly Asn Asn Ser Ala
        35   40   45

Ser Leu
    50

<210> 76
<211> 50
<212> PRT
<213> Photorhabdus

<400> 76

Met Glu Arg Glu Tyr Ser Glu Lys Glu Lys His Lys Lys His Pro Ile
1   5   10   15

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

Ser Leu Gly Leu Gly Leu Asp Leu His Gln Ala Ile Asn Thr Pro Lys
        35   40   45

Val Pro
    50

<210> 77
<211> 50
<212> PRT
<213> Photorhabdus

<400> 77

Met Val His Glu Tyr Ser Ile Asn Asp Arg Gln Lys Arg His Ser Phe
1   5   10   15

Ser Ser Ala Asn Pro Ile Asp Pro Glu Val Thr Asn Arg Glu Asn Ser
            20   25   30

Arg His Arg Phe Pro Lys Asp Asn Tyr Asn Lys Gly His Gly Asp Leu
        35   40   45

Phe Tyr
    50

<210> 78
<211> 50
<212> PRT
<213> Photorhabdus

<400> 78

Met Leu Lys Tyr Ala Asn Pro Gln Thr Val Ala Thr Gln Arg Thr Lys
1   5   10   15

Asn Thr Ala Lys Lys Pro Pro Ser Ser Thr Ser Phe Asp Gly His Leu
            20   25   30

Glu Leu Ser Asn Gly Glu Asn Gln Pro Tyr Glu Gly His Lys Ile Arg
        35   40   45

Lys Ile
    50

<210> 79
<211> 50
<212> PRT
<213> Photorhabdus

<400> 79

Met Pro Arg Tyr Ala Asn Tyr Gln Ile Asn Pro Lys Gln Asn Ile Lys
1   5   10   15

Asn Ser His Gly Lys Ser Ser Ser Ser Asp Phe Ser Ser Gly Tyr Leu
            20   25   30

Ser Phe Ser Asn Asn Ser Leu Asp Asp Pro Phe Ile Arg Gln Gln Val
        35   40   45

Lys Arg
    50

<210> 80
<211> 50
<212> PRT
<213> Photorhabdus

<400> 80

Met Pro Asn Lys Lys Tyr Ser Glu Asn Thr His Gln Gly Lys Asn Pro
1   5   10   15

Leu Met Lys Ser Gly Ala Asn Asn Glu His Asp Leu Gln Asp Ser Pro
            20   25   30

Leu Gly Ile Gly Leu Asp Leu Asn Ser Met Leu Val Asn Ser Ser Thr
        35   40   45

Ser Leu
    50

<210> 81
<211> 50
<212> PRT
<213> Photorhabdus

<400> 81

Met Leu Ser Thr Glu Lys His Asn Lys Asp Thr Lys His Pro Arg Asn
1   5   10   15

Arg Glu Lys Lys Phe Ser Ile Gln Pro Glu Asn Ser Thr Gln Asp Asp
            20   25   30

Glu Asp Ile Lys Asn Asn Ser Leu Gly Val Gly Leu Asp Leu Asp Gln
        35   40   45

Met Ile
    50

<210> 82
<211> 50

<212> PRT
<213> Photorhabdus

<400> 82

Met Pro Ile Asn Asp Leu Lys Lys Lys Phe Glu Ile Ser Pro Gln Ala
1   5   10   15

Ala Gln Ala Ile Gly Ala Pro Ala Arg Ser Asn Ser Ser Lys Gln Ala
            20   25   30

Glu His Gln Thr Glu His Leu Glu Leu Asp Thr Ser Lys Asn Arg Arg
        35   40   45

Asp Arg
    50

<210> 83
<211> 50
<212> PRT
<213> Photorhabdus

<400> 83

Met Pro Asn Ser Lys Tyr Ser Glu Lys Val Asn His Ser Ala Asn Gly
1   5   10   15

Ala Glu Lys Cys Ser Ile His Ser Asn Gln Tyr Asn Ile Asn Asn Cys
            20   25   30

Thr Leu Gly Leu Gly Leu Asp Leu Asn Lys Lys Leu Arg Thr Gly Asn
        35   40   45

Glu Arg
    50

<210> 84
<211> 50
<212> PRT
<213> Photorhabdus

<400> 84

```
Met Pro Lys Leu Thr Glu Leu Leu Ser Arg Phe Glu Asn Pro Ile Gln
1               5                   10                  15


Asn Gln Pro Asn His Ile Ser Lys Lys Asn Pro Ile Ser Asn Ser Lys
            20                  25                  30


Val Leu Asn Asn Ser Glu Glu Lys Thr Ala Pro Leu Glu Leu Lys His
        35                  40                  45


Asp Asp
    50
```

<210> 85
<211> 50
<212> PRT
<213> Photorhabdus

<400> 85

```
Met Pro Arg Tyr Ser Asn Ser Gln Arg Thr Pro Thr Gln Ser Thr Lys
1               5                   10                  15


Asn Thr Arg Arg Thr Ser Pro Ser Ser Asn Ser Ser Thr Glu His Leu
            20                  25                  30


Ser Leu Ser Asn Ala Pro Thr Asn Asp Ser Ser Val Arg Gln Glu Val
        35                  40                  45


Lys Glu
    50
```

<210> 86
<211> 50
<212> PRT
<213> Photorhabdus

<400> 86

```
Met Phe Ser Thr Tyr Ser Ser Lys Asn Asp Asn Gln Thr Ile Asn Lys
1               5                   10                  15
```

```
Ile Asn Thr Glu Glu Lys His Glu Asn Thr Glu Thr Asp Asn His Leu
            20                  25                  30


Glu Ile Asn Leu Glu His Thr Gly Lys Ser Lys Pro Asp Ile Glu Pro
        35                  40                  45


Lys Asp
    50


<210>  87
<211>  50
<212>  PRT
<213>  Photorhabdus

<400>  87

Met Lys Lys Thr Asp Glu Lys Tyr Gly Gln Tyr Glu Tyr Lys Asp Glu
1               5                   10                  15


Asp Ile Thr Ser Tyr Pro Ile Ala Trp Thr Asn Pro Asp Asn Gly Lys
            20                  25                  30


Ile Tyr Ile Gly Ile Asn Ser Pro Glu Tyr Ser His Leu Asn Asn Lys
        35                  40                  45


Gly Glu
    50


<210>  88
<211>  50
<212>  PRT
<213>  Photorhabdus

<400>  88

Met Val Tyr Glu Tyr Asp Lys Thr Ile Glu Arg Arg Arg Asn Pro Ser
1               5                   10                  15


Ile Gln Leu Asn Asn Asn Glu Lys Ser Ser Glu Gln Ala Leu Glu Leu
            20                  25                  30
```

```
Ser Gln Asn Asn Pro Leu Leu His Asp Leu Ile Thr Ser Asn Asn Leu
        35                  40                  45


Arg Lys
    50
```

<210> 89
<211> 50
<212> PRT
<213> Photorhabdus

<400> 89

```
Met Glu His Glu Tyr Ser Glu Lys Glu Lys Pro Gln Lys Cys Pro Ile
1               5                   10                  15


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


Thr Pro Leu Glu Leu Asn Ser Gln Tyr Thr Asn Arg Lys Arg Ala Gly
        35                  40                  45


Leu Arg
    50
```

<210> 90
<211> 50
<212> PRT
<213> Photorhabdus

<400> 90

```
Met Tyr Asp Ser Lys Lys Lys Asn Ser Glu Pro Thr Thr Lys Lys Lys
1               5                   10                  15


Phe Glu Arg Ser Asn Tyr Ser Gln Trp Asp Asp Ser Ile Asn His Tyr
            20                  25                  30


Glu Asp Met Asn Arg Ala Arg Ile Lys Asn Arg Asn Asp Ile Leu Thr
        35                  40                  45
```

Thr Val
    50

<210> 91
<211> 50
<212> PRT
<213> Photorhabdus

<400> 91

Met Pro Ile Ser Asn Leu Ala Lys Glu Ser Glu Val Arg Ala Val Lys
1   5   10   15

Asp Ile Pro Cys Lys Asn Ile Glu Thr Asp Asn His Leu Glu Ile Gly
            20   25   30

Leu Ser Ser Gly Leu Ser Arg Ser Lys Asp Thr Ser Lys Phe Lys Lys
        35   40   45

Asn Ser
    50

<210> 92
<211> 50
<212> PRT
<213> Photorhabdus

<400> 92

Met Leu Ala Asn Val Leu Pro Asn Leu Ala Ser Phe Leu Lys Tyr Glu
1   5   10   15

Lys Glu Thr Pro Leu Phe Phe Ile Glu Asp Gly Phe Asn Phe Gln Asn
            20   25   30

Leu Asn Pro Gly Arg Val Pro Leu Ile Lys Thr Pro Glu Gln Arg Lys
        35   40   45

Ala Gly
    50

<210> 93
<211> 19592
<212> DNA
<213> Photorhabdus

<400> 93
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gacaccattg aataccgaga tggtgttggt aattggttca aaatgccggg tcagagtcag 180

agcactaata tcaccttgcg taaaggcgtt ttcccgggga aaacagaact gtttgattgg 240

attaactcta ttcagcttaa tcaggtagag aaaaaggata ttaccatcag tttaactaat 300

gatgcaggta ccgaattatt aatgacctgg aatgtttcta atgcttttcc cacttcattg 360

acttcacctt catttgatgc caccagtaat gatattgcag tacaggaaat tacgctgatg 420

gcagatcggg tgattatgca ggctgtttga agcattgata tttaatcatc tcatataagg 480

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accaatatat tagtgaagat aatgcaatcc gtattaattc gtggatggat tatcttaatc 660

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50 55 60

Leu Ala Thr Ala Leu Glu Gln Leu Leu Gln Ala Tyr Pro Arg Asp Met
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Glu Lys Glu Lys Thr Met Leu Val Leu Ala Leu Leu Leu Ala Lys Lys
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Val Ala Ser His Thr Pro Ser Leu Leu Arg Asp Val Phe His Thr Thr
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