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(54) Title: COMBINATION OF BACTERICIDAL AGENT WITH A LYSOSOMOTROPIC ALKALINISING AGENT FOR THE TREATMENT OF A BACTERIAL INFECTION

(57) Abstract: The present invention relates to the field of medicine, specifically the field of bacterial infection and treatment thereof.

# A METHOD OF TREATMENT OF A BACTERIAL INFECTION

## FIELD OF THE INVENTION

The present invention relates to the field of medicine, specifically the field of bacterial infection and treatment thereof.

## BACKGROUND OF THE INVENTION

The human pathogen *Staphylococcus aureus* colonizes approximately a third of all humans and is one of the leading causes of bacteremia and infective endocarditis in the industrialized world (1). In addition to emerging antibiotic resistance, persisting and recurrent infections substantially add to morbidity and mortality (2,3). Recurrence rates, in particular after osteomyelitis or endocarditis, are high and infections may relapse even years after apparent cure (4). Infection recurrence is associated with SCVs (small colony variants) and/or non-replicating persisters for several reasons (5-8). Their arrested or slow growth and reduced metabolism renders antibiotics inefficient (9-13). Moreover, they preferentially hide in privileged locations such as in abscesses and within host cells (14-16). These privileged locations shield them from the host's innate immune system and from extracellularly active antibiotics. In addition, antibiotics do not penetrate abscesses efficiently and are less active due to the low pH (17-21). Therefore the 'ubi pus ibi evacua' – the necessity of surgical removal of abscesses formulated in the antiquity still applies nowadays despite highly active antibiotics. In contrast to abscesses, intracellular bacteria cannot be mechanically removed and often resist eradication by currently available antibiotics. Most SCVs isolated in clinics revert to the large colony phenotype upon sub-cultivation. Due to these unstable properties, stable genetically-modified SCV mutants with defects in the electron transport system have been used to find new strategies to target SCVs and have been found to localize in host cell lysosomes (22). However, stable SCVs only partially reflect the clinical SCVs. They are less virulent (23) and do not revert to the highly virulent and fast-growing phenotype. Consequently, there is an urgent need for means to study clinical SCVs and persisters and ultimately an effective method of treatment of SCVs and persisters.

**DETAILED DESCRIPTION OF THE INVENTION**

Surprisingly, the inventors have established that reversible persisters and reversible SCV's can be induced by low pH and that low pH adapted bacteria persisted intracellularly, specifically within lysosomes (low pH organelles). Low pH induced SCVs and persisters reverted to the highly virulent phenotype upon raising the pH. Raising the pH intracellularly reverted the low pH adapted bacteria *in vitro* and *in vivo* and rendered the SCV's and persisters susceptible to antibacterial agents that are usually not effective intracellularly. This provide a completely new way of preventing and/or treating infections that persist primarily or at least partly intracellularly in intracellular compartments, such as but not limited to infections of the skin, of the respiratory or tonsillar epithelium (pharyngotonsillitis), (bovine) mastitis, or eradicating vaginal *S. agalactiae* infection (in macrophages) in pregnant women to prevent neonatal sepsis or preventing/treating *S. pneumoniae*–induced monocyte–derived macrophage apoptosis, or treating tuberculosis, leprosy, listeriosis, typhoid fever, bacillary dysenteria, plague, brucellosis, typhus, Rocky Mountains spotted fever, chlamydia, trachoma..

Accordingly, in a first aspect the invention provides for a method of treatment of a bacterial infection in a subject in need thereof, comprising:

- administration of an effective amount of an agent that increases the intracellular pH of a host cell and/or of an intracellular compartment of a host cell, wherein the agent is an alkalinizing agent; and
- administration of an effective amount of a bactericidal agent, wherein the bactericidal agent is a bacterial lysin or autolysin, or a bacteriophage lysin. Said method is herein referred to as a method according to the invention.

Preferably, in the embodiments of the invention, the increase in pH activates a non-replicating intracellular bacterium and the bactericidal agent kills the activated intracellular bacterium.

In the embodiments of the invention, the bacterial infection is preferably a persistent bacterial infection and may be related to a persistent *S. aureus* infection of various tissues such as but not limited to skin, respiratory epithelium, tonsillar tissue, mastitis. In the embodiments of the invention, the bacterial infection is preferably an infection by a species selected from the group bacteria consisting of Staphylococcus, Streptococcus (such as *S. pyogenes*, *S. agalactiae* and *S.pneumonia*), Actinomyces, Nocardia, Bacillus (such as *B. anthracis*), Coxiella (such as *Coxiella burnetii*), Rickettsia, Mycobacteria (such as *M. tuberculosis* and *M. leprae*), Legionella (such as *L. pneumophila*), Mycoplasma, Salmonella (such as *S. typhimurium*), Shigella (such as *S. dysenteriae*),

Yersinia (such as *Y. pestis*), Brucella, Listeria (such as *L. monocytogenesis*), Actinobacillus (such as *A. actinomycetemcomitans*), Gardnerella (such as *G. vaginalis*), Chlamydia (such as *C. trachomatis*), and Chlamidophila; a more preferred bacterium is a species of Staphylococcus; a preferred species of Staphylococcus is *S. aureus*.

In the embodiments of the invention, a bacterium causing the bacterial infection is preferably present intracellularly in a host cell, such as in the cytosol; more preferably a bacterium causing the bacterial infection is preferably present within an intracellular compartment *S. aureus* Preferably, the bacterial infection comprises a population of bacteria comprising at least one subpopulation of bacteria that is resistant to a bactericidal agent (e.g. an antibiotic), such as, but not limited to MRSA. In the embodiments of the invention, the intracellular compartment may be any intracellular compartment wherein a bacterium can be persistently present and/or persistently present; preferably the intracellular compartment is a compartment with low pH. A preferred intracellular compartment is a compartment selected from the group consisting of an endosome, a lysozome, a phagosome, a phagolysosome, an autophagosome and an autolysosome'a more preferred intracellular compartment is a phagosome, lysozome of phagolysosome; an even more preferred intracellular compartment is a phagolysosome..

In the embodiments of the invention within a subject in need of treatment, the infected host cell is preferably a eukaryotic host cell; the eukaryotic host cell is preferably selected from the group consisting of professional and non-professional phagocytes, a lymphoid cell, a tonsillar tissue cell, a respiratory epithelial cell, a buccal epithelial cell, a bone marrow cell, an osteoblast, a keratinocyte, a muscle cell, a monocyte, a macrophage, a dendritic cell, an endothelial cell, an epithelial cell, a fibroblasts, an astrocyte, and an microglial cell; a more preferred eukaryotic host cell is a professional or a non-professional phagocyte. The subject may be any subject susceptible to or suffering from a persistent bacterial infection, such as, but not limited to, a human being or an animal. The animal may be a domestic animal or may be a breeding animal, pet, cattle, poultry or the like. A preferred subject is a human being and may be a newborn, a juvenile, an adult or an aged subject.

In the embodiments of the invention, the agent that increases the intracellular pH and/or the pH of the intracellular compartment may be any agent known to the person skilled in the art that effectively increases the intracellular pH and/or the pH of the intracellular compartment.

Preferably, in the embodiments of the invention, the agent that increases the intracellular pH and/or the pH of the intracellular compartment is an alkalizing agent, preferably an lysosomotropic alkalizing agent, preferably selected from the group of chloroquine, bafilomycin A1, ammonium chloride; a more preferred alkalizing agent is chloroquine. A preferred alkalyzing agent is one that is capable of entering the host cell and more preferably is targeted to the intracellular compartment wherein the infecting bacterium is present. The alkalizing agent may passively enter the cell or a vehicle may be used. The vehicle may be any vehicle known to a person skilled in the art that enables delivery into a host cell.

The term "low pH" in the embodiments of the invention is defined as a pH that is lower than pH 7.4; preferably low pH is about pH 7.0, 6.8, 6.6, 6.4, 6.2, 6.0, 5.8, 5.6, 5.4, 5.2, 5.0, 4.8, 4.6, 4.4, 4.2, 4.0, 3.8, 3.6, 3.4, 3.2, 3.0 or about 2.8. A low pH is preferably a pH lower than about 6.5 A more preferred low pH is about 5.0.

In the embodiments of the present invention, the term raising the pH and increasing the pH are used interchangeably and are defined as raising the pH about 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.2, 3.4, 3.6, 3.8, 4.0, 4.2, 4.4, 4.6 or about 4.8. Preferably, the pH is raised to within the range of about pH 6 to about7; preferably to within the range of about 6.5 to about 7

The term "an effective amount" in the embodiments of the invention in the context of an agent that increases the intracellular pH and/or the pH of an intracellular compartment is defined as any amount that is sufficient to raise the intracellular pH and/or the pH of an intracellular compartment at least about 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0 to reach the range as depicted here above.. The exact amount used will *inter alia* depend on the agent used and on the bodyweight of the subject.

The term "an effective amount" in the embodiments of the invention in the context of a bactericidal agent is defined as any amount that is sufficient to have a bactericidal affect intracellularly and/or within the intracellular compartment. The exact amount used will *inter alia* depend on the agent used and on the bodyweight of the subject.

Intracellular pH and the pH of an intracellular compartment can be assessed by any means known to the person skilled in the art. In the embodiments of the invention, the bactericidal agent may be any bactericidal agent known to the person skilled in the art and preferably is a bactericidal agent capable of entering the host cell and/or the intracellular compartment of the host cell. A preferred bactericidal agent is a chimeric

bactericidal agent. A preferred bactericidal agent is selected from the group consisting of a bacteriocin or a functional part thereof, a bacterial lysin or autolysin or a functional part thereof, a bacteriophage lysin or a functional part thereof, a viral lysin or a part thereof, an antimicrobial peptide and an antibiotic. A further preferred bactericidal agent is a bacteriophage derived lytic structural protein (such as a tail lysin and a virion associated lytic protein) or an isolated lytic domain from such lytic structural protein or bacteriophage lysin. The bactericidal agents of the invention may be used alone or may be used in combinations of two or three or more bactericidal agents of the invention. A preferred bactericidal agent is one that is capable of entering the host cell and more preferably is targeted to the intracellular compartment wherein the infecting bacterium is present. The bactericidal agent may passively enter the cell or a vehicle may be used. The vehicle may be any vehicle known to a person skilled in the art that enables delivery into a host cell.

The antibiotic may be any antibiotic known to the person skilled in the art. A preferred antibiotic is selected from the group consisting of beta-lactam antibiotics such as penicillin derivatives, cephalosporins, monobactams, carbapenems, vancomycins, daptomycin, fluoroquinolones, metronidazole, nitrofurantoin, co-trimoxazole, telithromycin, aminoglycosidic antibiotics; a more preferred antibiotic is flucloxacillin.

The bacteriocin may be any bacteriocin known to the person skilled in the art, preferably a bacteriocin of any Class I –IV.

Class I bacteriocins herein are small peptide inhibitors and include nisin and other lantibiotics.

Class II bacteriocins herein are small (<10 kDa) heat-stable proteins. This class is subdivided into five subclassses. The class IIa bacteriocins (pediocin-like bacteriocins) are the largest subgroup and contain an N-terminal consensus sequence -Tyr-Gly-Asn-Gly-Val-Xaa-Cys across this group. The C-terminal is responsible for species-specific activity, causing cell-leakage by permeabilizing the target cell wall. The class IIb bacteriocins (two-peptide bacteriocins) require two different peptides for activity. One such an example is lactococcin G, which permeabilizes cell membranes for monovalent ions such as Na and K, but not for divalents ones. Almost all of these bacteriocins have a GxxxG motif. This motif is also found in transmembrane proteins where they are involved in helix-helix interactions. The bacteriocin's GxxxG motif can interact with the motifs in the membranes of the bacterial cells and kill the bacteria by doing so. Class IIc

encompasses cyclic peptides, which possesses the N-terminal and C-terminal regions covalentely linked. Enterocin AS-48 is the prototype of this group. Class IId cover single-peptide bacteriocins, which are not post-translated modified and do not show the pediocin-like signature. The best example of this group is the highly stable aureocin A53. This bacteriocin is stable under highly acidic environment (HCl 6 N), not affected by proteases and thermoresistant. The most recently proposed subclass is the Class IIe, which encompasses those bacteriocins composed by three or four non-pediocin like peptides. The best example is aureocin A70, a four-peptides bacteriocin, highly active against *L. monocytogenes*, with potential biotechnological applications.

Class III bacteriocins are large, heat-labile (>10 kDa) protein bacteriocins. This class is subdivided in two subclasses: subclass IIIa or bacteriolysins and subclass IIIb. Subclass IIIa comprises those peptides that kill bacterial cells by cell-wall degradation, thus causing cell lysis. The best studied bacteriolysin is lysostaphin, a 27 kDa peptide that hydrolises several *Staphylococcus* spp. cell walls, principally *S. aureus*. Subclass IIIb, in contrast, comprises those peptides that do not cause cell lysis, killing the target cells by disrupting the membrane potential, which causes ATP efflux .

Class IV bacteriocins are defined as complex bacteriocins containing lipid or carbohydrate moities. Confirmatory experimental data was only recently established with the characterisation of Sublancin and Glycocin F (GccF) by two independent groups.

A preferred bacteriocin is selected from the group consisting of an acidocin, actagardine, agrocin, alveicin, aureocin, aureocin A53, aureocin A70, carnocin, carnocyclin circularin A, colicin, Curvaticin, divercin, duramycin, Enterocin, enterolysin, epidermin/gallidermin, erwiniocin, gassericin A, glycinecin, halocin, haloduracin, lactocin S, lactococin, lacticin, leucoccin, lysostaphin macedocin, mersacidin, mesentericin, microbisporicin, microcin S, mutacin, nisin, paenibacillin, planosporicin, pediocin, pentocin, plantaricin, pyocin, reutericin 6, sakacin, salivaricin, subtilin, sulfolobicin, thuricin 17, trifolitoxin, variacin, vibriocin, warnericin and a warnerin.

The bacteriocin may be from a bacterium itself (24), such as, but not limited to a pyocin from *Pseudomonas aeruginosa*, preferably pyocin SA189 (25).

The antimicrobial peptide may be any antimicrobial peptide known to the person skilled in the art. Sometimes in the art, antimicrobial peptides are considered bacteriocins as listed here above. A preferred antimicrobial peptide is selected from the group consisting

of a cationic or polycationic peptide, an amphipatic peptide, a sushi peptide, a defensin and a hydrophobic peptide.

The bacterial autolysin may be any a bacterial autolysin known to the persons killed in the art. A preferred bacterial autolysin is LytM.

The bacteriophage lysin may be any bacteriophage lysin known to the persons skilled in the art. Herein, the terms bacteriophage lysin, bacteriophage endolysin and endolysin are used interchangeably. A preferred endolysin is selected from the group defined in WO2012/150858, in WO2013/169104, in WO2011/023702, and in WO2012146738, which are herein incorporated by reference with their entire content.

The bactericidal agent may be any agent described here above or be a functional fragment thereof. Herein, the term functional fragment is interchangeably used with the term functional domain. A functional fragment is herein defined as a fragment that still has at least 20, 30, 40, 50, 60, 70, 80, 90, 95, or 99, or at least or 99.9% bactericidal activity as compared to the parent wherefrom the functional fragment is derived when assayed in identical conditions. Preferred functional fragments of bactericidal agents are described in WO2012/150858 and in WO2013/169104.

The bactericidal agent may be a fusion of a bactericidal agent and a functional fragment of bactericidal agents or may be a fusion of different, similar or identical bactericidal agents or of functional fragments of bactericidal agents.

The inventors have come to the surprising finding that the efficiency of a method of treatment according to the invention is greatly enhance when the bactericidal agent is targeted into the host cell. Such targeting may be achieved any means known to the person skilled in the art, as already depicted here above. A preferred means is a protein transduction domain that is operably linked to the bactericidal agent; further referred to herein as a protein transduction domain according to the invention. The term “protein transduction domain” is herein interchangeably used with the term “cell permeable protein (CPP)” and with the term “membrane translocating sequence”. Operably linked is defined herein as such association of the protein transduction domain with the bactericidal agent that the bactericidal agent is targeted into the cell. A preferred operable linkage is fusion by means of covalent binding of the protein transduction domain to the bactericidal agent.

In the embodiments of the invention, the bactericidal agent preferably comprises a functional enzymatic domain of a cell wall lytic enzyme. A cell wall lytic enzyme is

herein defined as any bactericidal agent that acts upon the cell wall of the bacterium it is effective against.

Preferably in the embodiments of the present invention, the bactericidal agent comprises a functional domain from a cell wall lytic enzyme and further comprises a protein transduction domain according to the invention. Preferably in the embodiments according to the invention, the bactericidal agent may further comprise an antimicrobial peptide. Such fusion bactericidal agent preferably is a cell wall lytic enzyme fused to an antimicrobial peptide selected from the group consisting of a cationic or polycationic peptide, an amphipatic peptide, a sushi peptide, a defensin and a hydrophobic peptide, more preferably a fusion protein as defined in US8,383,102 which is herein incorporated by reference in its entirety. Such bactericidal agent fused to an antimicrobial peptide may further comprise a protein transduction domain according to the invention.

In the embodiments of the invention, the bactericidal agent as described here above comprising a functional enzymatic domain of a cell wall lytic enzyme and/or comprising a protein transduction domain and/or comprising an antimicrobial peptide, may further preferably further comprises a cell wall binding domain. Said cell wall binding domain preferably is a cell wall binding domain that binds the peptidoglycan cell wall of the bacteria causing the bacterial infection to be treated.

In the embodiments of the invention, the protein transduction domain may be any such domain known to the person skilled in the art. Preferably, in the bactericidal agent according to the invention, the protein transduction domain is selected from the group consisting of SEQ ID NO: 12 – 25, or a variant thereof, wherein the variant is a functional protein transduction domain and has at least 40%, 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 12 – 25, respectively.

Preferably, in the bactericidal agent according to the invention, the functional enzymatic domain from a cell wall lytic enzyme is selected from the group consisting of SEQ ID NO: 1 – 7, or a variant thereof, wherein the variant is a functional enzymatic domain from a cell wall lytic enzyme and has at least 40%, 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 1 – 7, respectively.

Preferably, in the bactericidal agent according to the invention, the cell wall binding domain is selected from the group consisting of SEQ ID NO: 8 – 11, or a variant thereof,

wherein the variant is a functional cell wall binding domain and has at least 40%, 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 8 – 11, respectively.

Preferably, in the bactericidal agent according to the invention, the antimicrobial peptide is selected from the group consisting of SEQ ID NO: 70 - 90, or a variant thereof, wherein the variant is a functional cell wall binding domain and has at least 40%, 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 70 - 90, respectively.

A preferred bactericidal agent according to the invention is a bactericidal agent with at least 40%, 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 27, 28, 29, 30 – 47, or is a bactericidal agent encoded by polynucleotide sequence with at least 40%, 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 50 – 67.

A preferred bactericidal agent according to the invention is an expression product from a vector with a sequence of at least 40%, 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 91 - 108.

A further preferred bactericidal agent according to the invention is one selected from the group consisting of a bactericidal agent comprising a protein transduction domain selected from the group consisting of SEQ ID NO: 12 – 25, or a variant thereof, a functional enzymatic domain from a cell wall lytic enzyme selected from the group consisting of SEQ ID NO: 1 – 7, or a variant thereof and, optionally, a cell wall binding domain selected from the group consisting of SEQ ID NO: 8 – 11, or a variant thereof and/or an antimicrobial peptide selected from the group consisting of SEQ ID NO: 70 - 90, or a variant thereof; wherein a variant has at least 40%, 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity with the respective original sequence.

Further to a method of treatment, this aspect relates to the embodiments of this aspect for the manufacture of a medicament for the treatment of a bacterial infection in a subject in need thereof. Further to a method of treatment, this aspect relates to the embodiments of this aspect for use in the treatment of a bacterial infection in a subject in need thereof.

In a second aspect, the invention provides for a chimeric bactericidal polypeptide comprising a functional enzymatic domain from a cell wall lytic enzyme selected from the group consisting of SEQ ID NO: 1 – 7, or a variant thereof, wherein the variant is a functional enzymatic domain from a cell wall lytic enzyme and has at least 40%, 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 1 – 7, respectively; and a protein transduction domain selected from the group consisting of SEQ ID NO: 12 – 25, or a variant thereof, wherein the variant is a functional protein transduction domain and has at least 40%, 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or 100% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 12 – 25, respectively; and optionally comprising a cell wall binding domain selected from the group consisting of SEQ ID NO: 8 – 11, or a variant thereof, wherein the variant is a functional cell wall binding domain and has at least 40%, 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 8 – 11, respectively; and/or an antimicrobial peptide selected from the group consisting of SEQ ID NO: 70 - 90, or a variant thereof, wherein the variant is a functional cell wall binding domain and has at least 40%, 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 70 - 90, respectively.

The invention further provides for a chimeric bactericidal polypeptide having at least 40%, 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or 100% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 27, 28, 29, 30 – 47, or a chimeric bactericidal agent encoded by polynucleotide sequence with at least 40%, 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 50 – 67.

The invention further provides for a chimeric bactericidal polypeptide selected from the group consisting of a bactericidal agent comprising a protein transduction domain selected from the group consisting of SEQ ID NO: 12 – 25, or a variant thereof, a functional enzymatic domain from a cell wall lytic enzyme selected from the group consisting of SEQ ID NO: 1 – 7, or a variant thereof and, optionally, a cell wall binding domain selected from the group consisting of SEQ ID NO: 8 – 11, or a variant thereof and/or an antimicrobial peptide selected from the group consisting of SEQ ID NO: 70 - 90, or a variant thereof; wherein a variant has at least 40%, 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity with the respective original sequence.

The invention further provides for a polynucleotide encoding a chimeric bactericidal polypeptide according to this aspect of the invention.

The invention further provides for a polynucleotide construct comprising a polynucleotide encoding a chimeric bactericidal polypeptide according to the invention.

The invention further provides for a vector for expression and production of a chimeric bactericidal polypeptide according to the invention. A vector according to the invention preferably comprises a polynucleotide construct according to the invention comprising a polynucleotide encoding a chimeric bactericidal polypeptide according to the invention. A preferred vector according to the invention is a vector with a sequence of at least 40%, 45%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 91 - 108.

The invention further provides for a host cell for the production of a chimeric bactericidal polypeptide according to the invention, comprising a polynucleotide construct or a vector according to the invention. The host cell may be any host cell suitable for the production of a chimeric bactericidal polypeptide according to the invention such a prokaryotic and a eukaryotic host cell.

The invention further provides for the production of a chimeric bactericidal polypeptide according to the invention, comprising culturing a host cell according to the invention, comprising a polynucleotide construct or a vector according to the invention under

conditions conducive to the production of the a chimeric bactericidal polypeptide according to the invention and, optionally, isolating and/or purifying the chimeric bactericidal polypeptide produced.

Any suitable route of administration can be used to administer the alkalizing agent according to the invention and the bactericidal agent according to the invention including but not limited to: oral, aerosol or other device for delivery to the lungs, nasal spray, intravenous, intramuscular, intraperitoneal, intrathecal, vaginal, rectal, topical, lumbar puncture, intrathecal, and direct application to the brain and/or meninges. The alkalizing agent according to the invention and the bactericidal agent the invention may be administered to a subject in need thereof or to a cell, tissue or organ of said subject at least once a day, once a week, once a month, once every six months, once a year or whatever regime is suitable for the treatment.

In this document and in its claims, the verb "to comprise" and its conjugations is used in its non-limiting sense to mean that items following the word are included, but items not specifically mentioned are not excluded. In addition, reference to an element by the indefinite article "a" or "an" does not exclude the possibility that more than one of the element is present, unless the context clearly requires that there be one and only one of the elements. The indefinite article "a" or "an" thus usually means "at least one".

The word “about” or “approximately” when used in association with a numerical value (e.g. about 10) preferably means that the value may be the given value (of 10) more or less 0.1% of the value.

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

Herein, sequence identity with a particular sequence preferably means sequence identity over the entire length of said particular polypeptide or polynucleotide sequence. The sequence information as provided herein should not be so narrowly construed as to require inclusion of erroneously identified bases. The skilled person is capable of identifying such erroneously identified bases and knows how to correct for such errors.

"Similarity" between two amino acid sequences is determined by comparing the amino acid sequence and its conserved amino acid substitutes of one peptide or polypeptide to the sequence of a second peptide or polypeptide. Preferably, identity or similarity is calculated over the whole SEQ ID NO as identified herein. "Identity" and "similarity"

can be readily calculated by known methods, including but not limited to those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heine, G., Academic Press, 1987; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; and Carillo, H., and Lipman, D., SIAM J. Applied Math., 48:1073 (1988).

Preferred methods to determine identity are designed to give the largest match between the sequences tested. Methods to determine identity and similarity are codified in publicly available computer programs. Preferred computer program methods to determine identity and similarity between two sequences include e.g. the GCG program package (Devereux, J., et al., Nucleic Acids Research 12 (1): 387 (1984)), BestFit, BLASTP, BLASTN, and FASTA (Altschul, S. F. et al., J. Mol. Biol. 215:403-410 (1990). The BLAST X program is publicly available from NCBI and other sources (BLAST Manual, Altschul, S., et al., NCBI NLM NIH Bethesda, MD 20894; Altschul, S., et al., J. Mol. Biol. 215:403-410 (1990). The well-known Smith Waterman algorithm may also be used to determine identity.

Preferred parameters for polypeptide sequence comparison include the following: Algorithm: Needleman and Wunsch, J. Mol. Biol. 48:443-453 (1970); Comparison matrix: BLOSSUM62 from Hentikoff and Hentikoff, Proc. Natl. Acad. Sci. USA. 89:10915-10919 (1992); Gap Penalty: 12; and Gap Length Penalty: 4. A program useful with these parameters is publicly available as the "Ogap" program from Genetics Computer Group, located in Madison, WI. The aforementioned parameters are the default parameters for amino acid comparisons (along with no penalty for end gaps).

Preferred parameters for nucleic acid comparison include the following: Algorithm: Needleman and Wunsch, J. Mol. Biol. 48:443-453 (1970); Comparison matrix: matches=+10, mismatch=0; Gap Penalty: 50; Gap Length Penalty: 3. Available as the Gap program from Genetics Computer Group, located in Madison, Wis. Given above are the default parameters for nucleic acid comparisons.

Optionally, in determining the degree of amino acid similarity, the skilled person may also take into account so-called "conservative" amino acid substitutions, as will be clear to the skilled person. Conservative amino acid substitutions refer to the

interchangeability of residues having similar side chains. For example, a group of amino acids having aliphatic side chains is glycine, alanine, valine, leucine, and isoleucine; a group of amino acids having aliphatic-hydroxyl side chains is serine and threonine; a group of amino acids having amide-containing side chains is asparagine and glutamine; a group of amino acids having aromatic side chains is phenylalanine, tyrosine, and tryptophan; a group of amino acids having basic side chains is lysine, arginine, and histidine; and a group of amino acids having sulphur-containing side chains is cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, and asparagine-glutamine. Substitutional variants of the amino acid sequence disclosed herein are those in which at least one residue in the disclosed sequences has been removed and a different residue inserted in its place. Preferably, the amino acid change is conservative. Preferred conservative substitutions for each of the naturally occurring amino acids are as follows: Ala to ser; Arg to lys; Asn to gln or his; Asp to glu; Cys to ser or ala; Gln to asn; Glu to asp; Gly to pro; His to asn or gln; Ile to leu or val; Leu to ile or val; Lys to arg; gln or glu; Met to leu or ile; Phe to met, leu or tyr; Ser to thr; Thr to ser; Trp to tyr; Tyr to trp or phe; and, Val to ile or leu.

A polynucleotide is represented by a nucleotide sequence. A polypeptide is represented by an amino acid sequence.

**Table 1.** Sequences

| SEQ ID NO | Gene / Polypeptide | Sequence |
|---|---|---|
| 1 | EAD Ami2638 | MLKHIYSNHIKGNKITAPKPSIQGVVIHNDYGSMTPSQYLPWLYARE NNGTHVNGWASVYANRNEVLWYHPTDYVEWHCGNQWANANLIGFEVC ESYPGRISDKLFLENEEATLKVAADVMKSYGLPVNRNTVRLHNEFFG TSCPHRSWDLHVGKGEPYTTTNINKMKDYFIKRIKHYYD |
| 2 | EAD M23-LST | AATHEHSAQWLNNYKKGYGYGPYPLGINGGMHYGVDFFMNIGTPVKA ISSGKIVEAGWSNYGGGNQIGLIENDGVHRQWYMHLSKYNVKVGDYV KAGQIIGWSGSTGYSTAPHLHFQRMVNSFSNSTAQDPMPFLKSAGYG |
| 3 | EAD CHAP11 | MSIIMEVATMQAKLTKNEFIEWLKTSEGKQFNVDLWYGFQCFDYANA GWKVLFGLLLKGLGAKDIPFANNFDGLATVYQNTPDFLAQPGDMVVF GSNYGAGYGHVAWVIEATLDYIIVYEQNWLGGGWTDGIEQPGWGWEK VTRRQHAYDFPMWFIRPNFK |
| 4 | EAD CHAPTw | MKTLKQAESYIKSKVNTGTDFDGLYGYQCMDLAVDYIYHVTDGKIRM WGNAKDAINNSFGGTATVYKNYPAFRPKYGDVVVWTTGNFATYGHIA |

| | | |
|---|---|---|
| | | IVTNPDPYGDLQYVTVLEQNWNGNGIYKTELATIRTHDYTGITHFIR PNFA |
| 5 | EAD C118II | MGLPSPKKRKPTASEVAAWAKRMIGRRVDVDGYHGAQCWDLPNYIFN RYWHFKTTGNAIAMAWYRYPKGFKFYRNTRNFVPKPGDMAVWGKGSF NNGVGHTAVVIGPSTKSYFTSVDQNWIGANSYTGSPGAKIKHSYNGI SGFVRPPYHA |
| 6 | EAD TC187 | MALPKTGKPTAKQVVDWAINLIGSGVDVDGYYGRQCWDLPNYIFNRY WNFKTPGNARDMAWYRYPEGFKVFRNTSDFVPKPGDIAVWTGGNYNW NTWGHTGIVVGPSTKSYFYSVDQNWNNSNSYVGSPAAKIKHSYFGVT HFVRPA |
| 7 | EAD CHAPK/GH15 | MAKTQAEINKRLDAYAKGTVDSPYRIKKATSYDPSFGVMEAGAIDAD GYYHAQCQDLITDYVLWLTDNKVRTWGNAKDQIKQSYGTGFKIHENK PSTVPKKGWIAVFTSGSYQQWGHIGIVYDGGNTSTFTILEQNWNGYA NKKPTKRVDNYYGLTHFIEIPVKA |
| 8 | CBD CBD2638 | GGKLEVSKAATIKQSDVKQEVKKQEAKQIVKATDWKQNKDGIWYKAE HASFTVTAPEGIITRYKGPWTGHPQAGVLQKGQTIKYDEVQKFDGHV WVSWETFEGETVYMPVRTWDAKTGKVGKLWGEIK |
| 9 | CBD CBD118II | APKSKPSKIKTTWNWGGKFTANSTIKVRKSPGLKGIVVESGSWLYKG NYVPFDQVIKKDGYWWIRFKYVQPGSSNKHF |
| 10 | CBD CWT-LST | WKTNKYGTLYKSESASFTPNTDIITRTTGPFRSMPQSGVLKAGQTIH YDEVMKQDGHVWVGYTGNSGQRIYLPVRTWNKSTNTLGVLWGTIK |
| 11 | CBD CWT-Ale-1 | YKTNKYGTLYKSESASFTANTDIITRLTGPFRSMPQSGVLRKGLTIK YDEVMKQDGHVWVGYNTNSGKRVYLPVRTWNESTGELGPLWGTIK |
| 12 | CPP 1: Kala Syn | WEAKLAKALAKALAKHLAKALAKALKACEA |
| 13 | CPP 2: M918 | MVTVLFRRLRIRRASGPPRVRV |
| 14 | CPP 3: MAP | KLALKLALKALKAALKLA |
| 15 | CPP 4: MPG | GALFLGFLGAAGSTMGAWSQPKKKRKV |
| 16 | CPP 5: Penetratin | RQIKIWFQNRRMKWKK |
| 17 | CPP 6: Pep-1 | KETWWETWWTEWSQPKKKRKV |
| 18 | CPP 7: PTD5-Syn | RRQRRTSKLMKR |
| 19 | CPP 8: pVEC | LLIILRRRIRKQAHAHSK |
| 20 | CPP 9: $R_6W_3$ | RRWWRRWRR |
| 21 | CPP10: Polyarginines | (R)n: 6 < n < 15 |
| 22 | CPP 11: TAT | GRKKRRQRRRPPQ |

| | | |
|---|---|---|
| 23 | CPP 12: TAT | RKKRRQRRR |
| 24 | CPP 13: Transportan | GWTLNSAGYLLGKINLKALAALAKKIL |
| 25 | CPP 14: Transportan 10 | AGYLLGKINLKALAALAKKIL |
| 26 | - | |
| 27 | M23-CBD | MAATHEHSAQWLNNYKKGYGYGPYPLGINGGMHYGVDFFMNIGTPVK AISSGKIVEAGWSNYGGGNQIGLIENDGVHRQWYMHLSKYNVKVGDY VKAGQIIGWSGSTGYSTAPHLHFQRMVNSFSNSTAQDPMPFLKSAGY GGKLEVSKAATIKQSDVKQEVKKQEAKQIVKATDWKQNKDGIWYKAE HASFTVTAPEGIITRYKGPWTGHPQAGVLQKGQTIKYDEVQKFDGHV WVSWETFEGETVYMPVRTWDAKTGKVGKLWGEIK |
| 28 | CHAP-CBD | MSIIMEVATMQAKLTKNEFIEWLKTSEGKQFNVDLWYGFQCFDYANA GWKVLFGLLLKGLGAKDIPFANNFDGLATVYQNTPDFLAQPGDMVVF GSNYGAGYGHVAWVIEATLDYIIVYEQNWLGGGWTDGIEQPGWGWEK VTRRQHAYDFPMWFIRPNFKGGKLEVSKAATIKQSDVKQEVKKQEAK QIVKATDWKQNKDGIWYKAEHASFTVTAPEGIITRYKGPWTGHPQAG VLQKGQTIKYDEVQKFDGHVWVSWETFEGETVYMPVRTWDAKTGKVG KLWGEIK |
| 29 | Ami-CBD | MLKHIYSNHIKGNKITAPKPSIQGVVIHNDYGSMTPSQYLPWLYARE NNGTHVNGWASVYANRNEVLWYHPTDYVEWHCGNQWANANLIGFEVC ESYPGRISDKLFLENEEATLKVAADVMKSYGLPVNRNTVRLHNEFFG TSCPHRSWDLHVGKGEPYTTTNINKMKDYFIKRIKHYYDGGKLEVSK AATIKQSDVKQEVKKQEAKQIVKATDWKQNKDGIWYKAEHASFTVTA PEGIITRYKGPWTGHPQAGVLQKGQTIKYDEVQKFDGHVWVSWETFE GETVYMPVRTWDAKTGKVGKLWGEIK |
| 30 | Ami-CBD-Penetratin | MLKHIYSNHIKGNKITAPKPSIQGVVIHNDYGSMTPSQYLPWLYARE NNGTHVNGWASVYANRNEVLWYHPTDYVEWHCGNQWANANLIGFEVC ESYPGRISDKLFLENEEATLKVAADVMKSYGLPVNRNTVRLHNEFFG TSCPHRSWDLHVGKGEPYTTTNINKMKDYFIKRIKHYYDGGKLEVSK AATIKQSDVKQEVKKQEAKQIVKATDWKQNKDGIWYKAEHASFTVTA PEGIITRYKGPWTGHPQAGVLQKGQTIKYDEVQKFDGHVWVSWETFE GETVYMPVRTWDAKTGKVGKLWGEIKELRQIKIWFQNRRMKWKK |
| 31 | Ami-CBD-R9 | MLKHIYSNHIKGNKITAPKPSIQGVVIHNDYGSMTPSQYLPWLYARE NNGTHVNGWASVYANRNEVLWYHPTDYVEWHCGNQWANANLIGFEVC ESYPGRISDKLFLENEEATLKVAADVMKSYGLPVNRNTVRLHNEFFG TSCPHRSWDLHVGKGEPYTTTNINKMKDYFIKRIKHYYDGGKLEVSK AATIKQSDVKQEVKKQEAKQIVKATDWKQNKDGIWYKAEHASFTVTA |

| | | |
|---|---|---|
| | | PEGIITRYKGPWTGHPQAGVLQKGQTIKYDEVQKFDGHVWVSWETFE GETVYMPVRTWDAKTGKVGKLWGEIKELRRRRRRRRR |
| 32 | Ami-CBD-TAT | MLKHIYSNHIKGNKITAPKPSIQGVVIHNDYGSMTPSQYLPWLYARE NNGTHVNGWASVYANRNEVLWYHPTDYVEWHCGNQWANANLIGFEVC ESYPGRISDKLFLENEEATLKVAADVMKSYGLPVNRNTVRLHNEFFG TSCPHRSWDLHVGKGEPYTTTNINKMKDYFIKRIKHYYDGGKLEVSK AATIKQSDVKQEVKKQEAKQIVKATDWKQNKDGIWYKAEHASFTVTA PEGIITRYKGPWTGHPQAGVLQKGQTIKYDEVQKFDGHVWVSWETFE GETVYMPVRTWDAKTGKVGKLWGEIKELGRKKRRQRRRPPQ |
| 33 | Ami-Penetratin | MLKHIYSNHIKGNKITAPKPSIQGVVIHNDYGSMTPSQYLPWLYARE NNGTHVNGWASVYANRNEVLWYHPTDYVEWHCGNQWANANLIGFEVC ESYPGRISDKLFLENEEATLKVAADVMKSYGLPVNRNTVRLHNEFFG TSCPHRSWDLHVGKGEPYTTTNINKMKDYFIKRIKHYYDGELRQIKI WFQNRRMKWKK |
| 34 | Ami-R9 | MLKHIYSNHIKGNKITAPKPSIQGVVIHNDYGSMTPSQYLPWLYARE NNGTHVNGWASVYANRNEVLWYHPTDYVEWHCGNQWANANLIGFEVC ESYPGRISDKLFLENEEATLKVAADVMKSYGLPVNRNTVRLHNEFFG TSCPHRSWDLHVGKGEPYTTTNINKMKDYFIKRIKHYYDGELRRRRR RRRR |
| 35 | Ami-TAT | MLKHIYSNHIKGNKITAPKPSIQGVVIHNDYGSMTPSQYLPWLYARE NNGTHVNGWASVYANRNEVLWYHPTDYVEWHCGNQWANANLIGFEVC ESYPGRISDKLFLENEEATLKVAADVMKSYGLPVNRNTVRLHNEFFG TSCPHRSWDLHVGKGEPYTTTNINKMKDYFIKRIKHYYDGELGRKKR RQRRRPPQ |
| 36 | CHAP11-CBD-Penetratin | MSIIMEVATMQAKLTKNEFIEWLKTSEGKQFNVDLWYGFQCFDYANA GWKVLFGLLLKGLGAKDIPFANNFDGLATVYQNTPDFLAQPGDMVVF GSNYGAGYGHVAWVIEATLDYIIVYEQNWLGGGWTDGIEQPGWGWEK VTRRQHAYDFPMWFIRPNFKGGKLEVSKAATIKQSDVKQEVKKQEAK QIVKATDWKQNKDGIWYKAEHASFTVTAPEGIITRYKGPWTGHPQAG VLQKGQTIKYDEVQKFDGHVWVSWETFEGETVYMPVRTWDAKTGKVG KLWGEIKELRQIKIWFQNRRMKWKK |
| 37 | CHAP11-CBD-R9 | MSIIMEVATMQAKLTKNEFIEWLKTSEGKQFNVDLWYGFQCFDYANA GWKVLFGLLLKGLGAKDIPFANNFDGLATVYQNTPDFLAQPGDMVVF GSNYGAGYGHVAWVIEATLDYIIVYEQNWLGGGWTDGIEQPGWGWEK VTRRQHAYDFPMWFIRPNFKGGKLEVSKAATIKQSDVKQEVKKQEAK QIVKATDWKQNKDGIWYKAEHASFTVTAPEGIITRYKGPWTGHPQAG VLQKGQTIKYDEVQKFDGHVWVSWETFEGETVYMPVRTWDAKTGKVG KLWGEIKELRRRRRRRRR |
| 38 | CHAP11-CBD-TAT | MSIIMEVATMQAKLTKNEFIEWLKTSEGKQFNVDLWYGFQCFDYANA GWKVLFGLLLKGLGAKDIPFANNFDGLATVYQNTPDFLAQPGDMVVF |

| | | |
|---|---|---|
| | | GSNYGAGYGHVAWVIEATLDYIIVYEQNWLGGGWTDGIEQPGWGWEK VTRRQHAYDFPMWFIRPNFKGGKLEVSKAATIKQSDVKQEVKKQEAK QIVKATDWKQNKDGIWYKAEHASFTVTAPEGIITRYKGPWTGHPQAG VLQKGQTIKYDEVQKFDGHVWVSWETFEGETVYMPVRTWDAKTGKVG KLWGEIKELGRKKRRQRRRPPQ |
| 39 | CHAP11-Penetratin | MSIIMEVATMQAKLTKNEFIEWLKTSEGKQFNVDLWYGFQCFDYANA GWKVLFGLLLKGLGAKDIPFANNFDGLATVYQNTPDFLAQPGDMVVF GSNYGAGYGHVAWVIEATLDYIIVYEQNWLGGGWTDGIEQPGWGWEK VTRRQHAYDFPMWFIRPNFKELRQIKIWFQNRRMKWKK |
| 40 | CHAP11-R9 | MSIIMEVATMQAKLTKNEFIEWLKTSEGKQFNVDLWYGFQCFDYANA GWKVLFGLLLKGLGAKDIPFANNFDGLATVYQNTPDFLAQPGDMVVF GSNYGAGYGHVAWVIEATLDYIIVYEQNWLGGGWTDGIEQPGWGWEK VTRRQHAYDFPMWFIRPNFKELRRRRRRRRR |
| 41 | CHAP11-TAT | MSIIMEVATMQAKLTKNEFIEWLKTSEGKQFNVDLWYGFQCFDYANA GWKVLFGLLLKGLGAKDIPFANNFDGLATVYQNTPDFLAQPGDMVVF GSNYGAGYGHVAWVIEATLDYIIVYEQNWLGGGWTDGIEQPGWGWEK VTRRQHAYDFPMWFIRPNFKELGRKKRRQRRRPPQ |
| 42 | M23-CBD-Penetratin | MAATHEHSAQWLNNYKKGYGYGPYPLGINGGMHYGVDFFMNIGTPVK AISSGKIVEAGWSNYGGGNQIGLIENDGVHRQWYMHLSKYNVKVGDY VKAGQIIGWSGSTGYSTAPHLHFQRMVNSFSNSTAQDPMPFLKSAGY GGKLEVSKAATIKQSDVKQEVKKQEAKQIVKATDWKQNKDGIWYKAE HASFTVTAPEGIITRYKGPWTGHPQAGVLQKGQTIKYDEVQKFDGHV WVSWETFEGETVYMPVRTWDAKTGKVGKLWGEIKELRQIKIWFQNRR MKWKK |
| 43 | M23-CBD-R9 | MAATHEHSAQWLNNYKKGYGYGPYPLGINGGMHYGVDFFMNIGTPVK AISSGKIVEAGWSNYGGGNQIGLIENDGVHRQWYMHLSKYNVKVGDY VKAGQIIGWSGSTGYSTAPHLHFQRMVNSFSNSTAQDPMPFLKSAGY GGKLEVSKAATIKQSDVKQEVKKQEAKQIVKATDWKQNKDGIWYKAE HASFTVTAPEGIITRYKGPWTGHPQAGVLQKGQTIKYDEVQKFDGHV WVSWETFEGETVYMPVRTWDAKTGKVGKLWGEIKELRRRRRRRRR |
| 44 | M23-CBD-TAT | MAATHEHSAQWLNNYKKGYGYGPYPLGINGGMHYGVDFFMNIGTPVK AISSGKIVEAGWSNYGGGNQIGLIENDGVHRQWYMHLSKYNVKVGDY VKAGQIIGWSGSTGYSTAPHLHFQRMVNSFSNSTAQDPMPFLKSAGY GGKLEVSKAATIKQSDVKQEVKKQEAKQIVKATDWKQNKDGIWYKAE HASFTVTAPEGIITRYKGPWTGHPQAGVLQKGQTIKYDEVQKFDGHV WVSWETFEGETVYMPVRTWDAKTGKVGKLWGEIKELGRKKRRQRRRP PQ |
| 45 | M23-Penetratin | MAATHEHSAQWLNNYKKGYGYGPYPLGINGGMHYGVDFFMNIGTPVK AISSGKIVEAGWSNYGGGNQIGLIENDGVHRQWYMHLSKYNVKVGDY |

| | | |
|---|---|---|
| | | VKAGQIIGWSGSTGYSTAPHLHFQRMVNSFSNSTAQDPMPFLKSAGY GELRQIKIWFQNRRMKWKK |
| 46 | M23-R9 | MAATHEHSAQWLNNYKKGYGYGPYPLGINGGMHYGVDFFMNIGTPVK AISSGKIVEAGWSNYGGGNQIGLIENDGVHRQWYMHLSKYNVKVGDY VKAGQIIGWSGSTGYSTAPHLHFQRMVNSFSNSTAQDPMPFLKSAGY GELRRRRRRRR |
| 47 | M23-TAT | MAATHEHSAQWLNNYKKGYGYGPYPLGINGGMHYGVDFFMNIGTPVK AISSGKIVEAGWSNYGGGNQIGLIENDGVHRQWYMHLSKYNVKVGDY VKAGQIIGWSGSTGYSTAPHLHFQRMVNSFSNSTAQDPMPFLKSAGY GELGRKKRRQRRRPPQ |
| 48 | - | |
| 49 | - | |
| 50 | Ami-CBD-Penetratin | Polynucleotide sequence; see sequence listing |
| 51 | Ami-CBD-R9 | Polynucleotide sequence; see sequence listing |
| 52 | Ami-CBD-TAT | Polynucleotide sequence; see sequence listing |
| 53 | Ami-Penetratin | Polynucleotide sequence; see sequence listing |
| 54 | Ami-R9 | Polynucleotide sequence; see sequence listing |
| 55 | Ami-TAT | Polynucleotide sequence; see sequence listing |
| 56 | CHAP11-CBD-Penetratin | Polynucleotide sequence; see sequence listing |
| 57 | CHAP11-CBD-R9 | Polynucleotide sequence; see sequence listing |
| 58 | CHAP11-CBD-TAT | Polynucleotide sequence; see sequence listing |
| 59 | CHAP11-Penetratin | Polynucleotide sequence; see sequence listing |
| 60 | CHAP11-R9 | Polynucleotide sequence; see sequence listing |
| 61 | CHAP11-TAT | Polynucleotide sequence; see sequence listing |
| 62 | M23-CBD-Penetratin | Polynucleotide sequence; see sequence listing |
| 63 | M23-CBD-R9 | Polynucleotide sequence; see sequence listing |
| 64 | M23-CBD-TAT | Polynucleotide sequence; see sequence listing |
| 65 | M23-Penetratin | Polynucleotide sequence; see sequence listing |
| 66 | M23-R9 | Polynucleotide sequence; see sequence listing |
| 67 | M23-TAT | Polynucleotide sequence; see sequence listing |
| 68 | - | |
| 69 | - | |

| | | |
|---|---|---|
| 70 | LL-37 | LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES |
| 71 | SMAP-29 | RGLRRLGRKIAHGVKKYGPTVLRIIRIAG |
| 72 | Indolicidin | ILPWKWPWWPWRR |
| 73 | Protegrin | RGGRLCYCRRRFCVCVGR |
| 74 | Cecropin P1 | SWLSKTAKKLENSAKKRISEGIAIAIQGGPR |
| 75 | Magainin | GIGKFLHSAKKFGKAFVGEIMNS |
| 76 | Pleurocidin | GWGSFFKKAAHVGKHVGKAALTHYL |
| 77 | Cecropin A *A. aegyptae* | GGLKKLGKKLEGAGKRVFNAAEKALPVVAGAKALRK |
| 78 | Cecroptin A *D. melanogaster* | GWLKKIGKKIERVGQHTRDATIQGLGIPQQAANVAATARG |
| 79 | Buforin II | TRSSRAGLQFPVGRVHRLLRK |
| 80 | Sarcotoxin IA | GWLKKIGKKIERVGQHTRDATIQGLGIAQQAANVAATAR |
| 81 | Ascaphine | GIKDWIKGAAKKLIKTVASHIANQ |
| 82 | Apidaecine | ANRPVYIPPPRPPHPRL |
| 83 | Nigrocine | GLLSKVLGVGKKVLCGVSGLVC |
| 84 | Pseudin 1 | GLNTLKKVFQGLHEAIKLINNHVQ |
| 85 | Parasin 1 | KGRGKQGGKVRAKAKTRSS |
| 86 | Lycotoxin | IWLTALKFLGKHAAKKLAKQQLSKL |
| 87 | Ranalexin | FLGGLIVPAMICAVTKKC |
| 88 | Melittin | GIGAVLKVLTTGLPALISWIKRKRQQ |
| 89 | OR-7 | KTYYGTNGVHCTKNSLWGKVRLKNMKYDQNTTYMGRLQDILLGWATG AFGKTFH |
| 90 | Buforin I | AGRGKQGGKVRAKAKTRSSRAGLQFPVGRVHRLLRKGNY |
| 91 | Ami-CBD-Penetratin | Vector construct: see sequence listing |
| 92 | Ami-CBD-R9 | Vector construct: see sequence listing |
| 93 | Ami-CBD-TAT | Vector construct: see sequence listing |
| 94 | Ami-Penetratin | Vector construct: see sequence listing |
| 95 | Ami-R9 | Vector construct: see sequence listing |
| 96 | Ami-TAT | Vector construct: see sequence listing |
| 97 | CHAP11-CBD-Penetratin | Vector construct: see sequence listing |
| 98 | CHAP11-CBD-R9 | Vector construct: see sequence listing |

| | | |
|---|---|---|
| 99 | CHAP11-CBD-TAT | Vector construct: see sequence listing |
| 100 | CHAP11-Penetratin | Vector construct: see sequence listing |
| 101 | CHAP11-R9 | Vector construct: see sequence listing |
| 102 | CHAP11-TAT | Vector construct: see sequence listing |
| 103 | M23-CBD-Penetratin | Vector construct: see sequence listing |
| 104 | M23-CBD-R9 | Vector construct: see sequence listing |
| 105 | M23-CBD-TAT | Vector construct: see sequence listing |
| 106 | M23-Penetratin | Vector construct: see sequence listing |
| 107 | M23-R9 | Vector construct: see sequence listing |
| 108 | M23-TAT | Vector construct: see sequence listing |
| | | |

## FIGURE LEGENDS

**Figure 1.**

Induction of *S. aureus* SCVs and non-replicating persisters by low pH and bacterial regrowth through pH increase.

MRSA *S. aureus* strains 6850 (a), JE2 (b) and Cowan (c) were inoculated in media buffered at different pH as indicated. Colony phenotypes of viable bacteria were determined and the percentage of SCVs plotted over time. Three independent experiments done in triplicates are presented as mean ± SEM.

Low pH-induced MRSA *S. aureus* strains 6850 (d), JE2 (e) and Cowan (f) persisters were re-inoculated in various buffered pH media as indicated and growth was followed over time. Three independent experiments done in triplicates presented as mean ± SEM.

**Figure 2**

Intracellular persistence of *S. aureus* within phagolysosomes.

A549 cells were infected with *S. aureus* Cowan and extracellular bacteria were killed by addition of flucloxacillin. The number (a) and phenotype (b) of viable intracellular persisting bacteria were determined at indicated time points. Data are pooled from two experiments performed in triplicates, mean ± SEM.

**Figure 3**

Reduction of *S. aureus* persisters through phagolysosome alkalinization. *S. aureus* Cowan-infected A549 cells were treated with flucloxacillin alone (control) or supplemented with lysosomotropic alkalinizing agents (chloroquine (a), bafilomycin A1 (b) and ammonium chloride (c)). Colony phenotypes of viable intracellular persisting bacteria were determined and enumerated at indicated time points. Data were pooled from three independent experiments done in triplicates, mean ± SEM. Two-way ANOVA found the factors time and treatment to be significant (p-value < 0.01).

**Figure 4**

Reduction of *S. aureus* persisters by chloroquine in an *in vivo* infection model.

Mice were infected with *S. aureus* Cowan intraperitoneally. Six hours and two days post-infection mice were treated with 1 mg flucloxacillin and 0.2 mg chloroquine (+ CQ). Mice treated with flucloxacillin only served as control (-CQ). †, sacrifice (a). Colony phenotypes of bacteria recovered from target tissues (b), peripheral blood and peritoneal lavage (c) were determined and enumerated. Each point represents one mouse. Horizontal bars indicate mean ± SEM, n = 11 mice per group. PL, peritoneal lavage. Two-way ANOVA found the factor treatment to be significant (p-value < 0.01).

**Figure 5**

Intracellular targeting of S. aureus in osteosarcoma cells by mixtures of engineered endolysins. (A) Cells infected for 3h with *S. aureus* Newman (MOI 0.1) treated by endolysin mixtures for 1h and 4h. (B) Cells infected for 3h with *S. aureus* Newman (MOI 0.1) treated by endolysin mixtures for 1h and 4h in the presence of 20 μM chloroquine. (C) Cells infected for 3h with *S. aureus* Cowan (MOI 0.01) treated by endolysin mixtures for 1h and 4h. (D) Cells infected for 3h with *S. aureus* Cowan (MOI 0.01) treated by endolysin mixtures for 1h and 4h in the presence of 20 μM chloroquine.

**Figure 6**

Intracellular targeting of S. aureus in osteosarcoma cells (MOI 1.0) by mixtures of engineered endolysins. (A) Cells infected for 24h with *S. aureus* Newman treated by endolysin mixtures for 4h. (B) Cells infected for 24h with *S. aureus* Newman treated by

endolysin mixtures for 4h in the presence of 20 μM chloroquine. (C) Cells infected for 72h with *S. aureus* Cowan treated by endolysin mixtures for 4h. (D) Cells infected for 72h with *S. aureus* Cowan treated by endolysin mixtures for 4h in the presence of 20 μM chloroquine.

**Figure 7**

Activity of bactericidal agents according to the invention comprising a functional enzymatic domain from a cell wall lytic enzyme and further comprising a protein transduction domain on the N-terminal side of the molecule: (A) R9-CHAP-CBD, (B) R9-M23-CBD, (C) TAT-Ami-CBD, (D) TAT-CHAP-CBD, and (E) TAT-M23-CBD.

## EXAMPLES

The present invention is further described by the following examples which should not be construed as limiting the scope of the invention.

Unless stated otherwise, the practice of the invention will employ standard conventional methods of molecular biology, virology, microbiology or biochemistry. Such techniques are described in Sambrook *et al.* (1989) Molecular Cloning, A Laboratory Manual (2nd edition), Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press; in Sambrook and Russell (2001) *Molecular Cloning: A Laboratory Manual,* Third Edition, Cold Spring Harbor Laboratory Press, NY; in Volumes 1 and 2 of Ausubel *et al.* (1994) *Current Protocols in Molecular Biology, Current Protocols*, USA; and in Volumes I and II of Brown (1998) *Molecular Biology LabFax*, Second Edition, Academic Press (UK); *Oligonucleotide Synthesis* (N. Gait editor); *Nucleic Acid Hybridization* (Hames and Higgins, eds.).

**Example 1.**

Induction of *Staphylococcus aureus* persisters by low pH, awakening by phagolysosomal alkalinization and effective treatment by phagolysosomal alkalinization combined with a bactericidal agent.

1.1 pH-dependent induction of *S. aureus* Small Colony Variants (SCVs)

The well-defined MSSA strains 6850 and Cowan and MRSA strain JE2 were grown in 4.0, 5.5, 6.5 and 7.4 pH media, mimicking the pH found in physiologic sites such as lysosomes, abscesses and blood. Directly after inoculation *S. aureus* showed a large colony phenotype, independent of the pH. The frequency of SCVs significantly increased over time in pH 4.0 growth medium and reached 39% (JE2 and 6850) and 28% (Cowan) after five days. In contrast pH 7.4 growth medium sustained SCVs below 2% in all strains tested (Fig. 1a - c). An intermediate percentage of SCVs was found at pH 5.5 and 6.5. Thus, we showed a clear correlation between low pH and SCV formation. This method permitted easy and controlled formation of unstable, non-genetically modified SCVs in various *S. aureus* strains.

1.2 Induction of non-replicating *S. aureus* by low pH

The pH-dependent growth of *S. aureus* Cowan was followed over time by labeling the bacterial cell wall with fluorescent cell wall binding domains (CBDs). Immediately after staining, bacterial cell walls were fully labeled. After three days in pH 4.0 growth medium, the majority of bacteria still exhibited fluorescent cell walls, consistent with absent bacterial replication. In contrast, bacteria grown at pH 7.4 proliferated extensively, demonstrated by highly fragmented and89 reduced fluorescent cell wall labeling . Scanning electron microscopy (SEM) of bacteria originating from a small colony, obtained under low-pH conditions, showed impaired cell division resulting in rod-shaped *S. aureus*, in contrast to large colony bacteria showing normal cell division.

1.3 Growth resumption of low pH-adapted *S. aureus* persisters

Our findings indicated that both, SCVs and non-replicating persisters, are induced by low pH. In clinics, the presence of these persisting bacteria correlates with increased recurrence of infection which implies that bacteria revert to a highly virulent and fast-growing form 14. We therefore tested *in vitro* whether low pH-induced SCVs and/or non-replicating persisters can restore normal growth in neutral pH. Non-replicating *S. aureus* persisters were induced and kept at pH 4.0 for three days and then transferred to pH 4.0, 5.5, 6.5 or 7.4 growth media. Bacteria in pH 7.4 and 6.5 resumed growth after approximately 12 hours (Fig. 1d - f) whereas bacteria kept at low pHs (< 6.5) remained in a nonproliferating state (Fig. 1d - f). These data suggest that both persisting phenotypes

were reversible adaptions to low pH as supported by the capability of regrowth upon neutralization of pH.

1.4 Intracellular induction of *S. aureus* SCVs

We investigated whether internalized *S. aureus* exhibited a SCV phenotype. MSSA strain Cowan is highly invasive, but not cytotoxic which allowed maintaining this strain intracellularly over several days in the lung epithelial cell line A549. Extracellular bacteria were killed by adding a high dose of flucloxacillin to the infected host cells. Flucloxacillin is typically used to treat *S. aureus* endocarditis in patients. Absence of extracellular bacteria was confirmed by sterility of culture supernatants. Host cells were lysed to release intracellular bacteria and colony counts, as well as colony phenotypes, were determined at various time points. Five hours after infection, 0.2% of all viable intracellular bacteria had a SCV phenotype (Fig. 2a - b). The number of viable intracellular persisting bacteria decreased during the course of infection while the frequency of SCVs increased and reached 5.6% after seven days.

1.5 Phagolysosomal localization of persisting *S. aureus*

Our data indicated that acidity favored SCV formation, suggesting that the acidic phagolysosomal milieu may have the same effect. A549 cells were infected with *S. aureus* Cowan. Intracellular bacteria were localized within LAMP-2 antibody positive vesicles, visualized by fluorescence microscopy. LAMP-2 (CD 107b) is highly expressed in phagolysosomes, suggesting that intracellular persisting *S. aureus* predominantly resided within phagolysosomes.

1.6 Reduction of *S. aureus* SCVs through phagolysosomal alkalinization

Since low pH induced SCVs and/or non-replicating *S. aureus* and medium pH neutralization resulted in bacterial regrowth, we treated infected host cells with lysosomotropic alkalinizing agents. Chloroquine, bafilomycin A1 or ammonium chloride all neutralized the phagolysosomal pH. Host cells treated with lysosomotropic alkalinizing agents exhibited significantly lower percentages of SCVs seven days after infection (Fig. 3). No differences in total colony counts between control and treated cells were observed. Lysosomotropic alkalinizing agents did not inhibit bacterial growth at the

concentrations used. No significant differences in host cell viability were observed after treatment with the alkalinizing agents.

1.7 Growth resumption of intra-phagolysosomal persisting *S. aureus* by chloroquine treatment resulting in reduction of SCV percentages in cells and in mice

Growth resumption of *S. aureus* persisters through treatment of host cells with chloroquine was assessed. Fluorescence microscopy revealed that *S. aureus* localized within phagolysosomes in both, control and chloroquine-treated host cells, three days post-infection. We observed no dividing bacteria in infected host cells without chloroquine treatment. However, chloroquine facilitated bacterial cell division as assessed by transmission electron microscopy (TEM).

Mice infected with *S. aureus* Cowan were treated with flucloxacillin alone (control), or in combination with chloroquine (Figure 5a). Chloroquine treatment significantly reduced the frequency of SCVs in mice in various organs (Fig. 5b) and compartments (Fig. 5c). Absolute bacterial numbers were comparable, independent of chloroquine treatment

1.8 Discussion

This study showed that low pH, as found in abscesses and within lysosomes, induced the persisting *S. aureus* subpopulations SCVs and non-replicating persisters. Raising pH in the culture medium or within the phagolysosomes using alkalinizing agents reverted *S. aureus* to normal growth. SCV formation was shown to be triggerd by antibiotic pressure. In addition, extreme environmental stresses such as prolonged exposure to low temperature, very acidic or alkaline environments, or osmotic stress may trigger SCV and/or persister formation in *S. aureus* and coagulase-negative staphylococci. These observations, together with our new findings, show how multiple stimuli lead to *S. aureus* persister formation. Localization within the host cell shields *S. aureus* from commonly used antibiotics such as the extracellularly active beta-lactams with poor cell penetration In addition, the low intraphagolysosomal pH renders antibiotics with intracellular activity such as clindamycin and fluoroquinolones less active. We found that the addition of lysosomotropic alkalinizing agents to the usually prescribed antibiotics such as flucloxacillin reduced the frequency of *S. aureus* SCVs *in vitro* as well as *in vivo*. We thus identified a simple strategy to circumvent the host dependent component of S.aureus

persister formation. In clinical settings, the presence of SCVs in osteomyelitis and device-related infections has been associated with increased relapse rates, despite administration of antibiotics. Bacteria adapt to antibiotic stress by SCV and/or persister formation. We now showed that *S. aureus* SCVs and non-replicating persisters retained the ability to revert to a highly virulent and fast-growing form. The capacity to revert to fast growth (phenotype switching) results in relapsing infection. In addition, it renders identification of SCVs difficult. Further aggravating the SCV problem in clinics is underestimation of SCVs in clinical microbiology laboratories, since they form tiny and thus difficult to detect colonies which are easily overgrown by their fast growing counterparts . We postulate that the addition of alkalinizing agents to the usually prescribed antibiotics will reduce the frequency of SCVs and could therefore reduce recurrence rates in the future.. Persisting bacteria are not unique to *S. aureus* but have also been described to occur in various other human pathogens, such as Salmonella spp., *Pseudomonas aeruginosa*, *Escherichia coli* and *Mycobacterium tuberculosis*. In addition to low pH, bacterial persisters can arise due to mechanisms that include the toxin-antitoxin systems. Accordingly, activation of a SOS response (ppGpp) in response to DNA damage due to oxidative stress results in decreased ATP levels. This leads to the shutdown of metabolism resulting in reduced growth. Various toxin-antitoxin modules are activated by acidification and/or nutrient starvation in Salmonella, causing formation of persisters. In accordance with our findings, Salmonella persister formation has been reported in macrophages triggered by the acidic and nutritionally poor environment of the Salmonella-containing vacuole that was reversible by addition of bafilomycin A1 44. In contrast to bafilomycin A1, chloroquine is routinely used in patients to treat malaria as well as some rheumatic diseases. Phagolysosomal pH neutralization with chloroquine may therefore provide a novel therapeutic eradication strategy against intracellular persisting staphylococcal reservoirs.

**Example 2.**

Effective treatment of *Staphylococcus aureus* persisters by phagolysosomal alkalinization combined with a bactericidal agent comprising a protein transduction domain.

The bactericidal agents according to the invention with a protein transduction domain for efficient delivery into the infected host cell with a sequence selected from the group

consisting of SEQ ID NO: 30 – 47 are used for combination with phagolysosomal pH neutralization for treatment of intracellular *S. aureus* infection *in vitro* and *in vivo*. The treatment results in effective treatment of the intracellular *S. aureus* infection, with some variety in the efficiency depending on the specific bactericidal agent according to the invention used.

**Example 3.**

Effective treatment of intracellular infection with *Staphylococcus aureus*.

The bactericidal agents according to the invention with a protein transduction domain for efficient delivery into the infected host cell with a sequence selected from the group consisting of SEQ ID NO: 27 – 47 were used for treatment of intracellular *S. aureus* infection, either combined or not with phagolysosomal pH neutralization.

Method intracellular *S. aureus* killing assay.

*S. aureus* was grown in LB broth at 37 °C, shaking at 220 rpm, overnight. The overnight culture was diluted in fresh LB (1:10) and grown further for 2 h. Then, the bacteria were centrifuged, the pellet was washed with PBS and the culture was re-suspended in PBS with the OD600 adjusted to 0.4 (c.a. $2\times10^8$ CFU/mL). Bacterial cells were sonicated prior to infection (SONOPULS HD 2070) for 1 minute with 1 second pulses at 40% of the power. MG-63 osteosarcoma cells were grown in 12-well dishes with the amount of $5\times10^5$ cells/well in 1 mL EMEM culture media with 10 % fetal bovine serum (FBS) for 24 h prior infection. Then, the cells were infected with *S. aureus* Newman and Cowan at the following conditions: (A) *S. aureus* Newman at MOI of 0.1 for 3 h, (B) *S. aureus* Newman at MOI of 1.0 for 24 h, and (C) *S. aureus* Cowan at MOI of 1.0 for 72 h. The plates were centrifuged at 1200 rpm for 5 min and incubated at 37 °C with the flush of CO2. After invasion, eukaryotic cells were washed 3× with PBS to remove remaining extracellular *S. aureus* and exposed to floxacillin (1 mg/mL) for 2 h to kill any left non-internalized bacteria. For each experiment (A, B, and C) one part of the samples was exposed to chloroquine treatment (20 μM) to increase lysosomal pH and evaluate its effect on further treatment with endolysins. The supernatant from the antibiotic-treated cells was plated to check for floxacillin treatment efficiency. Then, the eukaryotic cells were again washed with PBS (3×) to remove dead bacteria and subjected to endolysin treatment. The composition of applied endolysin preparations is summarized in Table 2.

Eukaryotic cells were treated with 1 mL of 1 μM endolysin preparation (diluted in EMEM supplemented with 1 mg/mL floxacillin and +/- 20 μM chloroquine) for (A) 1h and 4h, (B and C) 4h. The control was treated with 1 mL of 1 mg/mL floxacillin, +/- 20 μM chloroquine in EMEM. The cultures were then washed 3× with PBS and examined under microscope to determine if there had been osteoblast cell lysis. Next, they were trypsinized (Trypsin-EDTA 0.25%, Gibco®) and lysed with 800 μL 0.1 % Triton X-100. The cell lysate was subjected to serial dilution plating on LB and overnight incubation at 37 °C.

Table 2 Composition of the endolysin mixtures used for intracellular eradication of *S. aureus*.

| **Components of the endolysin mixture** | **Ratio** | **Concentration of each component** |
|---|---|---|
| CHAP-CBD + M23-CBD | 1:1 | 500nM:500nM |
| CHAP-CBD-TAT + M23-CBD-TAT | 1:1 | 500nM:500nM |
| CHAP-CBD-R9 + M23-CBD-R9 | 1:1 | 500nM:500nM |
| CHAP-CBD-Penetratin + M23-CBD-Penetratin | 1:1 | 500nM:500nM |
| CHAP-TAT + M23-TAT + Ami-TAT | 1:1:1 | 333nM:333nM:333nM |
| CHAP-R9 + M23-R9 + Ami-R9 | 1:1:1 | 333nM:333nM:333nM |
| CHAP-Penetratin + M23-Penetratin + Ami-Penetratin | 1:1:1 | 333nM:333nM:333nM |

Results

Successful expression and purification of all protein constructs was achieved. The summary of all expressed endolysin constructs with the corresponding molecular weights and concentrations is shown in Table 3. Relatively high concentrations were obtained for most of the endolysin constructs, implying that a correct protein expression and purification strategy was used.

Table 3 Summary of all expressed endolysin constructs with the corresponding molecular weight and concentration

| **SEQ ID NO:** | **Protein** | **Mol. Weight (KDa)** | **Concentration (mg/ml)** | **Concentration (μM)** |
|---|---|---|---|---|
| 27 | M23-CBD | 29.973 | 3.82 | 127.4 |
| 28 | CHAP-CBD | 33.088 | 2.36 | 71.33 |

| | | | | |
|---|---|---|---|---|
| 29 | Ami-CBD | 35.385 | 3.30 | 93.26 |
| 44 | M23-CBD-TAT | 31.916 | 1.13 | 34.30 |
| 38 | CHAP-CBD-TAT | 35.031 | 1.85 | 52.81 |
| 32 | Ami-CBD-TAT | 37.328 | 0.40 | 10.71 |
| 43 | M23-CBD-R9 | 31.620 | 0.45 | 14.23 |
| 37 | CHAP-CBD-R9 | 34.736 | 1.05 | 30.20 |
| 31 | Ami-CBD-R9 | 37.033 | 0.30 | 8.10 |
| 42 | M23-CBD-Penetratin | 32.444 | 0.56 | 17.26 |
| 36 | CHAP-CBD-Penetratin | 35.559 | 2.03 | 57.08 |
| 30 | Ami-CBD-Penetratin | 37.856 | 0.41 | 10.82 |
| 47 | M23-TAT | 17.485 | 1.26 | 72.00 |
| 41 | CHAP-TAT | 20.600 | 1.44 | 69.90 |
| 35 | Ami-TAT | 22.897 | 0.83 | 36.25 |
| 46 | M23-R9 | 17.189 | 2.51 | 146.00 |
| 40 | CHAP-R9 | 20.305 | 0.83 | 40.88 |
| 34 | Ami-R9 | 22.601 | 0.76 | 33.63 |
| 45 | M23-Penetratin | 18.012 | 0.80 | 44.41 |
| 39 | CHAP-Penetratin | 21.128 | 0.73 | 34.55 |
| 33 | Ami-Penetratin | 23.424 | 0.96 | 41.00 |

All expressed endolysins were effective in killing *S. aureus* Cowan in plate assay and in time-killing assay.

Intracellular *S. aureus* killing assay

The mixtures of endolysin constructs as listed in Table 2 were further tested for their bacterial killing efficacy in cell tissue cultures.

In our model MG-63 osteosarcoma cells were used to mimic the condition of osteomyelitis. Cells were first infected for a certain time with the pathogen S. aureus Newman or Cowan and then treated with the endolysin mixture in presence or absence of chloroquine. We expected that increasing intracellular pH by application of chloroquine would create more favorable conditions for endolysin activity.

Osteosarcoma cells were exposed to *S. aureus* Newman and Cowan for 3 h followed by 2 h floxacillin treatment to inactivate any non-internalized bacteria. Then, the tissue cells were treated for 1 h and 4 h with 1 μM of endolysin mixture with and without

chloroquine. The results are shown in Figure 5. Figure 5A shows the result of treatment of *S. aureus* Newman by endolysin mixtures exclusively and Figure 5B shows the result of a combination treatment with chloroquine. Clearly, 4h treatment was more effective in both experimental settings. Moreover, endolysin treatment in the presence of chloroquine resulted in greater decrease in bacterial counts. Interestingly, mixture of the CPP-free endolysins showed a very good killing efficacy, which was not expected. It is, however, possible that the vast amount of positive charge associated with CBD attracts the enzyme to the negatively charged cell membrane and induces its intracellular translocation. Such a putative mechanism for CPP-free endolysin translocation is the key of the translocation of CPPs. All endolysin mixtures displayed similar killing properties in this assay, even though their activity differed substantially depending on the presence of CBD and type of CPP tag. It is likely that different constructs have different penetrating properties, depending on the CPP, EAD and CBD presence. For instance, EAD-CBD mixture has very high activity but might not be transported via the cell membrane as efficient as any CPP-containing variants. Whereas, EAD-CPP constructs do not have as high activity but are smaller and contain the transduction domain, which make their intracellular transport more efficient and their diffusivity better due to the lack of immobilization of the enzyme on the cell surface mediated by CBD binding. As a result, enzymes with different properties might have given similar results eventually.

Figure 5C and Figure 5D show the results of the same experiment performed with a different strain of the pathogen: S. aureus Cowan. In this case, the treatment did not seem to be effective. For both samples, without chloroquine (Figure 5C) and with chloroquine (Figure 5D), the decrease in the viable counts is negligible. Only treatment with the mixture of CHAP-CBD-R9 + M23-CBD-R9 in presence of chloroquine resulted in a significant eradication of the pathogen. It is known that *S. aureus* Cowan resides intracellularly in the lysosomes. It is very likely that intracellular localization of *S. aureus* Newman is different – it may just reside in the cytoplasm, hence the results of the two experiments are different. Moreover, the intracellular fate of CPP-tagged endolysin constructs is unknown at this point, therefore one may only speculate that endolysin constructs fused with the R9 tag are the only ones that accumulate in the lysosomes, hence they showed good killing properties against *S. aureus* Cowan.

To simulate a real-life infection osteosarcoma tissue cells were infected with *S. aureus* for 24 h and 72 h before the treatment. Such a long infection time allowed the bacteria to

settle intracellularly in their final destinations. Again, the cells were treated with the mixtures of endolysin constructs in presence and in absence of chloroquine. Figure 6A and Figure 6B show the results of the treatment of osteosarcoma cells infected for 24 h with *S. aureus* Newman in absence and in presence of chloroquine, respectively. Figure 6C and Figure 6D correspond to the results of treated cells infected for 72 h with *S. aureus* Cowan. In both cases treatment with endolysin mixtures seems effective, especially with the addition of chloroquine. The best result was obtained for the treatment of *S. aureus* Newman with EAD-CBD-R9 mixture in the presence of chloroquine, where ca. 60 % of the pathogen was eradicated (Figure 6B). Equally good results were achieved for *S. aureus* Cowan treated with the mixtures of EAD-CBD, EAD-CBD-TAT, EAD-CBD-R9 and EAD-CBD-Penetratin, where around 50 % of the pathogen was killed. In general, CBD-containing endolysin constructs displayed better killing efficacy, including EAD-CBD mixture, not fused with the transduction domain.

Altogether it was demonstrated that treatment of intracellular *S. aureus* by engineered endolysins together with chloroquine was more effective that without chloroquine. Application of such alkalizing agents likely enhances the activity of lytic enzymes intracellularly and the combinatorial treatment of endolysins with chloroquine could be a good alternative to conventional antibiotic therapy.

In conclusion, this study showed the potential of CPP-fused endolysins in treatment of intracellular and extracellular *S. aureus*. Such a method of therapy could be used to treat patients with conditions like e.g. osteomyelitis, endocarditis, bacteremia or sepsis, as well as bovine mastitis in dairy cattle.

**Example 4.**

Several bactericidal agents according to the invention comprising a functional enzymatic domain from a cell wall lytic enzyme and further comprising a protein transduction domain on the N-terminal side of the molecule were prepared and analyzed according to methods as described elsewhere herein (R9-CHAP-CBD, R9-M23-CBD, TAT-Ami-CBD, TAT-CHAP-CBD, and TAT-M23-CBD). All data were collected in turbidity reduction assays on *S. aureus* SA113 substrate cells and at 100nM protein concentrations (except Ami-CBD constructs where 1 μM was used) according as described previously in WO2013/169104. Figure 7 depicts the performance of the constructs. As can be observed from Figure 7, in general, the N-terminal CPP tagged proteins are active, but

perform less compared to un-tagged or C-terminal tagged variants when analyzed on *S. aureus* cells. To analyze the efficiency of intracellular killing, the constructs should be tested in an intracellular *S. aureus* killing assay as in example 3.

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The discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises", is not intended to exclude other additives, components, integers or steps.

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**THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS**

1. A method of treatment of a bacterial infection in a subject in need thereof, comprising:

- administration of an effective amount of an agent that increases the intracellular pH of a host cell and/or of an intracellular compartment of a host cell, wherein the agent is an alkalinizing agent; and
- administration of an effective amount of a bactericidal agent, wherein the bactericidal agent is a bacterial lysin or autolysin, or a bacteriophage lysin.

2. The method of treatment according to claim 1, wherein the bacterial infection is an intracellular and/or persistent bacterial infection and/or is a *Staphylococcus* infection, including an *S. aureus* infection.

3. The method of treatment according to claim 1 or claim 2, wherein the host cell is a eukaryotic host cell within the subject in need of treatment and/or wherein the intracellular compartment is a phagolysosome.

4. The method of treatment according to any one of claims 1 to 3, wherein the agent that increases the intracellular pH and/or the pH of the intracellular compartment is a lysosomotropic alkalizing agent, including chloroquine, bafilomycin A1, and ammonium chloride.

5. The method of treatment according to any one of claims 1 to 4, wherein the bactericidal agent further comprises a protein transduction domain.

6. The method of treatment according to claim 5, wherein the bactericidal agent further comprises an antimicrobial peptide.

7. The method of treatment according to claim 5 or claim 6, wherein the bactericidal agent further comprises a cell wall binding domain.

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8. The method of treatment according to any one of claims 5 to 7, wherein the protein transduction domain is selected from the group consisting of SEQ ID NO: 12 - 25, or a functional variant thereof.

9. The method of treatment according to any one of claims 6 to 8, wherein the antimicrobial peptide is selected from the group consisting of SEQ ID NO: 70 - 90, or a functional variant thereof.

10. The method of treatment according to any one claims 1 to 9, wherein the bactericidal agent has at least 40% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 27 – 47, or is a bactericidal agent encoded by polynucleotide sequence with at least 40% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 50 – 67.

11. Use of an effective amount of:

- an agent that increases the intracellular pH of a host cell and/or of an intracellular compartment of a host cell wherein said agent is an alkalinizing agent; and
- an effective amount of a bactericidal agent, wherein said bactericidal agent is a bacterial lysin or autolysin, or a bacteriophage lysin,

for the preparation of a medicament for the treatment of a bacterial infection in a subject in need thereof.

12. The use according to claim 11, wherein the bacterial infection is an intracellular or persistent bacterial infection and is a *Staphylococcus* infection.

13. The use according to claim 12, wherein the *Staphylococcus* infection is a *Staphylococcus aureus* infection.

14. The use according to any one of claims 11 to 13, wherein the host cell is a eukaryotic host cell within the subject in need of treatment and the intracellular compartment is a phagolysosome.

15. The use according to any one of claims 11 to 14, wherein the alkalinizing agent is selected from the group of chloroquine, bafilomycin A1, and ammonium chloride.

16. The use according to any one of claims 11 to 15, wherein the bactericidal agent further comprises a protein transduction domain.

17. The use according to claim 16, wherein the bactericidal agent further comprises an antimicrobial peptide.

18. The use according to claim 16 or claim 17, wherein the protein transduction domain is selected from the group consisting of SEQ ID NO: 12 - 25.

19. The use according to claim 17, wherein the antimicrobial peptide is selected from the group consisting of SEQ ID NO: 70 - 90.

20. The use according to any one of claims 11 to 19, wherein the bactericidal agent comprises a chimeric bactericidal polypeptide having at least 40% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 27 – 47, or wherein the bactericidal agent is encoded by a polynucleotide sequence with at least 40% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 50 – 67.

Fig. 1a

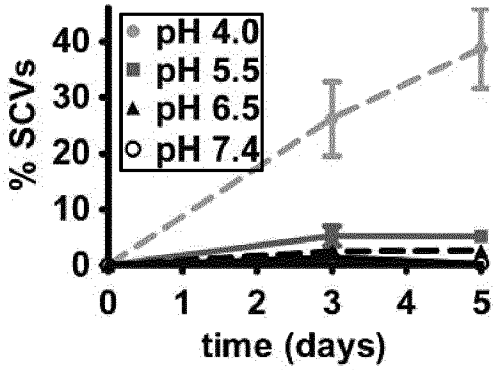



Fig. 1b

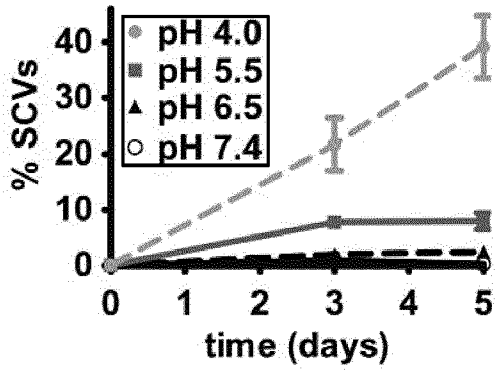



Fig. 1c

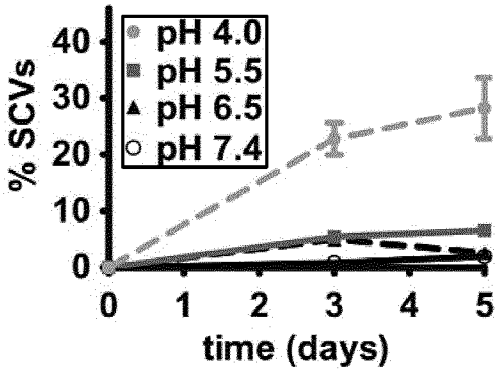


Fig. 1d

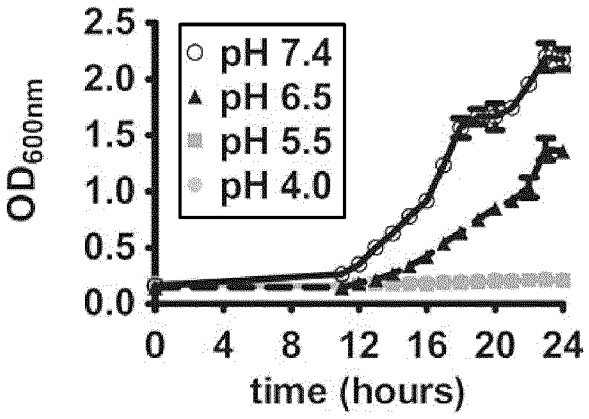



Fig. 1e

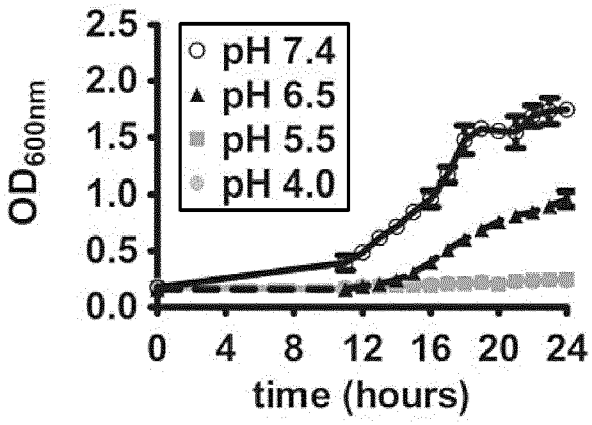
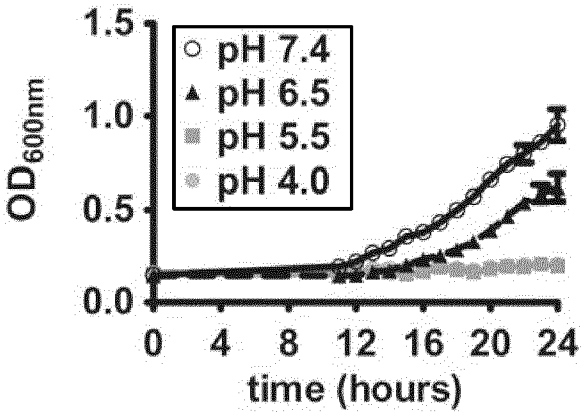



Fig. 1f



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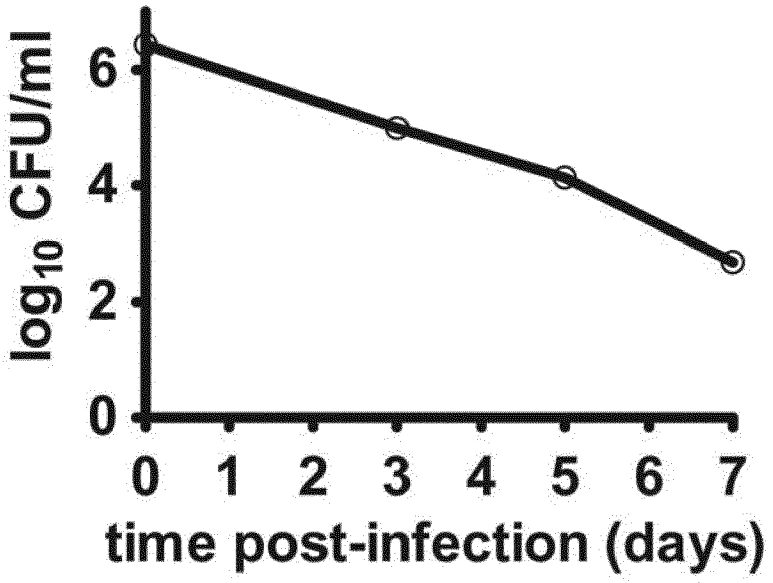

log10 CFU/ml
0
2
4
6
0 1 2 3 4 5 6 7
time post-infection (days)

Fig. 2b

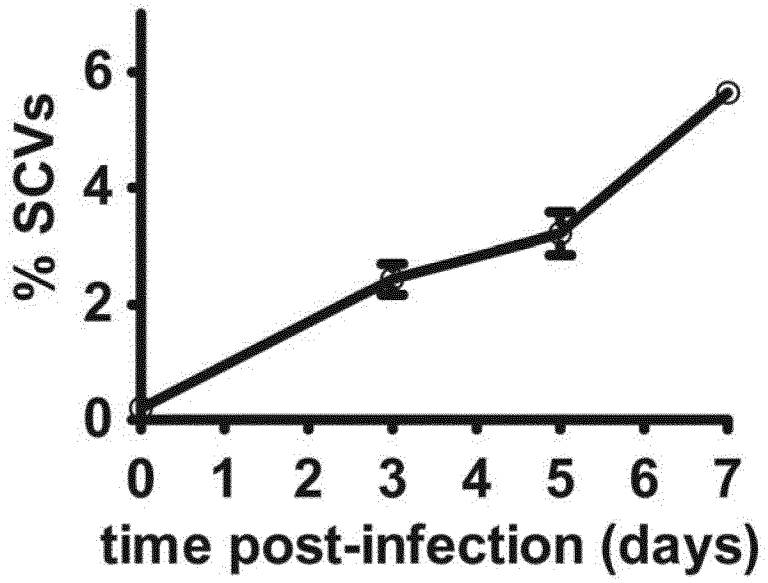

% SCVs
0
2
4
6
0 1 2 3 4 5 6 7
time post-infection (days)

Fig. 3a

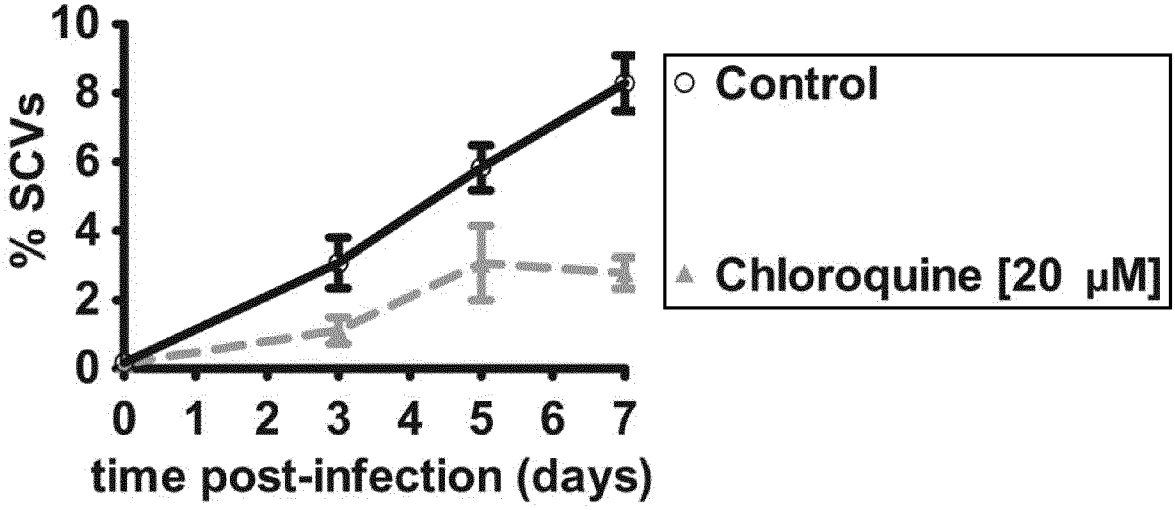



Fig. 3b

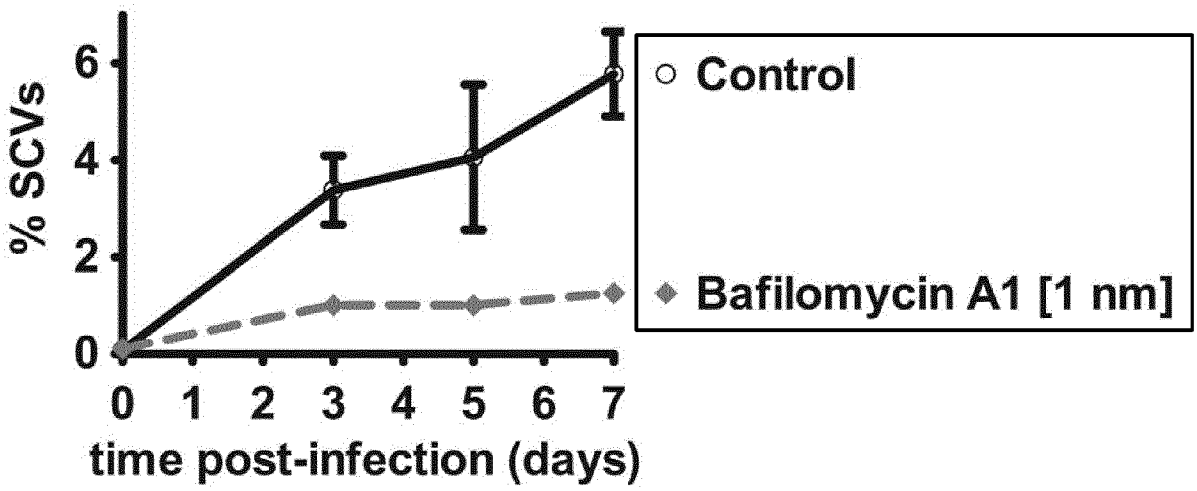



Fig. 3c

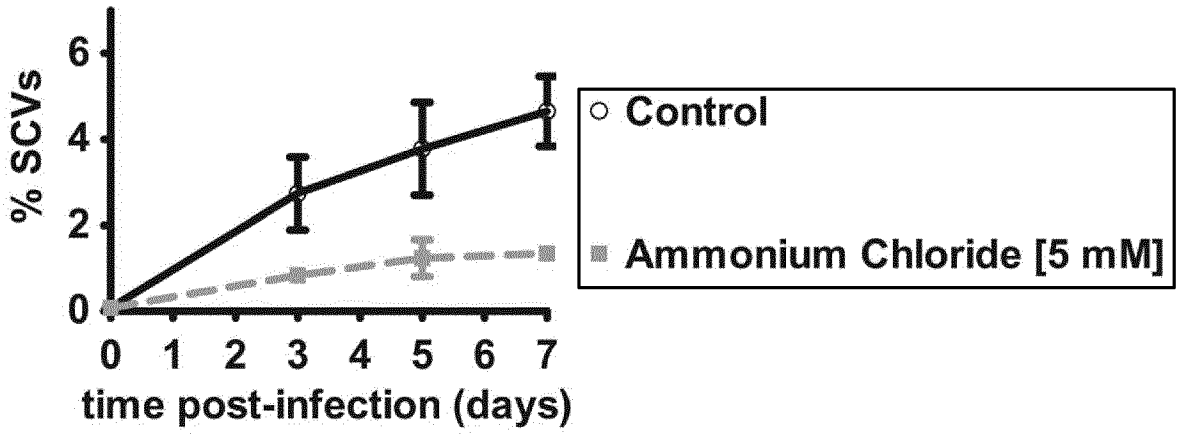


Fig. 4a

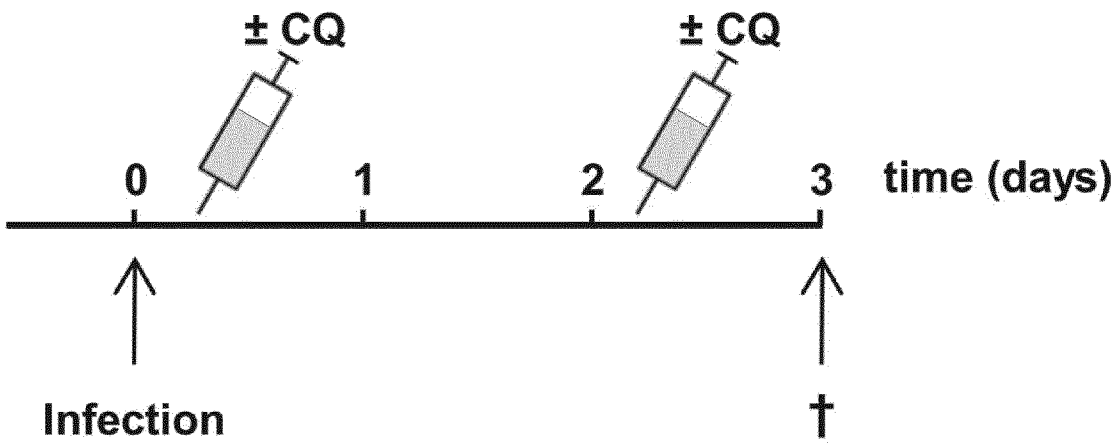

± CQ
± CQ
0
1
2
3
time (days)
Infection
†

Fig. 4b

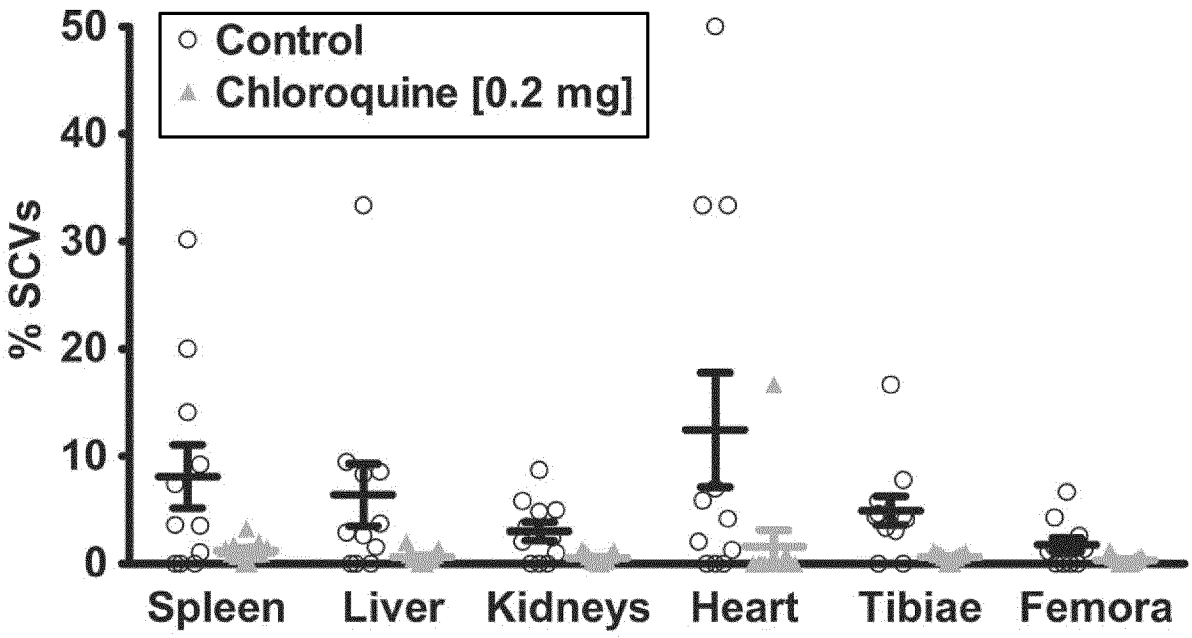
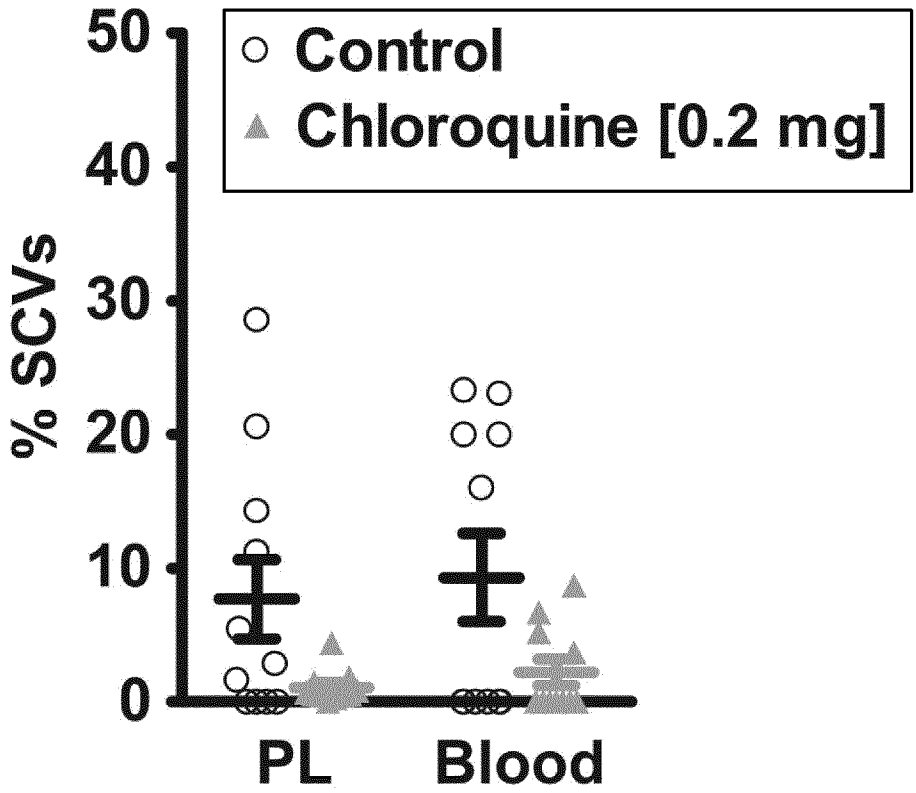

Control
Chloroquine [0.2 mg]
% SCVs
50
40
30
20
10
0
Spleen
Liver
Kidneys
Heart
Tibiae
Femora

Fig. 4c



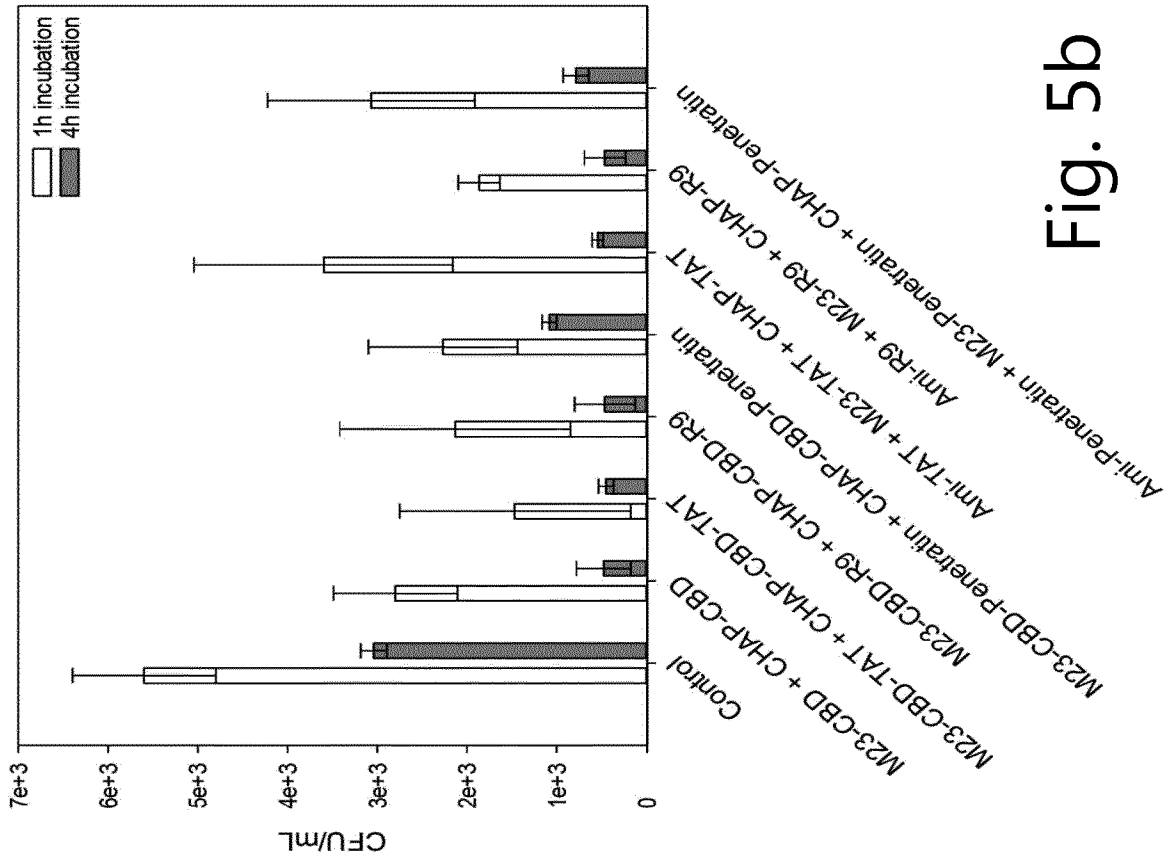

1h incubation
4h incubation
CFU/mL
7e+3
6e+3
5e+3
4e+3
3e+3
2e+3
1e+3
0
Control
M23-CBD + CHAP-CBD
M23-CBD-TAT + CHAP-CBD-TAT
M23-CBD-R9 + CHAP-CBD-R9
M23-CBD-Penetratin + CHAP-CBD-Penetratin
Ami-TAT + M23-TAT + CHAP-TAT
Ami-R9 + M23-R9 + CHAP-R9
Ami-Penetratin + M23-Penetratin + CHAP-Penetratin

Fig. 5b

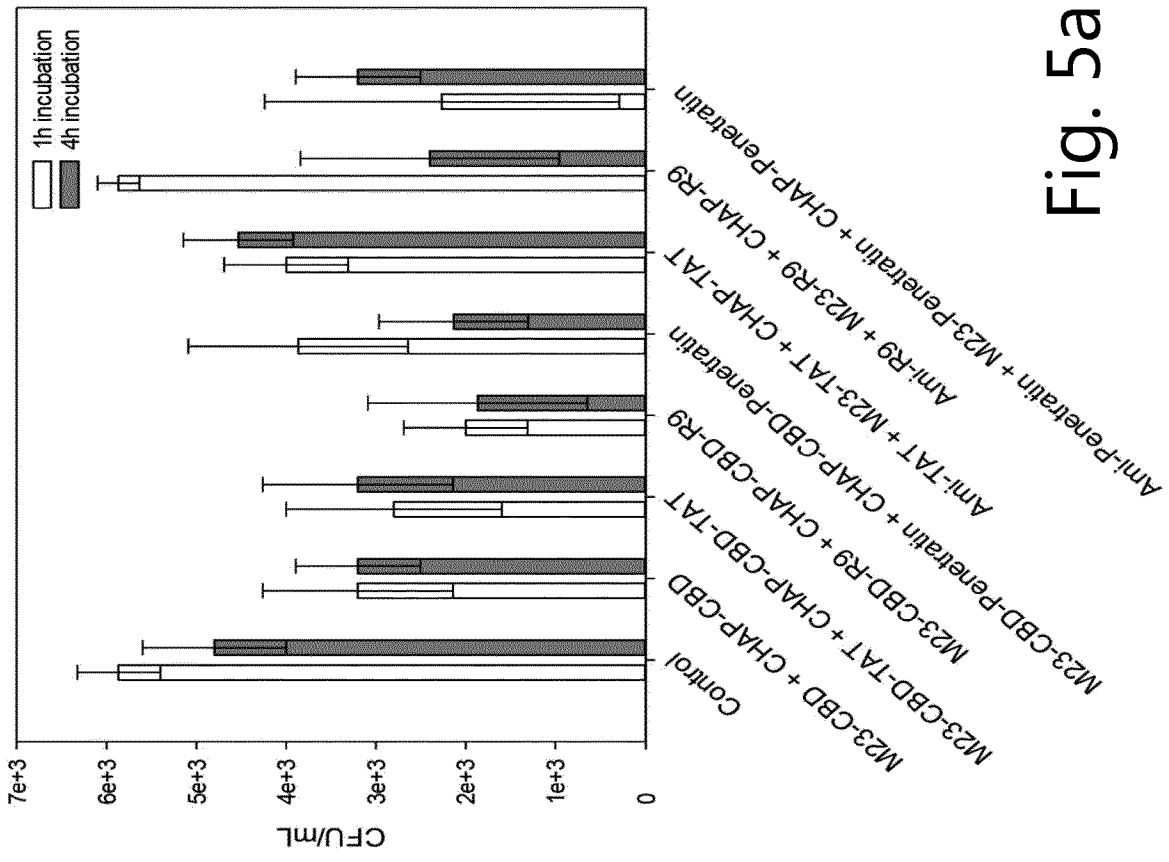

1h incubation
4h incubation
CFU/mL
7e+3
6e+3
5e+3
4e+3
3e+3
2e+3
1e+3
0
Control
M23-CBD + CHAP-CBD
M23-CBD-TAT + CHAP-CBD-TAT
M23-CBD-R9 + CHAP-CBD-R9
M23-CBD-Penetratin + CHAP-CBD-Penetratin
Ami-TAT + M23-TAT + CHAP-TAT
Ami-R9 + M23-R9 + CHAP-R9
Ami-Penetratin + M23-Penetratin + CHAP-Penetratin

Fig. 5a

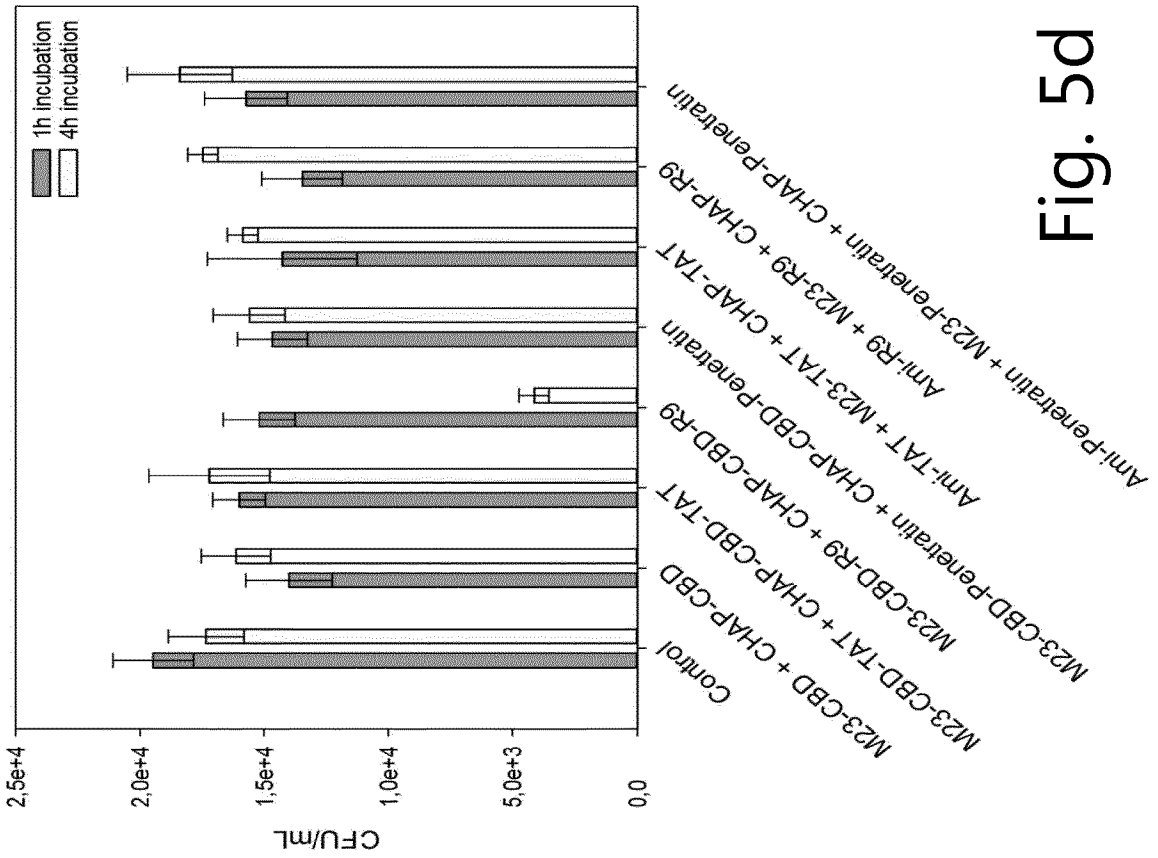

1h incubation
4h incubation
CFU/mL
2,5e+4
2,0e+4
1,5e+4
1,0e+4
5,0e+3
0,0
Control
M23-CBD + CHAP-CBD
M23-CBD-TAT + CHAP-CBD-TAT
M23-CBD-R9 + CHAP-CBD-R9
M23-CBD-Penetratin + CHAP-CBD-Penetratin
Ami-TAT + M23-TAT + CHAP-TAT
Ami-R9 + M23-R9 + CHAP-R9
Ami-Penetratin + M23-Penetratin + CHAP-Penetratin

Fig. 5d

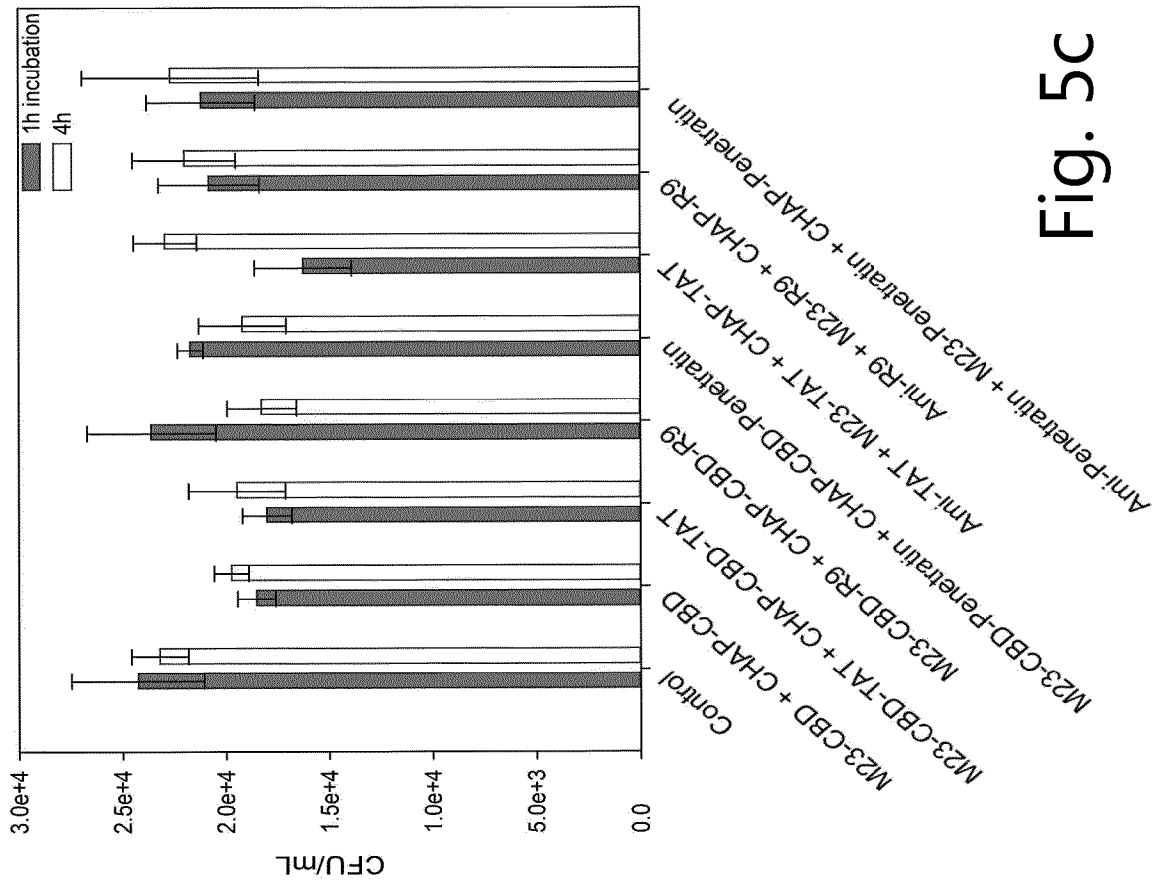

1h incubation
4h
CFU/mL
3.0e+4
2.5e+4
2.0e+4
1.5e+4
1.0e+4
5.0e+3
0.0
Control
M23-CBD + CHAP-CBD
M23-CBD-TAT + CHAP-CBD-TAT
M23-CBD-R9 + CHAP-CBD-R9
M23-CBD-Penetratin + CHAP-CBD-Penetratin
Ami-TAT + M23-TAT + CHAP-TAT
Ami-R9 + M23-R9 + CHAP-R9
Ami-Penetratin + M23-Penetratin + CHAP-Penetratin

Fig. 5c

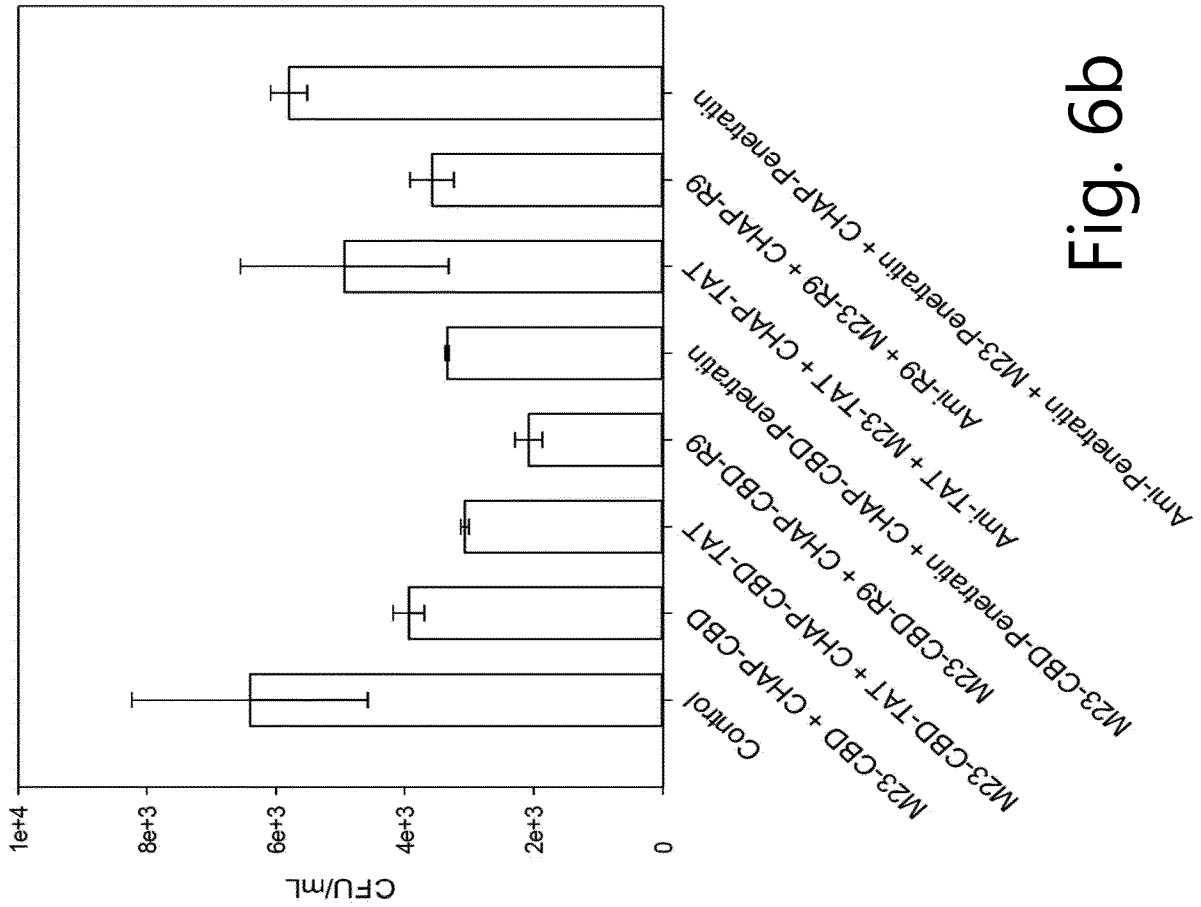

CFU/mL
0
2e+3
4e+3
6e+3
8e+3
1e+4
Control
M23-CBD + CHAP-CBD
M23-CBD-TAT + CHAP-CBD-TAT
M23-CBD-R9 + CHAP-CBD-R9
M23-CBD-Penetratin + CHAP-CBD-Penetratin
Ami-TAT + M23-TAT + CHAP-TAT
Ami-R9 + M23-R9 + CHAP-R9
Ami-Penetratin + M23-Penetratin + CHAP-Penetratin

Fig. 6b

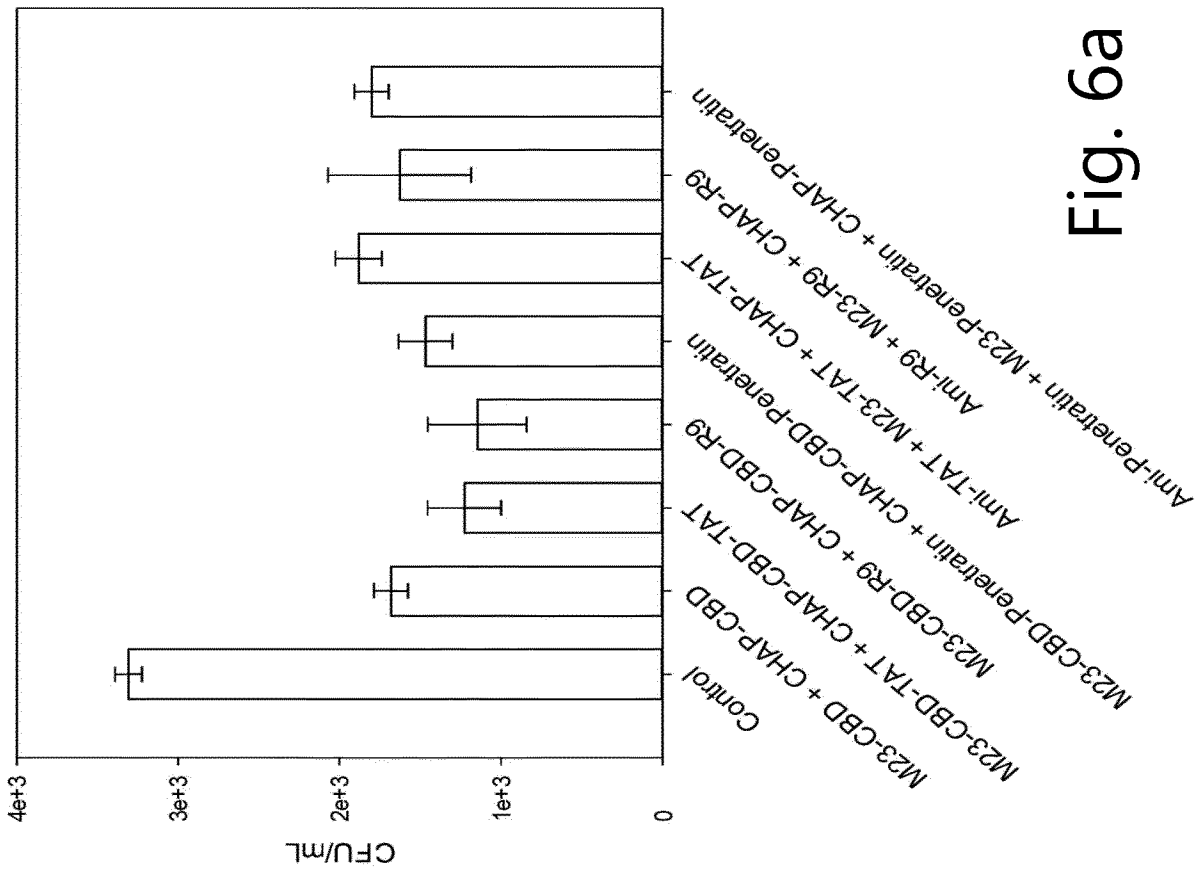

CFU/mL
0
1e+3
2e+3
3e+3
4e+3
Control
M23-CBD + CHAP-CBD
M23-CBD-TAT + CHAP-CBD-TAT
M23-CBD-R9 + CHAP-CBD-R9
M23-CBD-Penetratin + CHAP-CBD-Penetratin
Ami-TAT + M23-TAT + CHAP-TAT
Ami-R9 + M23-R9 + CHAP-R9
Ami-Penetratin + M23-Penetratin + CHAP-Penetratin

Fig. 6a

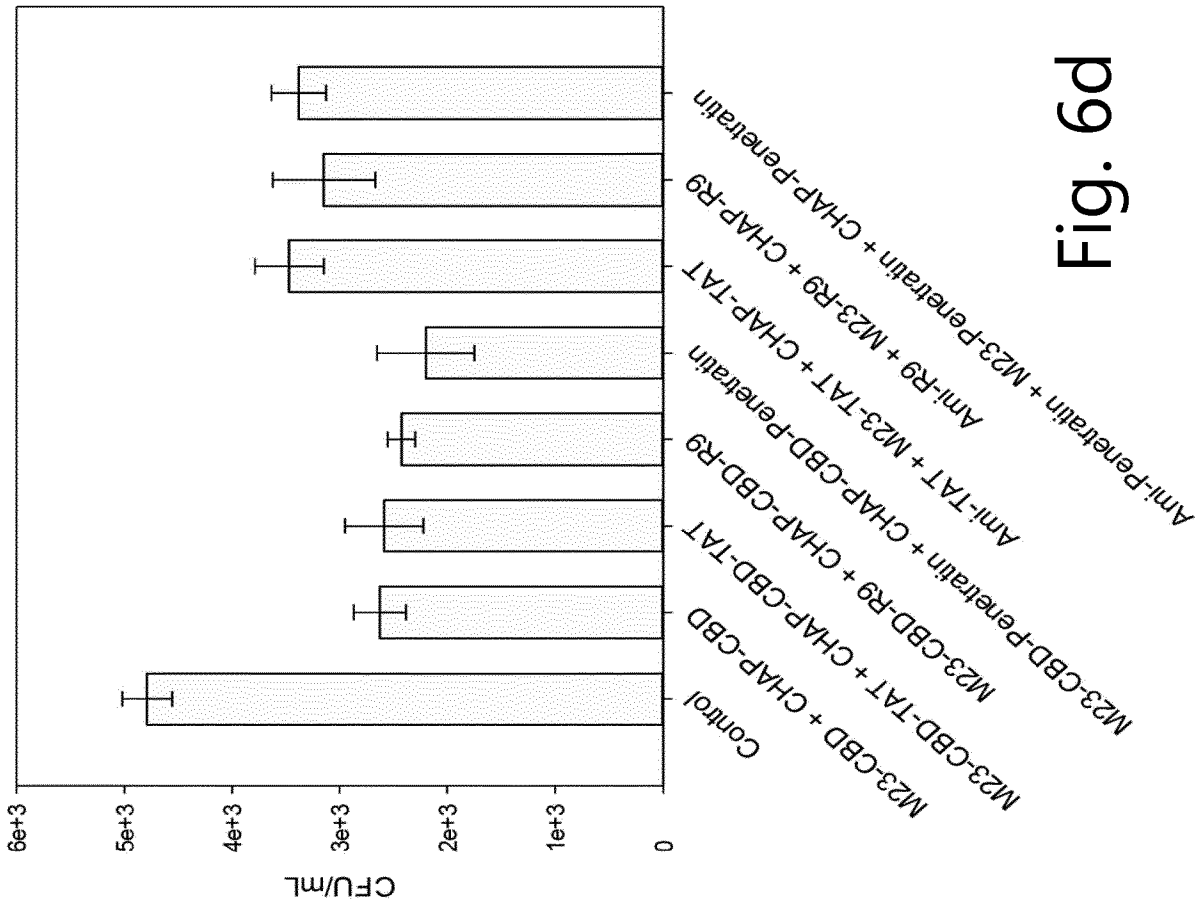
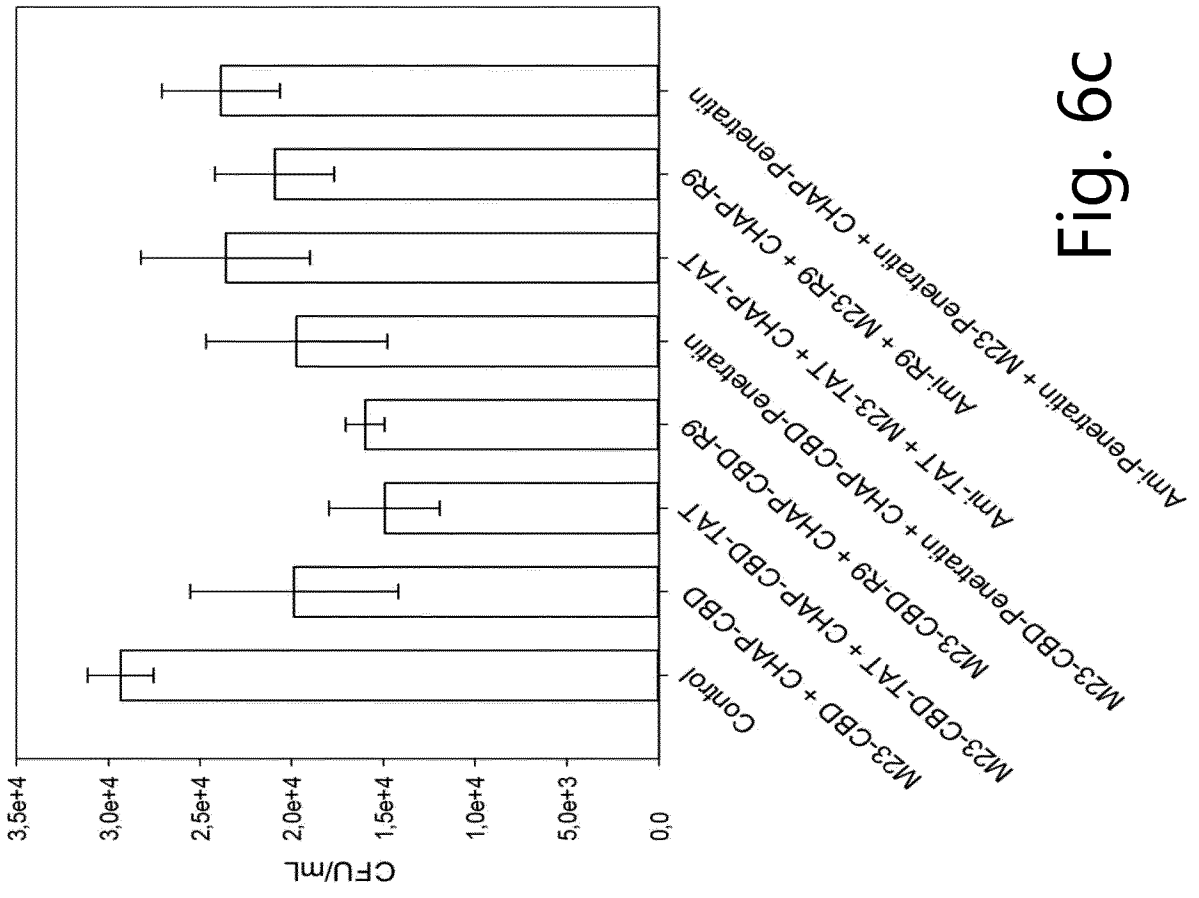

CFU/mL
6e+3
5e+3
4e+3
3e+3
2e+3
1e+3
0
Control
M23-CBD + CHAP-CBD
M23-CBD-TAT + CHAP-CBD-TAT
M23-CBD-R9 + CHAP-CBD-R9
M23-CBD-Penetratin + CHAP-CBD-Penetratin
Ami-TAT + M23-TAT + CHAP-TAT
Ami-R9 + M23-R9 + CHAP-R9
Ami-Penetratin + M23-Penetratin + CHAP-Penetratin

Fig. 6d


CFU/mL
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3,0e+4
2,5e+4
2,0e+4
1,5e+4
1,0e+4
5,0e+3
0,0
Control
M23-CBD + CHAP-CBD
M23-CBD-TAT + CHAP-CBD-TAT
M23-CBD-R9 + CHAP-CBD-R9
M23-CBD-Penetratin + CHAP-CBD-Penetratin
Ami-TAT + M23-TAT + CHAP-TAT
Ami-R9 + M23-R9 + CHAP-R9
Ami-Penetratin + M23-Penetratin + CHAP-Penetratin

Fig. 6c

Fig. 7a

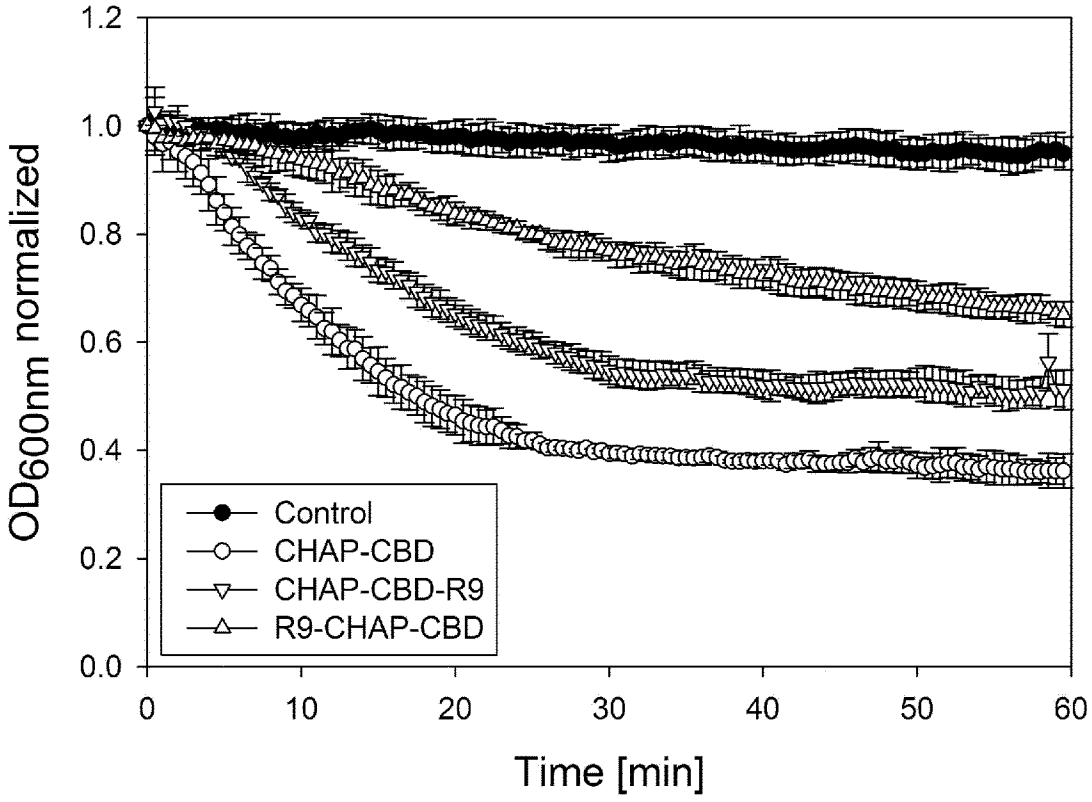

1.2
1.0
0.8
0.6
0.4
0.2
0.0
OD600nm normalized
0
10
20
30
40
50
60
Time [min]
Control
CHAP-CBD
CHAP-CBD-R9
R9-CHAP-CBD

Fig. 7b

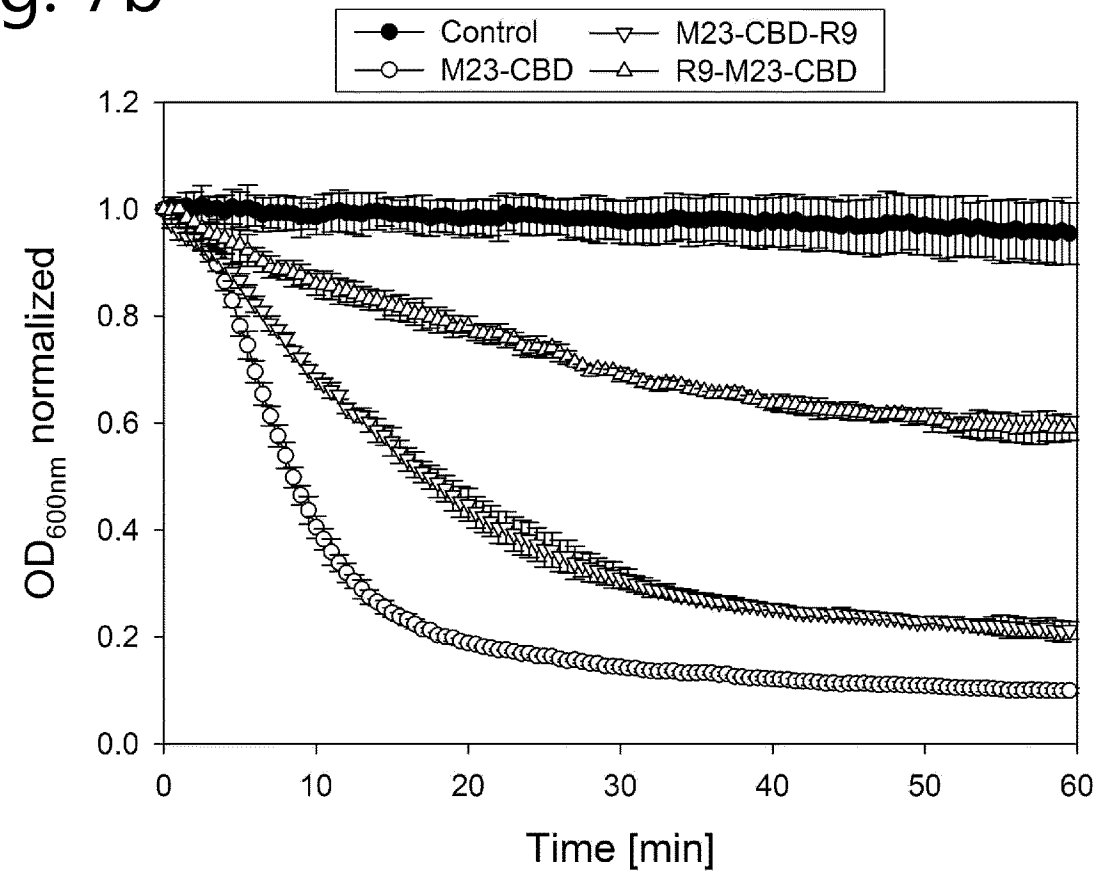
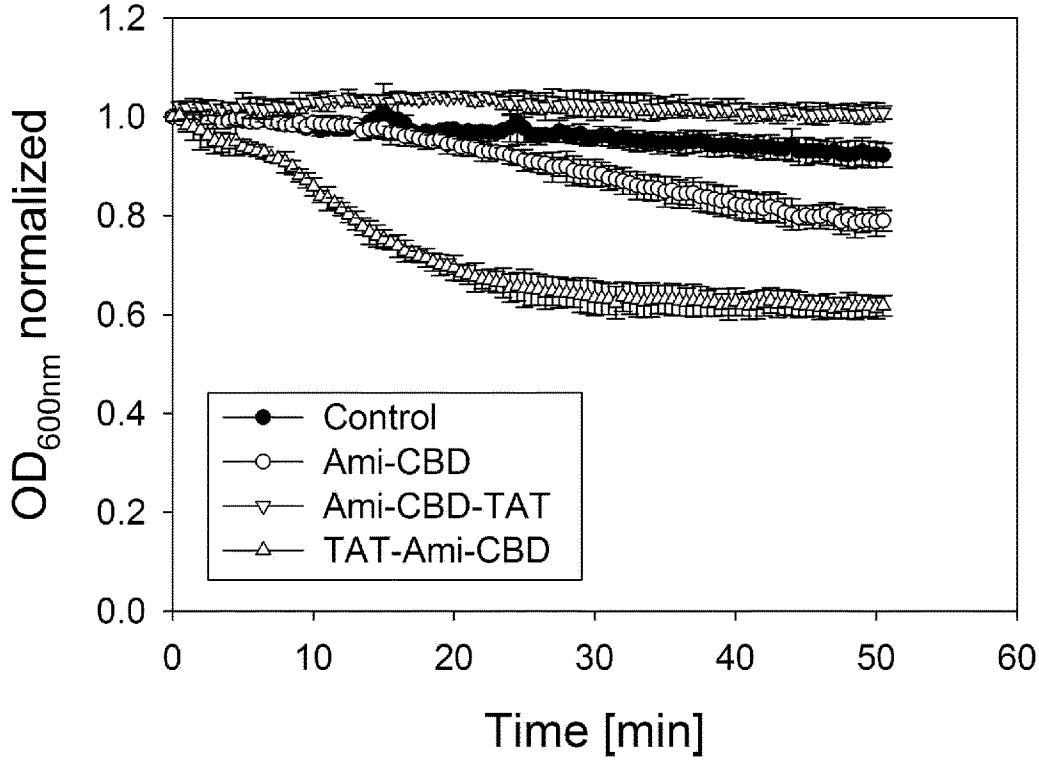

Control
M23-CBD
M23-CBD-R9
R9-M23-CBD
1.2
1.0
0.8
0.6
0.4
0.2
0.0
OD600nm normalized
0
10
20
30
40
50
60
Time [min]

Fig. 7c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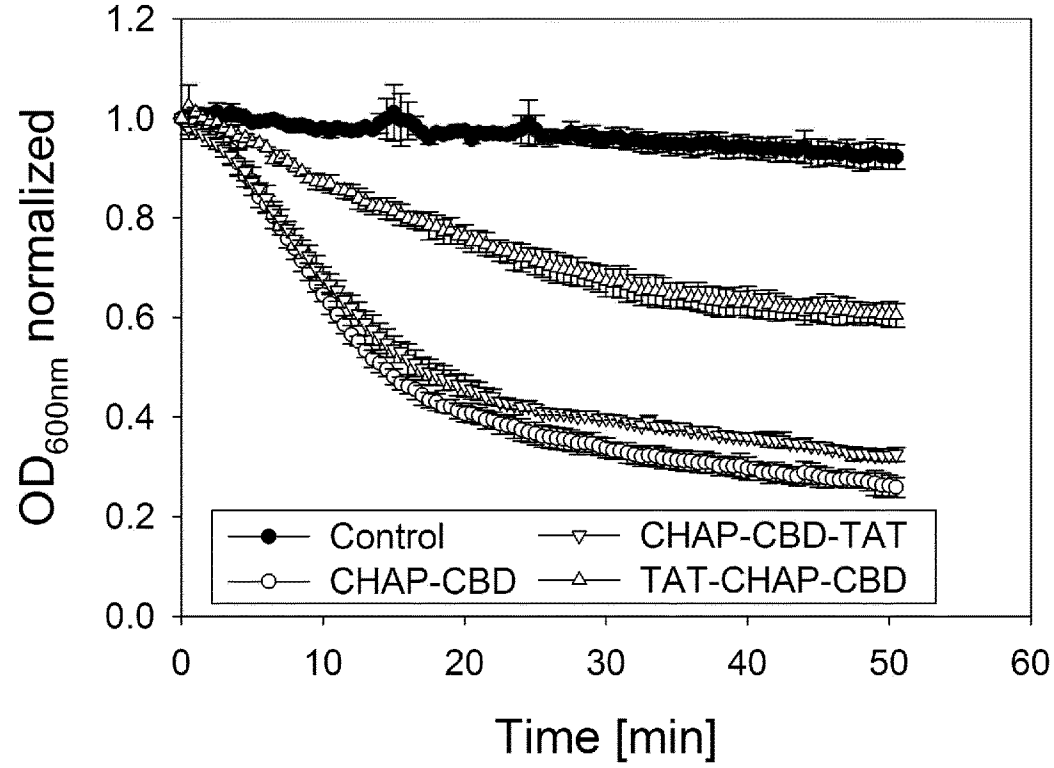
1.0
0.8
0.6
0.4
0.2
0.0
OD600nm normalized
0
10
20
30
40
50
60
Time [min]
Control
Ami-CBD
Ami-CBD-TAT
TAT-Ami-CBD

Fig. 7d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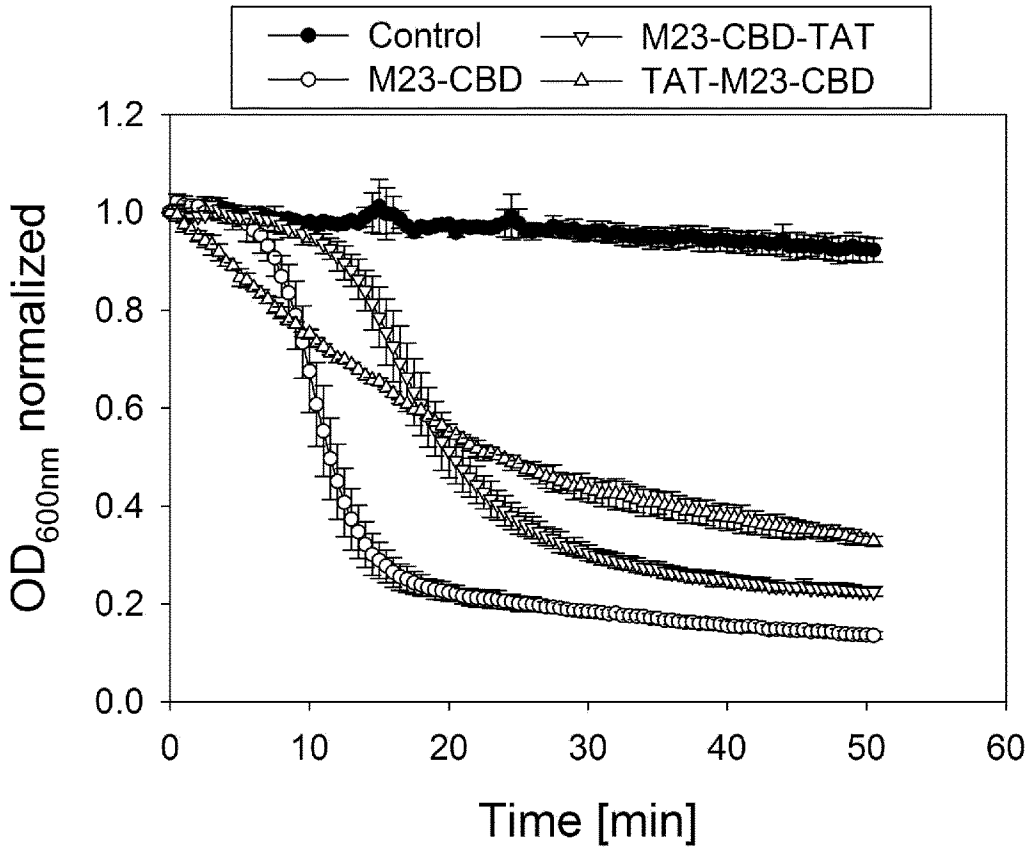
1.0
0.8
0.6
0.4
0.2
0.0
OD600nm normalized
0
10
20
30
40
50
60
Time [min]
Control
CHAP-CBD
CHAP-CBD-TAT
TAT-CHAP-CBD

Fig. 7e


Control
M23-CBD-TAT
M23-CBD
TAT-M23-CBD
1.2
1.0
0.8
0.6
0.4
0.2
0.0
OD600nm normalized
0
10
20
30
40
50
60
Time [min]

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<170> PatentIn version 3.5

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<213> Artificial

<220>
<223> Polypeptide fragment

<400> 1

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            20                  25                  30


Ser Met Thr Pro Ser Gln Tyr Leu Pro Trp Leu Tyr Ala Arg Glu Asn
        35                  40                  45


Asn Gly Thr His Val Asn Gly Trp Ala Ser Val Tyr Ala Asn Arg Asn
    50                  55                  60


Glu Val Leu Trp Tyr His Pro Thr Asp Tyr Val Glu Trp His Cys Gly
65                  70                  75                  80


Asn Gln Trp Ala Asn Ala Asn Leu Ile Gly Phe Glu Val Cys Glu Ser
                85                  90                  95


Tyr Pro Gly Arg Ile Ser Asp Lys Leu Phe Leu Glu Asn Glu Glu Ala
            100                 105                 110


Thr Leu Lys Val Ala Ala Asp Val Met Lys Ser Tyr Gly Leu Pro Val
        115                 120                 125


Asn Arg Asn Thr Val Arg Leu His Asn Glu Phe Phe Gly Thr Ser Cys
    130                 135                 140


Pro His Arg Ser Trp Asp Leu His Val Gly Lys Gly Glu Pro Tyr Thr
145                 150                 155                 160
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Thr Thr Asn Ile Asn Lys Met Lys Asp Tyr Phe Ile Lys Arg Ile Lys
165 170 175

His Tyr Tyr Asp
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Tyr Gly Val Asp Phe Phe Met Asn Ile Gly Thr Pro Val Lys Ala Ile
35 40 45

Ser Ser Gly Lys Ile Val Glu Ala Gly Trp Ser Asn Tyr Gly Gly Gly
50 55 60

Asn Gln Ile Gly Leu Ile Glu Asn Asp Gly Val His Arg Gln Trp Tyr
65 70 75 80

Met His Leu Ser Lys Tyr Asn Val Lys Val Gly Asp Tyr Val Lys Ala
85 90 95

Gly Gln Ile Ile Gly Trp Ser Gly Ser Thr Gly Tyr Ser Thr Ala Pro
100 105 110

His Leu His Phe Gln Arg Met Val Asn Ser Phe Ser Asn Ser Thr Ala
115 120 125

Gln Asp Pro Met Pro Phe Leu Lys Ser Ala Gly Tyr Gly
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1 5 10 15

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            20                  25                  30

Val Asp Leu Trp Tyr Gly Phe Gln Cys Phe Asp Tyr Ala Asn Ala Gly
        35                  40                  45

Trp Lys Val Leu Phe Gly Leu Leu Leu Lys Gly Leu Gly Ala Lys Asp
    50                  55                  60

Ile Pro Phe Ala Asn Asn Phe Asp Gly Leu Ala Thr Val Tyr Gln Asn
65                  70                  75                  80

Thr Pro Asp Phe Leu Ala Gln Pro Gly Asp Met Val Val Phe Gly Ser
                85                  90                  95

Asn Tyr Gly Ala Gly Tyr Gly His Val Ala Trp Val Ile Glu Ala Thr
            100                 105                 110

Leu Asp Tyr Ile Ile Val Tyr Glu Gln Asn Trp Leu Gly Gly Gly Trp
        115                 120                 125

Thr Asp Gly Ile Glu Gln Pro Gly Trp Gly Trp Glu Lys Val Thr Arg
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Arg Gln His Ala Tyr Asp Phe Pro Met Trp Phe Ile Arg Pro Asn Phe
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Lys
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Thr Gly Thr Asp Phe Asp Gly Leu Tyr Gly Tyr Gln Cys Met Asp Leu
            20                  25                  30

Ala Val Asp Tyr Ile Tyr His Val Thr Asp Gly Lys Ile Arg Met Trp
        35                  40                  45

Gly Asn Ala Lys Asp Ala Ile Asn Asn Ser Phe Gly Gly Thr Ala Thr
    50                  55                  60

Val Tyr Lys Asn Tyr Pro Ala Phe Arg Pro Lys Tyr Gly Asp Val Val
65                  70                  75                  80
```

```
Val Trp Thr Thr Gly Asn Phe Ala Thr Tyr Gly His Ile Ala Ile Val
                85                  90                  95

Thr Asn Pro Asp Pro Tyr Gly Asp Leu Gln Tyr Val Thr Val Leu Glu
            100                 105                 110

Gln Asn Trp Asn Gly Asn Gly Ile Tyr Lys Thr Glu Leu Ala Thr Ile
        115                 120                 125

Arg Thr His Asp Tyr Thr Gly Ile Thr His Phe Ile Arg Pro Asn Phe
    130                 135                 140

Ala
145


<210>  5
<211>  151
<212>  PRT
<213>  Artificial

<220>
<223>  Polypeptide fragement

<400>  5

Met Gly Leu Pro Ser Pro Lys Lys Arg Lys Pro Thr Ala Ser Glu Val
1               5                   10                  15

Ala Ala Trp Ala Lys Arg Met Ile Gly Arg Arg Val Asp Val Asp Gly
            20                  25                  30

Tyr His Gly Ala Gln Cys Trp Asp Leu Pro Asn Tyr Ile Phe Asn Arg
        35                  40                  45

Tyr Trp His Phe Lys Thr Thr Gly Asn Ala Ile Ala Met Ala Trp Tyr
    50                  55                  60

Arg Tyr Pro Lys Gly Phe Lys Phe Tyr Arg Asn Thr Arg Asn Phe Val
65                  70                  75                  80

Pro Lys Pro Gly Asp Met Ala Val Trp Gly Lys Gly Ser Phe Asn Asn
                85                  90                  95

Gly Val Gly His Thr Ala Val Val Ile Gly Pro Ser Thr Lys Ser Tyr
            100                 105                 110

Phe Thr Ser Val Asp Gln Asn Trp Ile Gly Ala Asn Ser Tyr Thr Gly
        115                 120                 125

Ser Pro Gly Ala Lys Ile Lys His Ser Tyr Asn Gly Ile Ser Gly Phe
    130                 135                 140
```

Val Arg Pro Pro Tyr His Ala
145 150

<210> 6
<211> 147
<212> PRT
<213> Artificial

<220>
<223> Polyppetide fragment

<400> 6

Met Ala Leu Pro Lys Thr Gly Lys Pro Thr Ala Lys Gln Val Val Asp
1 5 10 15

Trp Ala Ile Asn Leu Ile Gly Ser Gly Val Asp Val Asp Gly Tyr Tyr
20 25 30

Gly Arg Gln Cys Trp Asp Leu Pro Asn Tyr Ile Phe Asn Arg Tyr Trp
35 40 45

Asn Phe Lys Thr Pro Gly Asn Ala Arg Asp Met Ala Trp Tyr Arg Tyr
50 55 60

Pro Glu Gly Phe Lys Val Phe Arg Asn Thr Ser Asp Phe Val Pro Lys
65 70 75 80

Pro Gly Asp Ile Ala Val Trp Thr Gly Gly Asn Tyr Asn Trp Asn Thr
85 90 95

Trp Gly His Thr Gly Ile Val Val Gly Pro Ser Thr Lys Ser Tyr Phe
100 105 110

Tyr Ser Val Asp Gln Asn Trp Asn Asn Ser Asn Ser Tyr Val Gly Ser
115 120 125

Pro Ala Ala Lys Ile Lys His Ser Tyr Phe Gly Val Thr His Phe Val
130 135 140

Arg Pro Ala
145

<210> 7
<211> 165
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 7

Met Ala Lys Thr Gln Ala Glu Ile Asn Lys Arg Leu Asp Ala Tyr Ala
1 5 10 15

```
Lys Gly Thr Val Asp Ser Pro Tyr Arg Ile Lys Lys Ala Thr Ser Tyr
            20                  25                  30

Asp Pro Ser Phe Gly Val Met Glu Ala Gly Ala Ile Asp Ala Asp Gly
        35                  40                  45

Tyr Tyr His Ala Gln Cys Gln Asp Leu Ile Thr Asp Tyr Val Leu Trp
    50                  55                  60

Leu Thr Asp Asn Lys Val Arg Thr Trp Gly Asn Ala Lys Asp Gln Ile
65                  70                  75                  80

Lys Gln Ser Tyr Gly Thr Gly Phe Lys Ile His Glu Asn Lys Pro Ser
                85                  90                  95

Thr Val Pro Lys Lys Gly Trp Ile Ala Val Phe Thr Ser Gly Ser Tyr
            100                 105                 110

Gln Gln Trp Gly His Ile Gly Ile Val Tyr Asp Gly Gly Asn Thr Ser
        115                 120                 125

Thr Phe Thr Ile Leu Glu Gln Asn Trp Asn Gly Tyr Ala Asn Lys Lys
    130                 135                 140

Pro Thr Lys Arg Val Asp Asn Tyr Tyr Gly Leu Thr His Phe Ile Glu
145                 150                 155                 160

Ile Pro Val Lys Ala
                165


<210>  8
<211>  128
<212>  PRT
<213>  Artificial

<220>
<223>  Polypeptide fragment

<400>  8

Gly Gly Lys Leu Glu Val Ser Lys Ala Ala Thr Ile Lys Gln Ser Asp
1               5                   10                  15

Val Lys Gln Glu Val Lys Lys Gln Glu Ala Lys Gln Ile Val Lys Ala
            20                  25                  30

Thr Asp Trp Lys Gln Asn Lys Asp Gly Ile Trp Tyr Lys Ala Glu His
        35                  40                  45

Ala Ser Phe Thr Val Thr Ala Pro Glu Gly Ile Ile Thr Arg Tyr Lys
    50                  55                  60

Gly Pro Trp Thr Gly His Pro Gln Ala Gly Val Leu Gln Lys Gly Gln
65                  70                  75                  80
```

```
Thr Ile Lys Tyr Asp Glu Val Gln Lys Phe Asp Gly His Val Trp Val
                85                  90                  95


Ser Trp Glu Thr Phe Glu Gly Glu Thr Val Tyr Met Pro Val Arg Thr
            100                 105                 110


Trp Asp Ala Lys Thr Gly Lys Val Gly Lys Leu Trp Gly Glu Ile Lys
        115                 120                 125


<210>  9
<211>  78
<212>  PRT
<213>  Artificial

<220>
<223>  Polypeptide fragment

<400>  9

Ala Pro Lys Ser Lys Pro Ser Lys Ile Lys Thr Thr Trp Asn Trp Gly
1               5                   10                  15


Gly Lys Phe Thr Ala Asn Ser Thr Ile Lys Val Arg Lys Ser Pro Gly
            20                  25                  30


Leu Lys Gly Ile Val Val Glu Ser Gly Ser Trp Leu Tyr Lys Gly Asn
        35                  40                  45


Tyr Val Pro Phe Asp Gln Val Ile Lys Lys Asp Gly Tyr Trp Trp Ile
    50                  55                  60


Arg Phe Lys Tyr Val Gln Pro Gly Ser Ser Asn Lys His Phe
65                  70                  75


<210>  10
<211>  92
<212>  PRT
<213>  Artificial

<220>
<223>  Polypeptide fragment

<400>  10

Trp Lys Thr Asn Lys Tyr Gly Thr Leu Tyr Lys Ser Glu Ser Ala Ser
1               5                   10                  15


Phe Thr Pro Asn Thr Asp Ile Ile Thr Arg Thr Thr Gly Pro Phe Arg
            20                  25                  30


Ser Met Pro Gln Ser Gly Val Leu Lys Ala Gly Gln Thr Ile His Tyr
        35                  40                  45


Asp Glu Val Met Lys Gln Asp Gly His Val Trp Val Gly Tyr Thr Gly
    50                  55                  60
```

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


Thr Asn Thr Leu Gly Val Leu Trp Gly Thr Ile Lys
                85                  90


<210>  11
<211>  92
<212>  PRT
<213>  Artificial

<220>
<223>  Polypeptide fragment

<400>  11

Tyr Lys Thr Asn Lys Tyr Gly Thr Leu Tyr Lys Ser Glu Ser Ala Ser
1               5                   10                  15


Phe Thr Ala Asn Thr Asp Ile Ile Thr Arg Leu Thr Gly Pro Phe Arg
            20                  25                  30


Ser Met Pro Gln Ser Gly Val Leu Arg Lys Gly Leu Thr Ile Lys Tyr
        35                  40                  45


Asp Glu Val Met Lys Gln Asp Gly His Val Trp Val Gly Tyr Asn Thr
    50                  55                  60


Asn Ser Gly Lys Arg Val Tyr Leu Pro Val Arg Thr Trp Asn Glu Ser
65                  70                  75                  80


Thr Gly Glu Leu Gly Pro Leu Trp Gly Thr Ile Lys
                85                  90


<210>  12
<211>  30
<212>  PRT
<213>  Artificial

<220>
<223>  Polypeptide fragment

<400>  12

Trp Glu Ala Lys Leu Ala Lys Ala Leu Ala Lys Ala Leu Ala Lys His
1               5                   10                  15


Leu Ala Lys Ala Leu Ala Lys Ala Leu Lys Ala Cys Glu Ala
            20                  25                  30


<210>  13
<211>  22
<212>  PRT
<213>  Artificial

<220>
```

<223> Polypeptide fragment

<400> 13

Met Val Thr Val Leu Phe Arg Arg Leu Arg Ile Arg Arg Ala Ser Gly
1 5 10 15

Pro Pro Arg Val Arg Val
20

<210> 14
<211> 18
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 14

Lys Leu Ala Leu Lys Leu Ala Leu Lys Ala Leu Lys Ala Ala Leu Lys
1 5 10 15

Leu Ala

<210> 15
<211> 27
<212> PRT
<213> Artificial

<220>
<223> GALFLGFLGAAGSTMGAWSQPKKKRKV

<400> 15

Gly Ala Leu Phe Leu Gly Phe Leu Gly Ala Ala Gly Ser Thr Met Gly
1 5 10 15

Ala Trp Ser Gln Pro Lys Lys Lys Arg Lys Val
20 25

<210> 16
<211> 16
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 16

Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys
1 5 10 15

<210> 17
<211> 21
<212> PRT
<213> Artificial

<220>

<223> Polypeptide fragment

<400> 17

Lys Glu Thr Trp Trp Glu Thr Trp Trp Thr Glu Trp Ser Gln Pro Lys
1 5 10 15

Lys Lys Arg Lys Val
20

<210> 18
<211> 12
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 18

Arg Arg Gln Arg Arg Thr Ser Lys Leu Met Lys Arg
1 5 10

<210> 19
<211> 18
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 19

Leu Leu Ile Ile Leu Arg Arg Arg Ile Arg Lys Gln Ala His Ala His
1 5 10 15

Ser Lys

<210> 20
<211> 9
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 20

Arg Arg Trp Trp Arg Arg Trp Arg Arg
1 5

<210> 21
<211> 16
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment comprises 6 to 15 R residues

<400> 21

Arg Arg Arg Arg Arg Arg Arg Arg Arg Arg Arg Arg Arg Arg Arg
1 5 10 15

<210> 22
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 22

Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Pro Pro Gln
1 5 10

<210> 23
<211> 9
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 23

Arg Lys Lys Arg Arg Gln Arg Arg Arg
1 5

<210> 24
<211> 27
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 24

Gly Trp Thr Leu Asn Ser Ala Gly Tyr Leu Leu Gly Lys Ile Asn Leu
1 5 10 15

Lys Ala Leu Ala Ala Leu Ala Lys Lys Ile Leu
20 25

<210> 25
<211> 21
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 25

Ala Gly Tyr Leu Leu Gly Lys Ile Asn Leu Lys Ala Leu Ala Ala Leu
1 5 10 15

Ala Lys Lys Ile Leu
20

<210> 26

<400> 26
000

<210> 27
<211> 269
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide fragment

<400> 27

Met Ala Ala Thr His Glu His Ser Ala Gln Trp Leu Asn Asn Tyr Lys
1 5 10 15

Lys Gly Tyr Gly Tyr Gly Pro Tyr Pro Leu Gly Ile Asn Gly Gly Met
20 25 30

His Tyr Gly Val Asp Phe Phe Met Asn Ile Gly Thr Pro Val Lys Ala
35 40 45

Ile Ser Ser Gly Lys Ile Val Glu Ala Gly Trp Ser Asn Tyr Gly Gly
50 55 60

Gly Asn Gln Ile Gly Leu Ile Glu Asn Asp Gly Val His Arg Gln Trp
65 70 75 80

Tyr Met His Leu Ser Lys Tyr Asn Val Lys Val Gly Asp Tyr Val Lys
85 90 95

Ala Gly Gln Ile Ile Gly Trp Ser Gly Ser Thr Gly Tyr Ser Thr Ala
100 105 110

Pro His Leu His Phe Gln Arg Met Val Asn Ser Phe Ser Asn Ser Thr
115 120 125

Ala Gln Asp Pro Met Pro Phe Leu Lys Ser Ala Gly Tyr Gly Gly Lys
130 135 140

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

Glu Val Lys Lys Gln Glu Ala Lys Gln Ile Val Lys Ala Thr Asp Trp
165 170 175

Lys Gln Asn Lys Asp Gly Ile Trp Tyr Lys Ala Glu His Ala Ser Phe
180 185 190

Thr Val Thr Ala Pro Glu Gly Ile Ile Thr Arg Tyr Lys Gly Pro Trp
195 200 205

Thr Gly His Pro Gln Ala Gly Val Leu Gln Lys Gly Gln Thr Ile Lys

210 215 220

Tyr Asp Glu Val Gln Lys Phe Asp Gly His Val Trp Val Ser Trp Glu
225 230 235 240

Thr Phe Glu Gly Glu Thr Val Tyr Met Pro Val Arg Thr Trp Asp Ala
245 250 255

Lys Thr Gly Lys Val Gly Lys Leu Trp Gly Glu Ile Lys
260 265

<210> 28
<211> 289
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide fragment

<400> 28

Met Ser Ile Ile Met Glu Val Ala Thr Met Gln Ala Lys Leu Thr Lys
1 5 10 15

Asn Glu Phe Ile Glu Trp Leu Lys Thr Ser Glu Gly Lys Gln Phe Asn
20 25 30

Val Asp Leu Trp Tyr Gly Phe Gln Cys Phe Asp Tyr Ala Asn Ala Gly
35 40 45

Trp Lys Val Leu Phe Gly Leu Leu Leu Lys Gly Leu Gly Ala Lys Asp
50 55 60

Ile Pro Phe Ala Asn Asn Phe Asp Gly Leu Ala Thr Val Tyr Gln Asn
65 70 75 80

Thr Pro Asp Phe Leu Ala Gln Pro Gly Asp Met Val Val Phe Gly Ser
85 90 95

Asn Tyr Gly Ala Gly Tyr Gly His Val Ala Trp Val Ile Glu Ala Thr
100 105 110

Leu Asp Tyr Ile Ile Val Tyr Glu Gln Asn Trp Leu Gly Gly Gly Trp
115 120 125

Thr Asp Gly Ile Glu Gln Pro Gly Trp Gly Trp Glu Lys Val Thr Arg
130 135 140

Arg Gln His Ala Tyr Asp Phe Pro Met Trp Phe Ile Arg Pro Asn Phe
145 150 155 160

Lys Gly Gly Lys Leu Glu Val Ser Lys Ala Ala Thr Ile Lys Gln Ser
165 170 175

```
Asp Val Lys Gln Glu Val Lys Lys Gln Glu Ala Lys Gln Ile Val Lys
            180                 185                 190

Ala Thr Asp Trp Lys Gln Asn Lys Asp Gly Ile Trp Tyr Lys Ala Glu
        195                 200                 205

His Ala Ser Phe Thr Val Thr Ala Pro Glu Gly Ile Ile Thr Arg Tyr
    210                 215                 220

Lys Gly Pro Trp Thr Gly His Pro Gln Ala Gly Val Leu Gln Lys Gly
225                 230                 235                 240

Gln Thr Ile Lys Tyr Asp Glu Val Gln Lys Phe Asp Gly His Val Trp
                245                 250                 255

Val Ser Trp Glu Thr Phe Glu Gly Glu Thr Val Tyr Met Pro Val Arg
            260                 265                 270

Thr Trp Asp Ala Lys Thr Gly Lys Val Gly Lys Leu Trp Gly Glu Ile
        275                 280                 285

Lys
```

<210> 29
<211> 308
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide fragment

<400> 29

```
Met Leu Lys His Ile Tyr Ser Asn His Ile Lys Gly Asn Lys Ile Thr
1               5                   10                  15

Ala Pro Lys Pro Ser Ile Gln Gly Val Val Ile His Asn Asp Tyr Gly
            20                  25                  30

Ser Met Thr Pro Ser Gln Tyr Leu Pro Trp Leu Tyr Ala Arg Glu Asn
        35                  40                  45

Asn Gly Thr His Val Asn Gly Trp Ala Ser Val Tyr Ala Asn Arg Asn
    50                  55                  60

Glu Val Leu Trp Tyr His Pro Thr Asp Tyr Val Glu Trp His Cys Gly
65                  70                  75                  80

Asn Gln Trp Ala Asn Ala Asn Leu Ile Gly Phe Glu Val Cys Glu Ser
                85                  90                  95

Tyr Pro Gly Arg Ile Ser Asp Lys Leu Phe Leu Glu Asn Glu Glu Ala
```

100 105 110

Thr Leu Lys Val Ala Ala Asp Val Met Lys Ser Tyr Gly Leu Pro Val
115 120 125

Asn Arg Asn Thr Val Arg Leu His Asn Glu Phe Phe Gly Thr Ser Cys
130 135 140

Pro His Arg Ser Trp Asp Leu His Val Gly Lys Gly Glu Pro Tyr Thr
145 150 155 160

Thr Thr Asn Ile Asn Lys Met Lys Asp Tyr Phe Ile Lys Arg Ile Lys
165 170 175

His Tyr Tyr Asp Gly Gly Lys Leu Glu Val Ser Lys Ala Ala Thr Ile
180 185 190

Lys Gln Ser Asp Val Lys Gln Glu Val Lys Lys Gln Glu Ala Lys Gln
195 200 205

Ile Val Lys Ala Thr Asp Trp Lys Gln Asn Lys Asp Gly Ile Trp Tyr
210 215 220

Lys Ala Glu His Ala Ser Phe Thr Val Thr Ala Pro Glu Gly Ile Ile
225 230 235 240

Thr Arg Tyr Lys Gly Pro Trp Thr Gly His Pro Gln Ala Gly Val Leu
245 250 255

Gln Lys Gly Gln Thr Ile Lys Tyr Asp Glu Val Gln Lys Phe Asp Gly
260 265 270

His Val Trp Val Ser Trp Glu Thr Phe Glu Gly Glu Thr Val Tyr Met
275 280 285

Pro Val Arg Thr Trp Asp Ala Lys Thr Gly Lys Val Gly Lys Leu Trp
290 295 300

Gly Glu Ile Lys
305

<210> 30
<211> 326
<212> PRT
<213> Artificial

<220>
<223> Polypeptide construct

<400> 30

Met Leu Lys His Ile Tyr Ser Asn His Ile Lys Gly Asn Lys Ile Thr
1 5 10 15

```
Ala Pro Lys Pro Ser Ile Gln Gly Val Val Ile His Asn Asp Tyr Gly
            20                  25                  30

Ser Met Thr Pro Ser Gln Tyr Leu Pro Trp Leu Tyr Ala Arg Glu Asn
        35                  40                  45

Asn Gly Thr His Val Asn Gly Trp Ala Ser Val Tyr Ala Asn Arg Asn
    50                  55                  60

Glu Val Leu Trp Tyr His Pro Thr Asp Tyr Val Glu Trp His Cys Gly
65                  70                  75                  80

Asn Gln Trp Ala Asn Ala Asn Leu Ile Gly Phe Glu Val Cys Glu Ser
                85                  90                  95

Tyr Pro Gly Arg Ile Ser Asp Lys Leu Phe Leu Glu Asn Glu Glu Ala
            100                 105                 110

Thr Leu Lys Val Ala Ala Asp Val Met Lys Ser Tyr Gly Leu Pro Val
        115                 120                 125

Asn Arg Asn Thr Val Arg Leu His Asn Glu Phe Phe Gly Thr Ser Cys
    130                 135                 140

Pro His Arg Ser Trp Asp Leu His Val Gly Lys Gly Glu Pro Tyr Thr
145                 150                 155                 160

Thr Thr Asn Ile Asn Lys Met Lys Asp Tyr Phe Ile Lys Arg Ile Lys
                165                 170                 175

His Tyr Tyr Asp Gly Gly Lys Leu Glu Val Ser Lys Ala Ala Thr Ile
            180                 185                 190

Lys Gln Ser Asp Val Lys Gln Glu Val Lys Lys Gln Glu Ala Lys Gln
        195                 200                 205

Ile Val Lys Ala Thr Asp Trp Lys Gln Asn Lys Asp Gly Ile Trp Tyr
    210                 215                 220

Lys Ala Glu His Ala Ser Phe Thr Val Thr Ala Pro Glu Gly Ile Ile
225                 230                 235                 240

Thr Arg Tyr Lys Gly Pro Trp Thr Gly His Pro Gln Ala Gly Val Leu
                245                 250                 255

Gln Lys Gly Gln Thr Ile Lys Tyr Asp Glu Val Gln Lys Phe Asp Gly
            260                 265                 270

His Val Trp Val Ser Trp Glu Thr Phe Glu Gly Glu Thr Val Tyr Met
        275                 280                 285
```

```
Pro Val Arg Thr Trp Asp Ala Lys Thr Gly Lys Val Gly Lys Leu Trp
    290                 295                 300

Gly Glu Ile Lys Glu Leu Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg
305                 310                 315                 320

Arg Met Lys Trp Lys Lys
                325
```

<210> 31
<211> 319
<212> PRT
<213> Artificial

<220>
<223> Polypeptide construct

<400> 31

```
Met Leu Lys His Ile Tyr Ser Asn His Ile Lys Gly Asn Lys Ile Thr
1               5                   10                  15

Ala Pro Lys Pro Ser Ile Gln Gly Val Val Ile His Asn Asp Tyr Gly
            20                  25                  30

Ser Met Thr Pro Ser Gln Tyr Leu Pro Trp Leu Tyr Ala Arg Glu Asn
        35                  40                  45

Asn Gly Thr His Val Asn Gly Trp Ala Ser Val Tyr Ala Asn Arg Asn
    50                  55                  60

Glu Val Leu Trp Tyr His Pro Thr Asp Tyr Val Glu Trp His Cys Gly
65                  70                  75                  80

Asn Gln Trp Ala Asn Ala Asn Leu Ile Gly Phe Glu Val Cys Glu Ser
                85                  90                  95

Tyr Pro Gly Arg Ile Ser Asp Lys Leu Phe Leu Glu Asn Glu Glu Ala
            100                 105                 110

Thr Leu Lys Val Ala Ala Asp Val Met Lys Ser Tyr Gly Leu Pro Val
        115                 120                 125

Asn Arg Asn Thr Val Arg Leu His Asn Glu Phe Phe Gly Thr Ser Cys
    130                 135                 140

Pro His Arg Ser Trp Asp Leu His Val Gly Lys Gly Glu Pro Tyr Thr
145                 150                 155                 160

Thr Thr Asn Ile Asn Lys Met Lys Asp Tyr Phe Ile Lys Arg Ile Lys
                165                 170                 175

His Tyr Tyr Asp Gly Gly Lys Leu Glu Val Ser Lys Ala Ala Thr Ile
```

180 185 190

Lys Gln Ser Asp Val Lys Gln Glu Val Lys Lys Gln Glu Ala Lys Gln
195 200 205

Ile Val Lys Ala Thr Asp Trp Lys Gln Asn Lys Asp Gly Ile Trp Tyr
210 215 220

Lys Ala Glu His Ala Ser Phe Thr Val Thr Ala Pro Glu Gly Ile Ile
225 230 235 240

Thr Arg Tyr Lys Gly Pro Trp Thr Gly His Pro Gln Ala Gly Val Leu
245 250 255

Gln Lys Gly Gln Thr Ile Lys Tyr Asp Glu Val Gln Lys Phe Asp Gly
260 265 270

His Val Trp Val Ser Trp Glu Thr Phe Glu Gly Glu Thr Val Tyr Met
275 280 285

Pro Val Arg Thr Trp Asp Ala Lys Thr Gly Lys Val Gly Lys Leu Trp
290 295 300

Gly Glu Ile Lys Glu Leu Arg Arg Arg Arg Arg Arg Arg Arg Arg Arg
305 310 315

<210> 32
<211> 323
<212> PRT
<213> Artificial

<220>
<223> Polypeptide construct

<400> 32

Met Leu Lys His Ile Tyr Ser Asn His Ile Lys Gly Asn Lys Ile Thr
1 5 10 15

Ala Pro Lys Pro Ser Ile Gln Gly Val Val Ile His Asn Asp Tyr Gly
20 25 30

Ser Met Thr Pro Ser Gln Tyr Leu Pro Trp Leu Tyr Ala Arg Glu Asn
35 40 45

Asn Gly Thr His Val Asn Gly Trp Ala Ser Val Tyr Ala Asn Arg Asn
50 55 60

Glu Val Leu Trp Tyr His Pro Thr Asp Tyr Val Glu Trp His Cys Gly
65 70 75 80

Asn Gln Trp Ala Asn Ala Asn Leu Ile Gly Phe Glu Val Cys Glu Ser
85 90 95

```
Tyr Pro Gly Arg Ile Ser Asp Lys Leu Phe Leu Glu Asn Glu Glu Ala
            100                 105                 110

Thr Leu Lys Val Ala Ala Asp Val Met Lys Ser Tyr Gly Leu Pro Val
        115                 120                 125

Asn Arg Asn Thr Val Arg Leu His Asn Glu Phe Phe Gly Thr Ser Cys
    130                 135                 140

Pro His Arg Ser Trp Asp Leu His Val Gly Lys Gly Glu Pro Tyr Thr
145                 150                 155                 160

Thr Thr Asn Ile Asn Lys Met Lys Asp Tyr Phe Ile Lys Arg Ile Lys
                165                 170                 175

His Tyr Tyr Asp Gly Gly Lys Leu Glu Val Ser Lys Ala Ala Thr Ile
            180                 185                 190

Lys Gln Ser Asp Val Lys Gln Glu Val Lys Lys Gln Glu Ala Lys Gln
        195                 200                 205

Ile Val Lys Ala Thr Asp Trp Lys Gln Asn Lys Asp Gly Ile Trp Tyr
    210                 215                 220

Lys Ala Glu His Ala Ser Phe Thr Val Thr Ala Pro Glu Gly Ile Ile
225                 230                 235                 240

Thr Arg Tyr Lys Gly Pro Trp Thr Gly His Pro Gln Ala Gly Val Leu
                245                 250                 255

Gln Lys Gly Gln Thr Ile Lys Tyr Asp Glu Val Gln Lys Phe Asp Gly
            260                 265                 270

His Val Trp Val Ser Trp Glu Thr Phe Glu Gly Glu Thr Val Tyr Met
        275                 280                 285

Pro Val Arg Thr Trp Asp Ala Lys Thr Gly Lys Val Gly Lys Leu Trp
    290                 295                 300

Gly Glu Ile Lys Glu Leu Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg
305                 310                 315                 320

Pro Pro Gln
```

<210> 33
<211> 199
<212> PRT
<213> Artificial

<220>
<223> Polypeptide construct

<400> 33

Met Leu Lys His Ile Tyr Ser Asn His Ile Lys Gly Asn Lys Ile Thr
1 5 10 15

Ala Pro Lys Pro Ser Ile Gln Gly Val Val Ile His Asn Asp Tyr Gly
20 25 30

Ser Met Thr Pro Ser Gln Tyr Leu Pro Trp Leu Tyr Ala Arg Glu Asn
35 40 45

Asn Gly Thr His Val Asn Gly Trp Ala Ser Val Tyr Ala Asn Arg Asn
50 55 60

Glu Val Leu Trp Tyr His Pro Thr Asp Tyr Val Glu Trp His Cys Gly
65 70 75 80

Asn Gln Trp Ala Asn Ala Asn Leu Ile Gly Phe Glu Val Cys Glu Ser
85 90 95

Tyr Pro Gly Arg Ile Ser Asp Lys Leu Phe Leu Glu Asn Glu Glu Ala
100 105 110

Thr Leu Lys Val Ala Ala Asp Val Met Lys Ser Tyr Gly Leu Pro Val
115 120 125

Asn Arg Asn Thr Val Arg Leu His Asn Glu Phe Phe Gly Thr Ser Cys
130 135 140

Pro His Arg Ser Trp Asp Leu His Val Gly Lys Gly Glu Pro Tyr Thr
145 150 155 160

Thr Thr Asn Ile Asn Lys Met Lys Asp Tyr Phe Ile Lys Arg Ile Lys
165 170 175

His Tyr Tyr Asp Gly Glu Leu Arg Gln Ile Lys Ile Trp Phe Gln Asn
180 185 190

Arg Arg Met Lys Trp Lys Lys
195

<210> 34
<211> 192
<212> PRT
<213> Artificial

<220>
<223> Polypeptide construct

<400> 34

Met Leu Lys His Ile Tyr Ser Asn His Ile Lys Gly Asn Lys Ile Thr
1 5 10 15

```
Ala Pro Lys Pro Ser Ile Gln Gly Val Val Ile His Asn Asp Tyr Gly
            20                  25                  30

Ser Met Thr Pro Ser Gln Tyr Leu Pro Trp Leu Tyr Ala Arg Glu Asn
        35                  40                  45

Asn Gly Thr His Val Asn Gly Trp Ala Ser Val Tyr Ala Asn Arg Asn
    50                  55                  60

Glu Val Leu Trp Tyr His Pro Thr Asp Tyr Val Glu Trp His Cys Gly
65                  70                  75                  80

Asn Gln Trp Ala Asn Ala Asn Leu Ile Gly Phe Glu Val Cys Glu Ser
                85                  90                  95

Tyr Pro Gly Arg Ile Ser Asp Lys Leu Phe Leu Glu Asn Glu Glu Ala
            100                 105                 110

Thr Leu Lys Val Ala Ala Asp Val Met Lys Ser Tyr Gly Leu Pro Val
        115                 120                 125

Asn Arg Asn Thr Val Arg Leu His Asn Glu Phe Phe Gly Thr Ser Cys
    130                 135                 140

Pro His Arg Ser Trp Asp Leu His Val Gly Lys Gly Glu Pro Tyr Thr
145                 150                 155                 160

Thr Thr Asn Ile Asn Lys Met Lys Asp Tyr Phe Ile Lys Arg Ile Lys
                165                 170                 175

His Tyr Tyr Asp Gly Glu Leu Arg Arg Arg Arg Arg Arg Arg Arg Arg
            180                 185                 190


<210>  35
<211>  196
<212>  PRT
<213>  Artificial

<220>
<223>  Polypeptide construct

<400>  35

Met Leu Lys His Ile Tyr Ser Asn His Ile Lys Gly Asn Lys Ile Thr
1               5                   10                  15

Ala Pro Lys Pro Ser Ile Gln Gly Val Val Ile His Asn Asp Tyr Gly
            20                  25                  30

Ser Met Thr Pro Ser Gln Tyr Leu Pro Trp Leu Tyr Ala Arg Glu Asn
        35                  40                  45

Asn Gly Thr His Val Asn Gly Trp Ala Ser Val Tyr Ala Asn Arg Asn
```

50 55 60

Glu Val Leu Trp Tyr His Pro Thr Asp Tyr Val Glu Trp His Cys Gly
65 70 75 80

Asn Gln Trp Ala Asn Ala Asn Leu Ile Gly Phe Glu Val Cys Glu Ser
85 90 95

Tyr Pro Gly Arg Ile Ser Asp Lys Leu Phe Leu Glu Asn Glu Glu Ala
100 105 110

Thr Leu Lys Val Ala Ala Asp Val Met Lys Ser Tyr Gly Leu Pro Val
115 120 125

Asn Arg Asn Thr Val Arg Leu His Asn Glu Phe Phe Gly Thr Ser Cys
130 135 140

Pro His Arg Ser Trp Asp Leu His Val Gly Lys Gly Glu Pro Tyr Thr
145 150 155 160

Thr Thr Asn Ile Asn Lys Met Lys Asp Tyr Phe Ile Lys Arg Ile Lys
165 170 175

His Tyr Tyr Asp Gly Glu Leu Gly Arg Lys Lys Arg Arg Gln Arg Arg
180 185 190

Arg Pro Pro Gln
195

<210> 36
<211> 307
<212> PRT
<213> Artificial

<220>
<223> Polypeptide construct

<400> 36

Met Ser Ile Ile Met Glu Val Ala Thr Met Gln Ala Lys Leu Thr Lys
1 5 10 15

Asn Glu Phe Ile Glu Trp Leu Lys Thr Ser Glu Gly Lys Gln Phe Asn
20 25 30

Val Asp Leu Trp Tyr Gly Phe Gln Cys Phe Asp Tyr Ala Asn Ala Gly
35 40 45

Trp Lys Val Leu Phe Gly Leu Leu Leu Lys Gly Leu Gly Ala Lys Asp
50 55 60

Ile Pro Phe Ala Asn Asn Phe Asp Gly Leu Ala Thr Val Tyr Gln Asn
65 70 75 80

```
Thr Pro Asp Phe Leu Ala Gln Pro Gly Asp Met Val Val Phe Gly Ser
                85                  90                  95

Asn Tyr Gly Ala Gly Tyr Gly His Val Ala Trp Val Ile Glu Ala Thr
            100                 105                 110

Leu Asp Tyr Ile Ile Val Tyr Glu Gln Asn Trp Leu Gly Gly Gly Trp
        115                 120                 125

Thr Asp Gly Ile Glu Gln Pro Gly Trp Gly Trp Glu Lys Val Thr Arg
    130                 135                 140

Arg Gln His Ala Tyr Asp Phe Pro Met Trp Phe Ile Arg Pro Asn Phe
145                 150                 155                 160

Lys Gly Gly Lys Leu Glu Val Ser Lys Ala Ala Thr Ile Lys Gln Ser
                165                 170                 175

Asp Val Lys Gln Glu Val Lys Lys Gln Glu Ala Lys Gln Ile Val Lys
            180                 185                 190

Ala Thr Asp Trp Lys Gln Asn Lys Asp Gly Ile Trp Tyr Lys Ala Glu
        195                 200                 205

His Ala Ser Phe Thr Val Thr Ala Pro Glu Gly Ile Ile Thr Arg Tyr
    210                 215                 220

Lys Gly Pro Trp Thr Gly His Pro Gln Ala Gly Val Leu Gln Lys Gly
225                 230                 235                 240

Gln Thr Ile Lys Tyr Asp Glu Val Gln Lys Phe Asp Gly His Val Trp
                245                 250                 255

Val Ser Trp Glu Thr Phe Glu Gly Glu Thr Val Tyr Met Pro Val Arg
            260                 265                 270

Thr Trp Asp Ala Lys Thr Gly Lys Val Gly Lys Leu Trp Gly Glu Ile
        275                 280                 285

Lys Glu Leu Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys
    290                 295                 300

Trp Lys Lys
305


<210>  37
<211>  300
<212>  PRT
<213>  Artificial

<220>
<223>  Polypeptide construct
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<400> 37

```
Met Ser Ile Ile Met Glu Val Ala Thr Met Gln Ala Lys Leu Thr Lys
1               5                  10                  15

Asn Glu Phe Ile Glu Trp Leu Lys Thr Ser Glu Gly Lys Gln Phe Asn
            20                  25                  30

Val Asp Leu Trp Tyr Gly Phe Gln Cys Phe Asp Tyr Ala Asn Ala Gly
        35                  40                  45

Trp Lys Val Leu Phe Gly Leu Leu Leu Lys Gly Leu Gly Ala Lys Asp
    50                  55                  60

Ile Pro Phe Ala Asn Asn Phe Asp Gly Leu Ala Thr Val Tyr Gln Asn
65                  70                  75                  80

Thr Pro Asp Phe Leu Ala Gln Pro Gly Asp Met Val Val Phe Gly Ser
                85                  90                  95

Asn Tyr Gly Ala Gly Tyr Gly His Val Ala Trp Val Ile Glu Ala Thr
            100                 105                 110

Leu Asp Tyr Ile Ile Val Tyr Glu Gln Asn Trp Leu Gly Gly Gly Trp
        115                 120                 125

Thr Asp Gly Ile Glu Gln Pro Gly Trp Gly Trp Glu Lys Val Thr Arg
    130                 135                 140

Arg Gln His Ala Tyr Asp Phe Pro Met Trp Phe Ile Arg Pro Asn Phe
145                 150                 155                 160

Lys Gly Gly Lys Leu Glu Val Ser Lys Ala Ala Thr Ile Lys Gln Ser
                165                 170                 175

Asp Val Lys Gln Glu Val Lys Lys Gln Glu Ala Lys Gln Ile Val Lys
            180                 185                 190

Ala Thr Asp Trp Lys Gln Asn Lys Asp Gly Ile Trp Tyr Lys Ala Glu
        195                 200                 205

His Ala Ser Phe Thr Val Thr Ala Pro Glu Gly Ile Ile Thr Arg Tyr
    210                 215                 220

Lys Gly Pro Trp Thr Gly His Pro Gln Ala Gly Val Leu Gln Lys Gly
225                 230                 235                 240

Gln Thr Ile Lys Tyr Asp Glu Val Gln Lys Phe Asp Gly His Val Trp
                245                 250                 255

Val Ser Trp Glu Thr Phe Glu Gly Glu Thr Val Tyr Met Pro Val Arg
```

260 265 270

Thr Trp Asp Ala Lys Thr Gly Lys Val Gly Lys Leu Trp Gly Glu Ile
275 280 285

Lys Glu Leu Arg Arg Arg Arg Arg Arg Arg Arg Arg
290 295 300

<210> 38
<211> 304
<212> PRT
<213> Artificial

<220>
<223> Polypeptide construct

<400> 38

Met Ser Ile Ile Met Glu Val Ala Thr Met Gln Ala Lys Leu Thr Lys
1 5 10 15

Asn Glu Phe Ile Glu Trp Leu Lys Thr Ser Glu Gly Lys Gln Phe Asn
20 25 30

Val Asp Leu Trp Tyr Gly Phe Gln Cys Phe Asp Tyr Ala Asn Ala Gly
35 40 45

Trp Lys Val Leu Phe Gly Leu Leu Leu Lys Gly Leu Gly Ala Lys Asp
50 55 60

Ile Pro Phe Ala Asn Asn Phe Asp Gly Leu Ala Thr Val Tyr Gln Asn
65 70 75 80

Thr Pro Asp Phe Leu Ala Gln Pro Gly Asp Met Val Val Phe Gly Ser
85 90 95

Asn Tyr Gly Ala Gly Tyr Gly His Val Ala Trp Val Ile Glu Ala Thr
100 105 110

Leu Asp Tyr Ile Ile Val Tyr Glu Gln Asn Trp Leu Gly Gly Gly Trp
115 120 125

Thr Asp Gly Ile Glu Gln Pro Gly Trp Gly Trp Glu Lys Val Thr Arg
130 135 140

Arg Gln His Ala Tyr Asp Phe Pro Met Trp Phe Ile Arg Pro Asn Phe
145 150 155 160

Lys Gly Gly Lys Leu Glu Val Ser Lys Ala Ala Thr Ile Lys Gln Ser
165 170 175

Asp Val Lys Gln Glu Val Lys Lys Gln Glu Ala Lys Gln Ile Val Lys
180 185 190

```
Ala Thr Asp Trp Lys Gln Asn Lys Asp Gly Ile Trp Tyr Lys Ala Glu
        195                 200                 205

His Ala Ser Phe Thr Val Thr Ala Pro Glu Gly Ile Ile Thr Arg Tyr
    210                 215                 220

Lys Gly Pro Trp Thr Gly His Pro Gln Ala Gly Val Leu Gln Lys Gly
225                 230                 235                 240

Gln Thr Ile Lys Tyr Asp Glu Val Gln Lys Phe Asp Gly His Val Trp
                245                 250                 255

Val Ser Trp Glu Thr Phe Glu Gly Glu Thr Val Tyr Met Pro Val Arg
            260                 265                 270

Thr Trp Asp Ala Lys Thr Gly Lys Val Gly Lys Leu Trp Gly Glu Ile
        275                 280                 285

Lys Glu Leu Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Pro Pro Gln
    290                 295                 300
```

<210> 39
<211> 179
<212> PRT
<213> Artificial

<220>
<223> Polypeptide construct

<400> 39

```
Met Ser Ile Ile Met Glu Val Ala Thr Met Gln Ala Lys Leu Thr Lys
1               5                   10                  15

Asn Glu Phe Ile Glu Trp Leu Lys Thr Ser Glu Gly Lys Gln Phe Asn
            20                  25                  30

Val Asp Leu Trp Tyr Gly Phe Gln Cys Phe Asp Tyr Ala Asn Ala Gly
        35                  40                  45

Trp Lys Val Leu Phe Gly Leu Leu Leu Lys Gly Leu Gly Ala Lys Asp
    50                  55                  60

Ile Pro Phe Ala Asn Asn Phe Asp Gly Leu Ala Thr Val Tyr Gln Asn
65                  70                  75                  80

Thr Pro Asp Phe Leu Ala Gln Pro Gly Asp Met Val Val Phe Gly Ser
                85                  90                  95

Asn Tyr Gly Ala Gly Tyr Gly His Val Ala Trp Val Ile Glu Ala Thr
            100                 105                 110

Leu Asp Tyr Ile Ile Val Tyr Glu Gln Asn Trp Leu Gly Gly Gly Trp
```

115 120 125

Thr Asp Gly Ile Glu Gln Pro Gly Trp Gly Trp Glu Lys Val Thr Arg
130 135 140

Arg Gln His Ala Tyr Asp Phe Pro Met Trp Phe Ile Arg Pro Asn Phe
145 150 155 160

Lys Glu Leu Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys
165 170 175

Trp Lys Lys

<210> 40
<211> 172
<212> PRT
<213> Artificial

<220>
<223> Polypeptide construct

<400> 40

Met Ser Ile Ile Met Glu Val Ala Thr Met Gln Ala Lys Leu Thr Lys
1 5 10 15

Asn Glu Phe Ile Glu Trp Leu Lys Thr Ser Glu Gly Lys Gln Phe Asn
20 25 30

Val Asp Leu Trp Tyr Gly Phe Gln Cys Phe Asp Tyr Ala Asn Ala Gly
35 40 45

Trp Lys Val Leu Phe Gly Leu Leu Leu Lys Gly Leu Gly Ala Lys Asp
50 55 60

Ile Pro Phe Ala Asn Asn Phe Asp Gly Leu Ala Thr Val Tyr Gln Asn
65 70 75 80

Thr Pro Asp Phe Leu Ala Gln Pro Gly Asp Met Val Val Phe Gly Ser
85 90 95

Asn Tyr Gly Ala Gly Tyr Gly His Val Ala Trp Val Ile Glu Ala Thr
100 105 110

Leu Asp Tyr Ile Ile Val Tyr Glu Gln Asn Trp Leu Gly Gly Gly Trp
115 120 125

Thr Asp Gly Ile Glu Gln Pro Gly Trp Gly Trp Glu Lys Val Thr Arg
130 135 140

Arg Gln His Ala Tyr Asp Phe Pro Met Trp Phe Ile Arg Pro Asn Phe
145 150 155 160

Lys Glu Leu Arg Arg Arg Arg Arg Arg Arg Arg
165 170

<210> 41
<211> 176
<212> PRT
<213> Artificial

<220>
<223> Polypeptide construct

<400> 41

Met Ser Ile Ile Met Glu Val Ala Thr Met Gln Ala Lys Leu Thr Lys
1 5 10 15

Asn Glu Phe Ile Glu Trp Leu Lys Thr Ser Glu Gly Lys Gln Phe Asn
20 25 30

Val Asp Leu Trp Tyr Gly Phe Gln Cys Phe Asp Tyr Ala Asn Ala Gly
35 40 45

Trp Lys Val Leu Phe Gly Leu Leu Leu Lys Gly Leu Gly Ala Lys Asp
50 55 60

Ile Pro Phe Ala Asn Asn Phe Asp Gly Leu Ala Thr Val Tyr Gln Asn
65 70 75 80

Thr Pro Asp Phe Leu Ala Gln Pro Gly Asp Met Val Val Phe Gly Ser
85 90 95

Asn Tyr Gly Ala Gly Tyr Gly His Val Ala Trp Val Ile Glu Ala Thr
100 105 110

Leu Asp Tyr Ile Ile Val Tyr Glu Gln Asn Trp Leu Gly Gly Gly Trp
115 120 125

Thr Asp Gly Ile Glu Gln Pro Gly Trp Gly Trp Glu Lys Val Thr Arg
130 135 140

Arg Gln His Ala Tyr Asp Phe Pro Met Trp Phe Ile Arg Pro Asn Phe
145 150 155 160

Lys Glu Leu Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Pro Pro Gln
165 170 175

<210> 42
<211> 287
<212> PRT
<213> Artificial

<220>
<223> Polypeptide construct

<400> 42

```
Met Ala Ala Thr His Glu His Ser Ala Gln Trp Leu Asn Asn Tyr Lys
1               5                  10                  15

Lys Gly Tyr Gly Tyr Gly Pro Tyr Pro Leu Gly Ile Asn Gly Gly Met
            20                  25                  30

His Tyr Gly Val Asp Phe Phe Met Asn Ile Gly Thr Pro Val Lys Ala
        35                  40                  45

Ile Ser Ser Gly Lys Ile Val Glu Ala Gly Trp Ser Asn Tyr Gly Gly
    50                  55                  60

Gly Asn Gln Ile Gly Leu Ile Glu Asn Asp Gly Val His Arg Gln Trp
65                  70                  75                  80

Tyr Met His Leu Ser Lys Tyr Asn Val Lys Val Gly Asp Tyr Val Lys
                85                  90                  95

Ala Gly Gln Ile Ile Gly Trp Ser Gly Ser Thr Gly Tyr Ser Thr Ala
            100                 105                 110

Pro His Leu His Phe Gln Arg Met Val Asn Ser Phe Ser Asn Ser Thr
        115                 120                 125

Ala Gln Asp Pro Met Pro Phe Leu Lys Ser Ala Gly Tyr Gly Gly Lys
    130                 135                 140

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

Glu Val Lys Lys Gln Glu Ala Lys Gln Ile Val Lys Ala Thr Asp Trp
                165                 170                 175

Lys Gln Asn Lys Asp Gly Ile Trp Tyr Lys Ala Glu His Ala Ser Phe
            180                 185                 190

Thr Val Thr Ala Pro Glu Gly Ile Ile Thr Arg Tyr Lys Gly Pro Trp
        195                 200                 205

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

Tyr Asp Glu Val Gln Lys Phe Asp Gly His Val Trp Val Ser Trp Glu
225                 230                 235                 240

Thr Phe Glu Gly Glu Thr Val Tyr Met Pro Val Arg Thr Trp Asp Ala
                245                 250                 255

Lys Thr Gly Lys Val Gly Lys Leu Trp Gly Glu Ile Lys Glu Leu Arg
            260                 265                 270
```

```
Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys
        275                 280                 285


<210>  43
<211>  280
<212>  PRT
<213>  Artificial

<220>
<223>  Polypeptide construct

<400>  43

Met Ala Ala Thr His Glu His Ser Ala Gln Trp Leu Asn Asn Tyr Lys
1               5                   10                  15


Lys Gly Tyr Gly Tyr Gly Pro Tyr Pro Leu Gly Ile Asn Gly Gly Met
            20                  25                  30


His Tyr Gly Val Asp Phe Phe Met Asn Ile Gly Thr Pro Val Lys Ala
        35                  40                  45


Ile Ser Ser Gly Lys Ile Val Glu Ala Gly Trp Ser Asn Tyr Gly Gly
    50                  55                  60


Gly Asn Gln Ile Gly Leu Ile Glu Asn Asp Gly Val His Arg Gln Trp
65                  70                  75                  80


Tyr Met His Leu Ser Lys Tyr Asn Val Lys Val Gly Asp Tyr Val Lys
                85                  90                  95


Ala Gly Gln Ile Ile Gly Trp Ser Gly Ser Thr Gly Tyr Ser Thr Ala
            100                 105                 110


Pro His Leu His Phe Gln Arg Met Val Asn Ser Phe Ser Asn Ser Thr
        115                 120                 125


Ala Gln Asp Pro Met Pro Phe Leu Lys Ser Ala Gly Tyr Gly Gly Lys
    130                 135                 140


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


Glu Val Lys Lys Gln Glu Ala Lys Gln Ile Val Lys Ala Thr Asp Trp
                165                 170                 175


Lys Gln Asn Lys Asp Gly Ile Trp Tyr Lys Ala Glu His Ala Ser Phe
            180                 185                 190


Thr Val Thr Ala Pro Glu Gly Ile Ile Thr Arg Tyr Lys Gly Pro Trp
        195                 200                 205


Thr Gly His Pro Gln Ala Gly Val Leu Gln Lys Gly Gln Thr Ile Lys
```

210 215 220

Tyr Asp Glu Val Gln Lys Phe Asp Gly His Val Trp Val Ser Trp Glu
225 230 235 240

Thr Phe Glu Gly Glu Thr Val Tyr Met Pro Val Arg Thr Trp Asp Ala
245 250 255

Lys Thr Gly Lys Val Gly Lys Leu Trp Gly Glu Ile Lys Glu Leu Arg
260 265 270

Arg Arg Arg Arg Arg Arg Arg Arg
275 280

<210> 44
<211> 284
<212> PRT
<213> Artificial

<220>
<223> Polypeptide construct

<400> 44

Met Ala Ala Thr His Glu His Ser Ala Gln Trp Leu Asn Asn Tyr Lys
1 5 10 15

Lys Gly Tyr Gly Tyr Gly Pro Tyr Pro Leu Gly Ile Asn Gly Gly Met
20 25 30

His Tyr Gly Val Asp Phe Phe Met Asn Ile Gly Thr Pro Val Lys Ala
35 40 45

Ile Ser Ser Gly Lys Ile Val Glu Ala Gly Trp Ser Asn Tyr Gly Gly
50 55 60

Gly Asn Gln Ile Gly Leu Ile Glu Asn Asp Gly Val His Arg Gln Trp
65 70 75 80

Tyr Met His Leu Ser Lys Tyr Asn Val Lys Val Gly Asp Tyr Val Lys
85 90 95

Ala Gly Gln Ile Ile Gly Trp Ser Gly Ser Thr Gly Tyr Ser Thr Ala
100 105 110

Pro His Leu His Phe Gln Arg Met Val Asn Ser Phe Ser Asn Ser Thr
115 120 125

Ala Gln Asp Pro Met Pro Phe Leu Lys Ser Ala Gly Tyr Gly Gly Lys
130 135 140

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

```
Glu Val Lys Lys Gln Glu Ala Lys Gln Ile Val Lys Ala Thr Asp Trp
                165                 170                 175

Lys Gln Asn Lys Asp Gly Ile Trp Tyr Lys Ala Glu His Ala Ser Phe
            180                 185                 190

Thr Val Thr Ala Pro Glu Gly Ile Ile Thr Arg Tyr Lys Gly Pro Trp
        195                 200                 205

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

Tyr Asp Glu Val Gln Lys Phe Asp Gly His Val Trp Val Ser Trp Glu
225                 230                 235                 240

Thr Phe Glu Gly Glu Thr Val Tyr Met Pro Val Arg Thr Trp Asp Ala
                245                 250                 255

Lys Thr Gly Lys Val Gly Lys Leu Trp Gly Glu Ile Lys Glu Leu Gly
            260                 265                 270

Arg Lys Lys Arg Arg Gln Arg Arg Arg Pro Pro Gln
        275                 280
```

<210> 45
<211> 160
<212> PRT
<213> Artificial

<220>
<223> Polypeptide construct

<400> 45

```
Met Ala Ala Thr His Glu His Ser Ala Gln Trp Leu Asn Asn Tyr Lys
1               5                   10                  15

Lys Gly Tyr Gly Tyr Gly Pro Tyr Pro Leu Gly Ile Asn Gly Gly Met
            20                  25                  30

His Tyr Gly Val Asp Phe Phe Met Asn Ile Gly Thr Pro Val Lys Ala
        35                  40                  45

Ile Ser Ser Gly Lys Ile Val Glu Ala Gly Trp Ser Asn Tyr Gly Gly
    50                  55                  60

Gly Asn Gln Ile Gly Leu Ile Glu Asn Asp Gly Val His Arg Gln Trp
65                  70                  75                  80

Tyr Met His Leu Ser Lys Tyr Asn Val Lys Val Gly Asp Tyr Val Lys
                85                  90                  95

Ala Gly Gln Ile Ile Gly Trp Ser Gly Ser Thr Gly Tyr Ser Thr Ala
```

100 105 110

Pro His Leu His Phe Gln Arg Met Val Asn Ser Phe Ser Asn Ser Thr
115 120 125

Ala Gln Asp Pro Met Pro Phe Leu Lys Ser Ala Gly Tyr Gly Glu Leu
130 135 140

Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys
145 150 155 160

<210> 46
<211> 153
<212> PRT
<213> Artificial

<220>
<223> Polypeptide construct

<400> 46

Met Ala Ala Thr His Glu His Ser Ala Gln Trp Leu Asn Asn Tyr Lys
1 5 10 15

Lys Gly Tyr Gly Tyr Gly Pro Tyr Pro Leu Gly Ile Asn Gly Gly Met
20 25 30

His Tyr Gly Val Asp Phe Phe Met Asn Ile Gly Thr Pro Val Lys Ala
35 40 45

Ile Ser Ser Gly Lys Ile Val Glu Ala Gly Trp Ser Asn Tyr Gly Gly
50 55 60

Gly Asn Gln Ile Gly Leu Ile Glu Asn Asp Gly Val His Arg Gln Trp
65 70 75 80

Tyr Met His Leu Ser Lys Tyr Asn Val Lys Val Gly Asp Tyr Val Lys
85 90 95

Ala Gly Gln Ile Ile Gly Trp Ser Gly Ser Thr Gly Tyr Ser Thr Ala
100 105 110

Pro His Leu His Phe Gln Arg Met Val Asn Ser Phe Ser Asn Ser Thr
115 120 125

Ala Gln Asp Pro Met Pro Phe Leu Lys Ser Ala Gly Tyr Gly Glu Leu
130 135 140

Arg Arg Arg Arg Arg Arg Arg Arg Arg
145 150

<210> 47
<211> 157
<212> PRT

<213> Artificial

<220>
<223> Polypeptide construct

<400> 47

Met Ala Ala Thr His Glu His Ser Ala Gln Trp Leu Asn Asn Tyr Lys
1 5 10 15

Lys Gly Tyr Gly Tyr Gly Pro Tyr Pro Leu Gly Ile Asn Gly Gly Met
20 25 30

His Tyr Gly Val Asp Phe Phe Met Asn Ile Gly Thr Pro Val Lys Ala
35 40 45

Ile Ser Ser Gly Lys Ile Val Glu Ala Gly Trp Ser Asn Tyr Gly Gly
50 55 60

Gly Asn Gln Ile Gly Leu Ile Glu Asn Asp Gly Val His Arg Gln Trp
65 70 75 80

Tyr Met His Leu Ser Lys Tyr Asn Val Lys Val Gly Asp Tyr Val Lys
85 90 95

Ala Gly Gln Ile Ile Gly Trp Ser Gly Ser Thr Gly Tyr Ser Thr Ala
100 105 110

Pro His Leu His Phe Gln Arg Met Val Asn Ser Phe Ser Asn Ser Thr
115 120 125

Ala Gln Asp Pro Met Pro Phe Leu Lys Ser Ala Gly Tyr Gly Glu Leu
130 135 140

Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Pro Pro Gln
145 150 155

<210> 48

<400> 48
000

<210> 49

<400> 49
000

<210> 50
<211> 981
<212> DNA
<213> Artificial

<220>
<223> Polynucleotide

<400> 50
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tcaattcagg gcgtggtgat ccacaacgat tatggctcaa tgacccttc acagtacctg 120

ccttggctgt acgctcgcga aaacaacggt acacatgtga atggctgggc ctcagtgtat 180

gccaatcgca acgaggtgct gtggtatcat cctacagact acgtggaatg gcactgcggc 240

aaccaatggg ccaacgccaa cctgatcggc tttgaagttt gcgaatcata tcctggtcgc 300

atctcagaca aactgtttct ggaaaacgag gaagccacac tgaaagtagc tgccgacgtg 360

atgaaatcgt atggcctgcc tgtgaatcgc aacacagtgc gcctgcacaa cgaatttttc 420

ggtacatcat gccctcatcg ttcatgggac ctgcacgtgg gcaaaggcga gccttatacc 480

acaacaaata tcaataaaat gaaagattat ttcattaaac ggattaaaca ctactatgac 540

ggtggcaaac tggaagttag caaagcagcc accattaaac agagtgatgt taaacaagaa 600

gtgaaaaaac aagaggccaa acaaattgtg aaagccaccg attggaaaca gaacaaagat 660

ggcatctggt ataaagcaga acatgccagc tttaccgtga ccgcaccgga aggcattatt 720

acccgttata aaggtccgtg gaccggtcat ccgcaggcag gcgtgctgca gaaaggtcag 780

accatcaaat atgatgaagt gcagaaattt gatggccatg tttgggttag ctgggaaacc 840

tttgaaggtg aaaccgttta tatgccggtt cgtacctggg atgcaaaaac cggtaaagtt 900

ggtaaactgt ggggtgagat taaagagctc cgccagatca aaatttggtt tcagaatcgt 960

cgcatgaaat ggaaaaaata a 981

<210> 51
<211> 960
<212> DNA
<213> Artificial

<220>
<223> Polynucleotide

<400> 51
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ccttggctgt acgctcgcga aaacaacggt acacatgtga atggctgggc ctcagtgtat 180

gccaatcgca acgaggtgct gtggtatcat cctacagact acgtggaatg gcactgcggc 240

aaccaatggg ccaacgccaa cctgatcggc tttgaagttt gcgaatcata tcctggtcgc 300

atctcagaca aactgtttct ggaaaacgag gaagccacac tgaaagtagc tgccgacgtg 360

atgaaatcgt atggcctgcc tgtgaatcgc aacacagtgc gcctgcacaa cgaatttttc 420

ggtacatcat gccctcatcg ttcatgggac ctgcacgtgg gcaaaggcga gccttatacc 480

acaacaaata tcaataaaat gaaagattat ttcattaaac ggattaaaca ctactatgac 540

ggtggcaaac tggaagttag caaagcagcc accattaaac agagtgatgt taaacaagaa 600

gtgaaaaaac aagaggccaa acaaattgtg aaagccaccg attggaaaca gaacaaagat 660

ggcatctggt ataaagcaga acatgccagc tttaccgtga ccgcaccgga aggcattatt 720

acccgttata aaggtccgtg gaccggtcat ccgcaggcag gcgtgctgca gaaaggtcag 780

accatcaaat atgatgaagt gcagaaattt gatggccatg tttgggttag ctgggaaacc 840

tttgaaggtg aaaccgttta tatgccggtt cgtacctggg atgcaaaaac cggtaaagtt 900

ggtaaactgt ggggtgagat taaagagctc cgtcgtcgtc gccgtcggcg tcgtcgttaa 960

<210> 52
<211> 972
<212> DNA
<213> Artificial

<220>
<223> Polynucleotide

<400> 52
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tcaattcagg gcgtggtgat ccacaacgat tatggctcaa tgacccttc acagtacctg 120

ccttggctgt acgctcgcga aaacaacggt acacatgtga atggctgggc ctcagtgtat 180

gccaatcgca acgaggtgct gtggtatcat cctacagact acgtggaatg gcactgcggc 240

aaccaatggg ccaacgccaa cctgatcggc tttgaagttt gcgaatcata tcctggtcgc 300

atctcagaca aactgtttct ggaaaacgag gaagccacac tgaaagtagc tgccgacgtg 360

atgaaatcgt atggcctgcc tgtgaatcgc aacacagtgc gcctgcacaa cgaatttttc 420

ggtacatcat gccctcatcg ttcatgggac ctgcacgtgg gcaaaggcga gccttatacc 480

acaacaaata tcaataaaat gaaagattat ttcattaaac ggattaaaca ctactatgac 540

ggtggcaaac tggaagttag caaagcagcc accattaaac agagtgatgt taaacaagaa 600

gtgaaaaaac aagaggccaa acaaattgtg aaagccaccg attggaaaca gaacaaagat 660

ggcatctggt ataaagcaga acatgccagc tttaccgtga ccgcaccgga aggcattatt 720

acccgttata aaggtccgtg gaccggtcat ccgcaggcag gcgtgctgca gaaaggtcag 780

accatcaaat atgatgaagt gcagaaattt gatggccatg tttgggttag ctgggaaacc 840

tttgaaggtg aaaccgttta tatgccggtt cgtacctggg atgcaaaaac cggtaaagtt 900

ggtaaactgt ggggtgagat taaagagctc ggtcgtaaaa aacgtcgtca gcgtcgtcgt 960

ccgcctcagt aa 972

<210> 53
<211> 600
<212> DNA
<213> Artificial

<220>
<223> Polynucleotide

<400> 53
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ccttggctgt acgctcgcga aaacaacggt acacatgtga atggctgggc ctcagtgtat 180

gccaatcgca acgaggtgct gtggtatcat cctacagact acgtggaatg gcactgcggc 240

aaccaatggg ccaacgccaa cctgatcggc tttgaagttt gcgaatcata tcctggtcgc 300

atctcagaca aactgtttct ggaaaacgag gaagccacac tgaaagtagc tgccgacgtg 360

atgaaatcgt atggcctgcc tgtgaatcgc aacacagtgc gcctgcacaa cgaatttttc 420

ggtacatcat gccctcatcg ttcatgggac ctgcacgtgg gcaaaggcga gccttatacc 480

acaacaaata tcaataaaat gaaagattat ttcattaaac ggattaaaca ctactatgac 540

ggtgagctcc gccagatcaa aatttggttt cagaatcgtc gcatgaaatg gaaaaaataa 600

<210> 54
<211> 579
<212> DNA
<213> Artificial

<220>
<223> Polynucleotide

<400> 54
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ccttggctgt acgctcgcga aaacaacggt acacatgtga atggctgggc ctcagtgtat 180

gccaatcgca acgaggtgct gtggtatcat cctacagact acgtggaatg gcactgcggc 240

aaccaatggg ccaacgccaa cctgatcggc tttgaagttt gcgaatcata tcctggtcgc 300

atctcagaca aactgtttct ggaaaacgag gaagccacac tgaaagtagc tgccgacgtg 360

atgaaatcgt atggcctgcc tgtgaatcgc aacacagtgc gcctgcacaa cgaatttttc 420

ggtacatcat gccctcatcg ttcatgggac ctgcacgtgg gcaaaggcga gccttatacc 480

acaacaaata tcaataaaat gaaagattat ttcattaaac ggattaaaca ctactatgac 540

ggtgagctcc gtcgtcgtcg ccgtcggcgt cgtcgttaa 579

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<220>
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ccttggctgt acgctcgcga aaacaacggt acacatgtga atggctgggc ctcagtgtat 180

gccaatcgca acgaggtgct gtggtatcat cctacagact acgtggaatg gcactgcggc 240

aaccaatggg ccaacgccaa cctgatcggc tttgaagttt gcgaatcata tcctggtcgc 300

atctcagaca aactgtttct ggaaaacgag gaagccacac tgaaagtagc tgccgacgtg 360

atgaaatcgt atggcctgcc tgtgaatcgc aacacagtgc gcctgcacaa cgaatttttc 420

ggtacatcat gccctcatcg ttcatgggac ctgcacgtgg gcaaaggcga gccttatacc 480

acaacaaata tcaataaaat gaaagattat ttcattaaac ggattaaaca ctactatgac 540

ggtgagctcg gtcgtaaaaa acgtcgtcag cgtcgtcgtc cgcctcagta a 591

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<211> 924
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<213> Artificial

<220>
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tgtttcgact acgccaacgc tggctggaaa gtgctgttcg gcctgctgct gaaaggcctg 180

ggagccaaag acatcccttt tgcaaacaat ttcgatggcc tggccacagt ttatcaaaac 240

acccctgact ttctggccca accaggcgac atggtggtgt ttggttctaa ttatggcgca 300

ggctatggcc acgtagcctg ggtgatcgaa gccacactgg actacattat tgtttatgag 360

caaaactggc tgggaggcgg atggacagac ggcatcgaac agcctggctg gggctgggag 420

aaagtgacac gccgtcaaca tgcctatgac ttccctatgt ggttcatccg tcctaatttc 480

aaaggtggta aactggaagt tagcaaagca gcaaccatta aacagtccga tgttaaacaa 540

gaagtgaaaa aacaagaggc caaacaaatt gtgaaagcca ccgattggaa acagaacaaa 600

gatggcattt ggtataaagc agaacatgcc agctttaccg ttaccgcacc ggaaggcatt 660

attacccgtt ataaaggtcc gtggaccggt catccgcagg caggcgtact gcagaaaggt 720

cagaccatta aatacgatga agtgcagaaa tttgatggcc atgtttgggt tagctgggaa 780

acctttgaag gtgaaaccgt ttatatgccg gttcgtacct gggatgcaaa aaccggtaaa 840

gtgggcaaac tgtggggtga aatcaaagag ctccgccaga tcaaaatttg gtttcagaat 900

cgtcgcatga aatggaaaaa ataa 924

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<211> 903
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tgtttcgact acgccaacgc tggctggaaa gtgctgttcg gcctgctgct gaaaggcctg 180

ggagccaaag acatcccttt tgcaaacaat ttcgatggcc tggccacagt ttatcaaaac 240

acccctgact ttctggccca accaggcgac atggtggtgt ttggttctaa ttatggcgca 300

ggctatggcc acgtagcctg ggtgatcgaa gccacactgg actacattat tgtttatgag 360

caaaactggc tgggaggcgg atggacagac ggcatcgaac agcctggctg gggctgggag 420

aaagtgacac gccgtcaaca tgcctatgac ttccctatgt ggttcatccg tcctaatttc 480

aaaggtggta aactggaagt tagcaaagca gcaaccatta aacagtccga tgttaaacaa 540

gaagtgaaaa aacaagaggc caaacaaatt gtgaaagcca ccgattggaa acagaacaaa 600

gatggcattt ggtataaagc agaacatgcc agctttaccg ttaccgcacc ggaaggcatt 660

attacccgtt ataaaggtcc gtggaccggt catccgcagg caggcgtact gcagaaaggt 720

cagaccatta aatacgatga agtgcagaaa tttgatggcc atgtttgggt tagctgggaa 780

acctttgaag gtgaaaccgt ttatatgccg gttcgtacct gggatgcaaa aaccggtaaa 840

gtgggcaaac tgtggggtga aatcaaagag ctccgtcgtc gtcgccgtcg gcgtcgtcgt 900

taa 903

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<220>
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ggagccaaag acatcccttt tgcaaacaat ttcgatggcc tggccacagt ttatcaaaac 240

acccctgact ttctggccca accaggcgac atggtggtgt ttggttctaa ttatggcgca 300

ggctatggcc acgtagcctg ggtgatcgaa gccacactgg actacattat tgtttatgag 360

caaaactggc tgggaggcgg atggacagac ggcatcgaac agcctggctg gggctgggag 420

aaagtgacac gccgtcaaca tgcctatgac ttccctatgt ggttcatccg tcctaatttc 480

aaaggtggta aactggaagt tagcaaagca gcaaccatta aacagtccga tgttaaacaa 540

gaagtgaaaa aacaagaggc caaacaaatt gtgaaagcca ccgattggaa acagaacaaa 600

gatggcattt ggtataaagc agaacatgcc agctttaccg ttaccgcacc ggaaggcatt 660

attacccgtt ataaaggtcc gtggaccggt catccgcagg caggcgtact gcagaaaggt 720

cagaccatta aatacgatga agtgcagaaa tttgatggcc atgtttgggt tagctgggaa 780

acctttgaag gtgaaaccgt ttatatgccg gttcgtacct gggatgcaaa aaccggtaaa 840

gtgggcaaac tgtggggtga aatcaaagag ctcggtcgta aaaaacgtcg tcagcgtcgt 900

cgtccgcctc agtaa 915

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<211> 540
<212> DNA
<213> Artificial

<220>
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tgtttcgact acgccaacgc tggctggaaa gtgctgttcg gcctgctgct gaaaggcctg 180

ggagccaaag acatcccttt tgcaaacaat ttcgatggcc tggccacagt ttatcaaaac 240

acccctgact ttctggccca accaggcgac atggtggtgt ttggttctaa ttatggcgca 300

ggctatggcc acgtagcctg ggtgatcgaa gccacactgg actacattat tgtttatgag 360

caaaactggc tgggaggcgg atggacagac ggcatcgaac agcctggctg gggctgggag 420

aaagtgacac gccgtcaaca tgcctatgac ttccctatgt ggttcatccg tcctaatttc 480

aaagagctcc gccagatcaa aatttggttt cagaatcgtc gcatgaaatg gaaaaaataa 540

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<211> 519
<212> DNA
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<220>
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ggctatggcc acgtagcctg ggtgatcgaa gccacactgg actacattat tgtttatgag 360

caaaactggc tgggaggcgg atggacagac ggcatcgaac agcctggctg gggctgggag 420

aaagtgacac gccgtcaaca tgcctatgac ttccctatgt ggttcatccg tcctaatttc 480

aaagagctcc gtcgtcgtcg ccgtcggcgt cgtcgttaa 519

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<211> 531
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ggctatggcc acgtagcctg ggtgatcgaa gccacactgg actacattat tgtttatgag 360

caaaactggc tgggaggcgg atggacagac ggcatcgaac agcctggctg gggctgggag 420

aaagtgacac gccgtcaaca tgcctatgac ttccctatgt ggttcatccg tcctaatttc 480

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<210> 62
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aacatcggca cccctgtgaa agccattagc tcaggcaaaa tcgtggaagc cggttggtca 180

aactatggcg gtggcaacca gatcggtctg atcgagaacg atggtgtgca ccgccaatgg 240

tacatgcacc tgtccaaata caacgttaaa gttggtgact acgtgaaagc aggccagatt 300

atcggctggt caggttcaac cggttattca acagcccctc atctgcactt ccaacgcatg 360

gtgaatagtt ttagtaattc taccgctcaa gatccgatgc cattcctgaa atctgccggt 420

tatggtggca aactggaagt tagcaaagca gcaaccatta aacagtccga tgttaaacaa 480

gaagtgaaaa aacaagaggc caaacaaatt gtgaaagcga ccgattggaa acagaacaaa 540

gatggcattt ggtataaagc agaacatgcc agctttaccg tgaccgcacc ggaaggcatt 600

attacccgtt ataaaggtcc gtggaccggt catccgcagg caggcgtgct gcagaaaggt 660

cagaccatca aatatgatga ggtgcagaaa tttgatggcc atgtttgggt tagctgggaa 720

acctttgaag gtgaaaccgt ttatatgccg gttcgtacct gggatgcaaa aaccggtaaa 780

gtgggtaaac tgtggggtga aatcaaagag ctccgccaga tcaaaatttg gtttcagaat 840

cgtcgcatga aatggaaaaa ataa 864

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<211> 843
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<220>
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aacatcggca cccctgtgaa agccattagc tcaggcaaaa tcgtggaagc cggttggtca 180

aactatggcg gtggcaacca gatcggtctg atcgagaacg atggtgtgca ccgccaatgg 240

tacatgcacc tgtccaaata caacgttaaa gttggtgact acgtgaaagc aggccagatt 300

atcggctggt caggttcaac cggttattca acagcccctc atctgcactt ccaacgcatg 360

gtgaatagtt ttagtaattc taccgctcaa gatccgatgc cattcctgaa atctgccggt 420

tatggtggca aactggaagt tagcaaagca gcaaccatta aacagtccga tgttaaacaa 480

gaagtgaaaa aacaagaggc caaacaaatt gtgaaagcga ccgattggaa acagaacaaa 540

gatggcattt ggtataaagc agaacatgcc agctttaccg tgaccgcacc ggaaggcatt 600

attacccgtt ataaaggtcc gtggaccggt catccgcagg caggcgtgct gcagaaaggt 660

cagaccatca aatatgatga ggtgcagaaa tttgatggcc atgtttgggt tagctgggaa 720

acctttgaag gtgaaaccgt ttatatgccg gttcgtacct gggatgcaaa aaccggtaaa 780

gtgggtaaac tgtggggtga aatcaaagag ctccgtcgtc gtcgccgtcg gcgtcgtcgt 840

taa 843

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<213> Artificial

<220>
<223> Polynucleotide

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aacatcggca cccctgtgaa agccattagc tcaggcaaaa tcgtggaagc cggttggtca 180

aactatggcg gtggcaacca gatcggtctg atcgagaacg atggtgtgca ccgccaatgg 240

tacatgcacc tgtccaaata caacgttaaa gttggtgact acgtgaaagc aggccagatt 300

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gtgaatagtt ttagtaattc taccgctcaa gatccgatgc cattcctgaa atctgccggt 420

tatggtggca aactggaagt tagcaaagca gcaaccatta aacagtccga tgttaaacaa 480

gaagtgaaaa aacaagaggc caaacaaatt gtgaaagcga ccgattggaa acagaacaaa 540

gatggcattt ggtataaagc agaacatgcc agctttaccg tgaccgcacc ggaaggcatt 600

attacccgtt ataaaggtcc gtggaccggt catccgcagg caggcgtgct gcagaaaggt 660

cagaccatca aatatgatga ggtgcagaaa tttgatggcc atgtttgggt tagctgggaa 720

acctttgaag gtgaaaccgt ttatatgccg gttcgtacct gggatgcaaa aaccggtaaa 780

gtgggtaaac tgtggggtga aatcaaagag ctcggtcgta aaaaacgtcg tcagcgtcgt 840

cgtccgcctc agtaa 855

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<213> Artificial

<220>
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aactatggcg gtggcaacca gatcggtctg atcgagaacg atggtgtgca ccgccaatgg 240

tacatgcacc tgtccaaata caacgttaaa gttggtgact acgtgaaagc aggccagatt 300

atcggctggt caggttcaac cggttattca acagcccctc atctgcactt ccaacgcatg 360

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tatggtgagc tccgccagat caaaatttgg tttcagaatc gtcgcatgaa atggaaaaaa 480

taa 483

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<211> 462
<212> DNA
<213> Artificial

<220>
<223> Polynucleotide

<400> 66
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aacatcggca cccctgtgaa agccattagc tcaggcaaaa tcgtggaagc cggttggtca 180

aactatggcg gtggcaacca gatcggtctg atcgagaacg atggtgtgca ccgccaatgg 240

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tatggtgagc tccgtcgtcg tcgccgtcgg cgtcgtcgtt aa 462

<210> 67
<211> 474
<212> DNA
<213> Artificial

<220>
<223> Polynucleotide

<400> 67
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aactatggcg gtggcaacca gatcggtctg atcgagaacg atggtgtgca ccgccaatgg 240

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gtgaatagtt ttagtaattc taccgctcaa gatccgatgc cattcctgaa atctgccggt 420

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<210> 68

<400> 68
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<210> 69

<400> 69
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<210> 70
<211> 37
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 70

Leu Leu Gly Asp Phe Phe Arg Lys Ser Lys Glu Lys Ile Gly Lys Glu
1 5 10 15

Phe Lys Arg Ile Val Gln Arg Ile Lys Asp Phe Leu Arg Asn Leu Val
20 25 30

Pro Arg Thr Glu Ser
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<210> 71
<211> 29
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 71

Arg Gly Leu Arg Arg Leu Gly Arg Lys Ile Ala His Gly Val Lys Lys
1 5 10 15

Tyr Gly Pro Thr Val Leu Arg Ile Ile Arg Ile Ala Gly
20 25

<210> 72
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 72

Ile Leu Pro Trp Lys Trp Pro Trp Trp Pro Trp Arg Arg

1 5 10

<210> 73
<211> 18
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 73

Arg Gly Gly Arg Leu Cys Tyr Cys Arg Arg Arg Phe Cys Val Cys Val
1 5 10 15

Gly Arg

<210> 74
<211> 31
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 74

Ser Trp Leu Ser Lys Thr Ala Lys Lys Leu Glu Asn Ser Ala Lys Lys
1 5 10 15

Arg Ile Ser Glu Gly Ile Ala Ile Ala Ile Gln Gly Gly Pro Arg
20 25 30

<210> 75
<211> 23
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 75

Gly Ile Gly Lys Phe Leu His Ser Ala Lys Lys Phe Gly Lys Ala Phe
1 5 10 15

Val Gly Glu Ile Met Asn Ser
20

<210> 76
<211> 25
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 76

Gly Trp Gly Ser Phe Phe Lys Lys Ala Ala His Val Gly Lys His Val

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1               5                  10                  15

Gly Lys Ala Ala Leu Thr His Tyr Leu
            20                  25


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<211>  36
<212>  PRT
<213>  Artificial

<220>
<223>  Polypeptide fragment

<400>  77

Gly Gly Leu Lys Lys Leu Gly Lys Lys Leu Glu Gly Ala Gly Lys Arg
1               5                  10                  15

Val Phe Asn Ala Ala Glu Lys Ala Leu Pro Val Val Ala Gly Ala Lys
            20                  25                  30

Ala Leu Arg Lys
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<210>  78
<211>  40
<212>  PRT
<213>  Artificial

<220>
<223>  Polypeptide fragment

<400>  78

Gly Trp Leu Lys Lys Ile Gly Lys Lys Ile Glu Arg Val Gly Gln His
1               5                  10                  15

Thr Arg Asp Ala Thr Ile Gln Gly Leu Gly Ile Pro Gln Gln Ala Ala
            20                  25                  30

Asn Val Ala Ala Thr Ala Arg Gly
        35                  40


<210>  79
<211>  21
<212>  PRT
<213>  Artificial

<220>
<223>  Polypeptide fragment

<400>  79

Thr Arg Ser Ser Arg Ala Gly Leu Gln Phe Pro Val Gly Arg Val His
1               5                  10                  15

Arg Leu Leu Arg Lys
            20
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<210> 80
<211> 39
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 80

Gly Trp Leu Lys Lys Ile Gly Lys Lys Ile Glu Arg Val Gly Gln His
1 5 10 15

Thr Arg Asp Ala Thr Ile Gln Gly Leu Gly Ile Ala Gln Gln Ala Ala
20 25 30

Asn Val Ala Ala Thr Ala Arg
35

<210> 81
<211> 24
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 81

Gly Ile Lys Asp Trp Ile Lys Gly Ala Ala Lys Lys Leu Ile Lys Thr
1 5 10 15

Val Ala Ser His Ile Ala Asn Gln
20

<210> 82
<211> 17
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragement

<400> 82

Ala Asn Arg Pro Val Tyr Ile Pro Pro Pro Arg Pro Pro His Pro Arg
1 5 10 15

Leu

<210> 83
<211> 22
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 83

Gly Leu Leu Ser Lys Val Leu Gly Val Gly Lys Lys Val Leu Cys Gly
1 5 10 15

Val Ser Gly Leu Val Cys
20

<210> 84
<211> 24
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 84

Gly Leu Asn Thr Leu Lys Lys Val Phe Gln Gly Leu His Glu Ala Ile
1 5 10 15

Lys Leu Ile Asn Asn His Val Gln
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<210> 85
<211> 19
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 85

Lys Gly Arg Gly Lys Gln Gly Gly Lys Val Arg Ala Lys Ala Lys Thr
1 5 10 15

Arg Ser Ser

<210> 86
<211> 25
<212> PRT
<213> Artificial

<220>
<223> Polypeptide fragment

<400> 86

Ile Trp Leu Thr Ala Leu Lys Phe Leu Gly Lys His Ala Ala Lys Lys
1 5 10 15

Leu Ala Lys Gln Gln Leu Ser Lys Leu
20 25

<210> 87
<211> 18
<212> PRT
<213> Artificial

<220>
<223>  Polypeptide fragment

<400>  87

Phe Leu Gly Gly Leu Ile Val Pro Ala Met Ile Cys Ala Val Thr Lys
1               5                   10                  15

Lys Cys

<210>  88
<211>  26
<212>  PRT
<213>  Artificial

<220>
<223>  Polypeptide fragment

<400>  88

Gly Ile Gly Ala Val Leu Lys Val Leu Thr Thr Gly Leu Pro Ala Leu
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Ile Ser Trp Ile Lys Arg Lys Arg Gln Gln
            20                  25

<210>  89
<211>  54
<212>  PRT
<213>  Artificial

<220>
<223>  Polypeptide fragment

<400>  89

Lys Thr Tyr Tyr Gly Thr Asn Gly Val His Cys Thr Lys Asn Ser Leu
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Trp Gly Lys Val Arg Leu Lys Asn Met Lys Tyr Asp Gln Asn Thr Thr
            20                  25                  30

Tyr Met Gly Arg Leu Gln Asp Ile Leu Leu Gly Trp Ala Thr Gly Ala
        35                  40                  45

Phe Gly Lys Thr Phe His
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